〈Case Report〉

A case of gastrointestinal stromal tumor (GIST) with peritoneal dissemination －Imatinib re-challenged case－

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ABSTRACT Unresectable, metastatic, recurrent gastrointestinal stromal tumor (GIST) is primarily treated with a molecular-targeted therapeutic agent, imatinib. However, after an initial response, a secondary resistance to the drug often occurs after a few years. We report here a case of a resected giant GIST of the jejunum that disseminated following treatment with imatinib. A 59-year-old male presented with a giant tumor in the abdominal cavity, which was diagnosed as GIST by needle biopsy; he was administered 400 mg/day imatinib. Eight months later, the tumor had considerably decreased, but multiple tumors in small intestine and mesenterium, indicating dissemination, appeared. Administration of imatinib was continued for 36 months from the initial treatment and the dissemination gradually reduced and almost disappeared except for a tumor in the right upper abdomen. Three years later, follow-up computed tomography revealed that the disseminated lesions had enlarged; a part of the intrapelvic tumor was suspected to be viable. We deduced that the tumor developed partial resistance to imatinib: therefore, we surgically removed as many disseminated tumors as possible. Pathologically, resected tumors appeared to have no viable tumor cells except for a small part of the primary tumor in which mitosis was 0-1/50 high-power fields. Genetic analysis of surgically resected specimen for c-kit mutation revealed an exon 11 c554-559 deletion.

17 months after operation, another disseminated tumor was detected. Imaninib therapy was re-introduced. The dissemination was diminished after three months re-challenged imatinib and continues to be recurrence-free for two years. When partial resistance to imatinib is observed, combined modality therapy that involves chemotherapy with surgical intervention at early stages is expected to improve the outcome. doi:10.11482/KMJ-E43(1)5 *(Accepted on January 11, 2017)*

Key words：Gastrointestinal stromal tumor, Imatinib, Surgical intervention, Multimodal therapy

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INTRODUCTION

Gastrointestinal stromal tumors (GIST) are specific, generally Kit (CD117)-positive and Kit or platelet-derived growth factor receptor alpha (PDGFRA) mutation-driven mesenchymal tumors of the gastorointestinal tract. Imatinib mesylate (Glivec®, Novartis Pharma, Switzerland), a selective inhibitor of BCR-ABL tyrosine kinase and KIT and PDGFRA tyrosine kinases, has become the standard therapy for advanced/metastatic GISTs worldwide.

However, following an initial response, a secondary resistance to the drug occurs at a median time of two years following the initiation of treatment and affects most patients after four years. Therefore, additional therapy including surgery is essential.

Here we report a case of a resected giant GIST of the jejunum that disseminated following treatment with imatinib, for considering multimodal therapy that combines adjuvant surgery and molecular-targeted agent.

CASE REPORT

A 59-years-old male consulted his family doctor for a two month history of lower abdominal mass in July 2007. Laboratory tests showed no abnormalities including tumor markers. Abdominal computed tomography (CT) images revealed a giant tumor, $210 \times 120 \times 200$ mm in size, in the abdominal cavity (Fig. 1). Following transabdominal wall needle biopsy at the hospital, the tumor cells were strongly positive for the c-Kit oncogene, positive for Actin and negative for S100 protein and CD34; thus, GIST was diagnosed. The patient was referred to a hospital in Tokyo by his personal reason and admitted to the hospital. Administration of 400 mg/day imatinib, which continued for 36 months from the initial treatment, was initiated to confirm the diagnosis; five months later he was referred to Okayama University hospital. Eight months after initiating the treatment, CT showed that the tumor had considerably decreased in size, $130 \times 110 \times 110$ mm (Fig. 2) but revealed multiple tumors in the small intestine and mesenterium, indicating dissemination. Administration of imatinib was continued and the main tumor has not changed in size since that time but the maximum standard

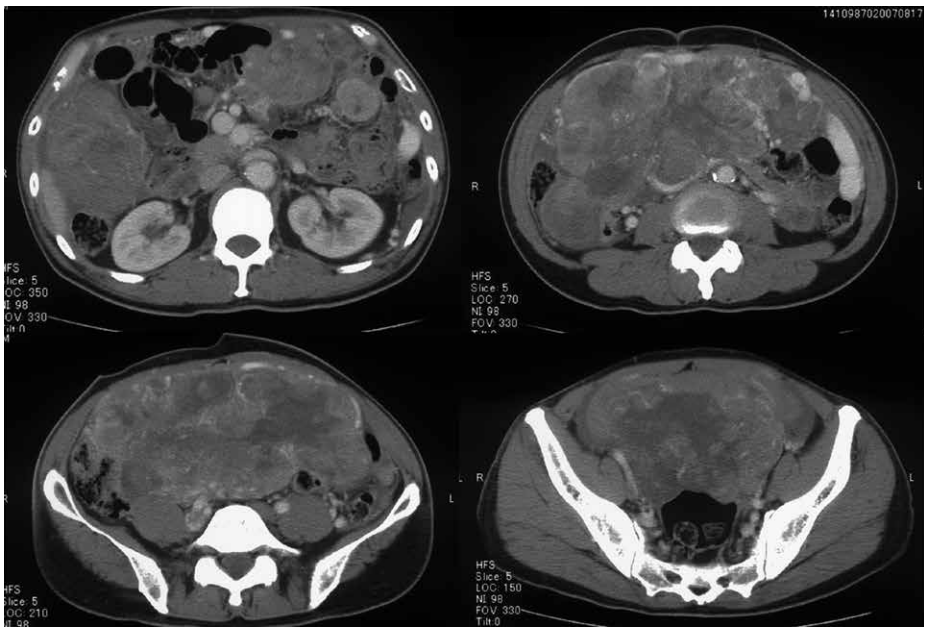

Fig. 1. Abdominal CT images reveled a giant tumor $210 \times 120 \times 200$ mm in size in the abdominal cavity.

uptake value (SUV) from 18-FDG PET scans of the main tumor was less than 2.5 in May 2008. The dissemination gradually diminished thereafter and almost disappeared except for a tumor in the right upper abdomen (Fig. 3). We deduced the effect of imatinib was a partial response, and we continued

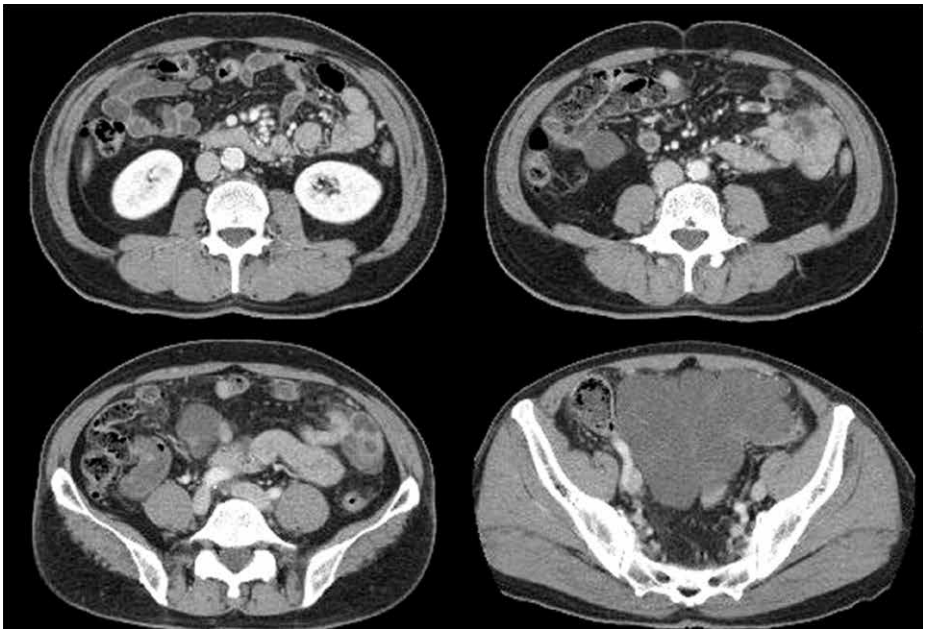

Fig. 2. CT showed that the tumor had shrunk remarkably to 130 × 110 × 110 mm in size.

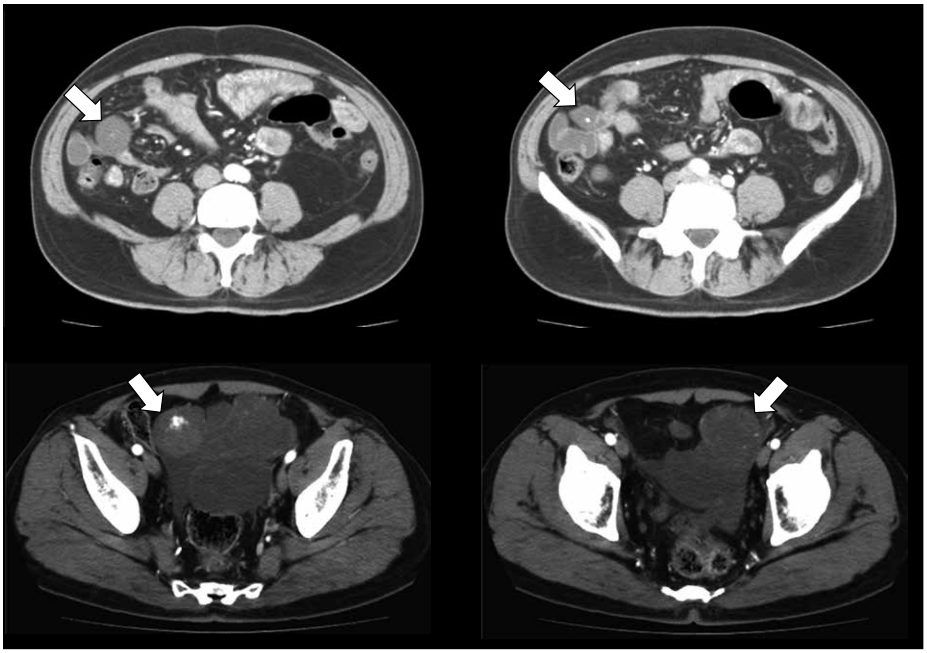

Fig. 3. Three years later, follow-up CT showed multiple disseminated lesions (white arrows) and a part of the intrapelvic primary tumor was suspected to be viable.

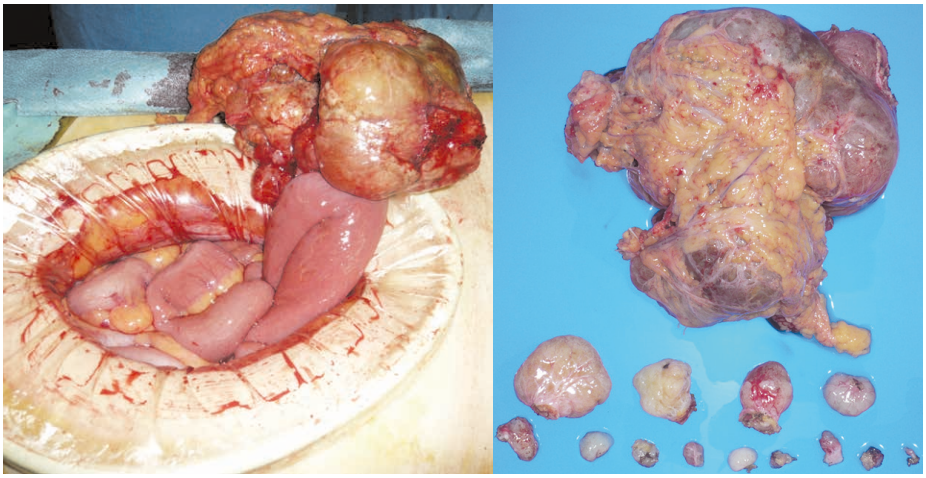

Fig. 4. The primary tumor, 125 mm in diameter, and disseminated tumors of 5-30 mm in size were resected.

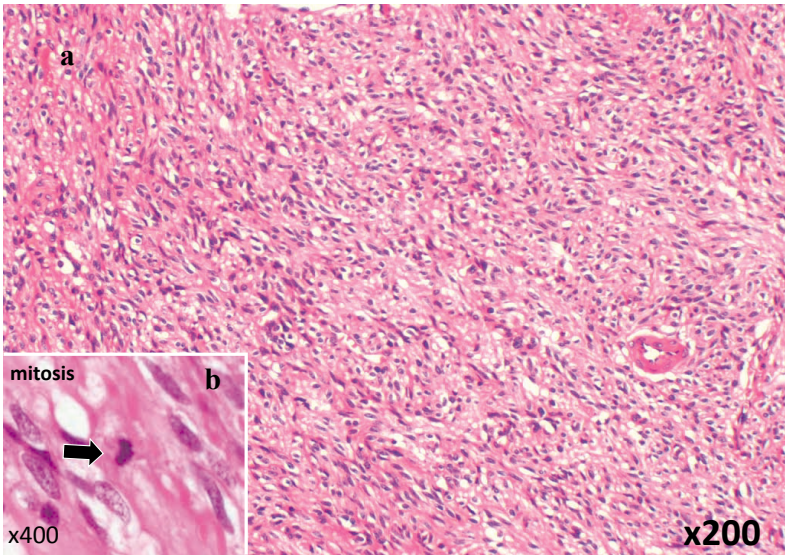

Fig. 5. Pathological findings: Most tumors showed hyalinization/edematous change/necrosis/apoplexy lesions. Viable tumor cells remained in a small part of primary tumor, in which mitosis (black arrow) was 0-1/50 HPFs. H&E ×200.

its administration.

Three years after initiating the treatment, follow-up CT demonstrated that the multiple disseminated lesions, and a part of the intrapelvic tumor was suspected to be viable (Fig. 3). We concluded that the tumor had developed partial resistance to imatinib. We surgically resected the tumor, which was the size of a child's head and had developed within the jejunum approximately 200 mm at the back of Treitz' ligament, along with a small part of jejunum. In addition, several tumors 5-30 mm in size were observed throughout the intra-abdominal mesenterium and peritoneum. We surgically removed as many of these tumors as possible (Fig. 4), but the tumors less than 5 mm in size were abandoned.

Pathologically, most tumors showed hyalinization/edematous change/necrosis/apoplexy lesions, and

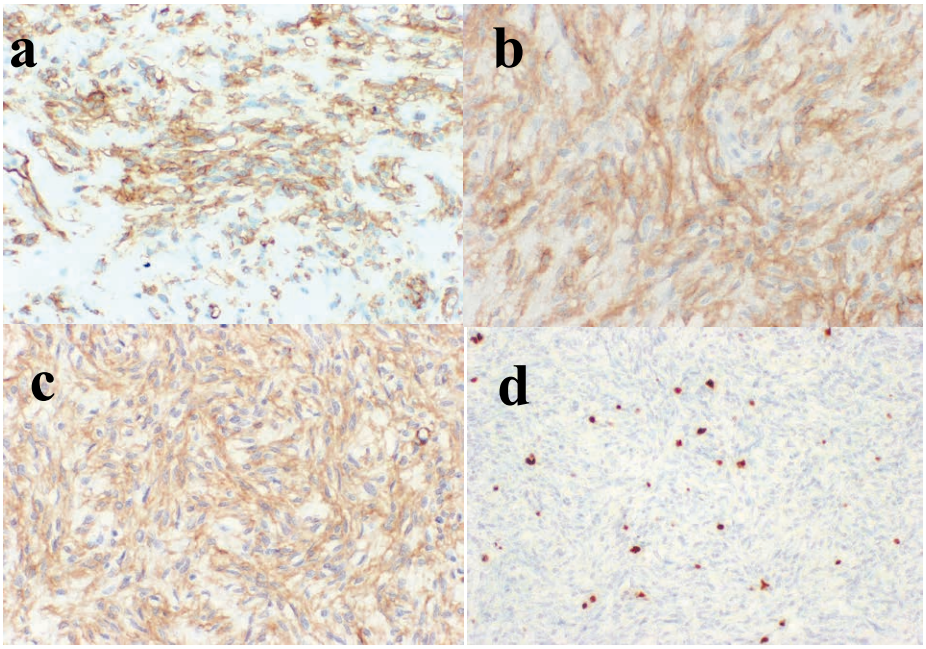

Fig. 6. Immunohistochemical features of the tumor.
(a) CD34 was positive in the tumor cells. Immunostaining ×200 (b) c-kit was positive in the tumor cells. Immunostaining ×200 (c) α-SMA was positive in the tumor cells. Immunostaining ×200 (d) The MIB-1 index of the tumor was approximately 5%.

no viable tumor cells were found except those in a small part of the primary tumor, in which mitosis was 0-1/50 high power fields (HPFs) (Fig. 5). Immunostaining revealed that the tumor cells were positive for CD34 (Fig. 6a), c-kit (Fig. 6b) and α-smooth muscle actin (SMA) (Fig. 6c) and negative for S100 and p53. MIB-1 index, also known as labeling index positive for Ki-67 and proliferation -related antigen, was approximately 5% (Fig. 6d). Genetic analysis of surgically resected specimen for the c-kit mutation revealed an exon 11 c554-559 deletion.

However, 17 months after operation, another disseminated tumor was detected by follow-up CT (Fig.7a). Imaninib therapy (400mg/day) was re-introduced. The dissemination was diminished after three months re-challenged imatinib therapy (Fig.7b). The patient continues to be recurrence-free for two years since re-challenged imatinib.

DISCUSSION

The efficacy of imatinib for the treatment of unresectable, metastatic, recurrent GIST has been established, and imatinib is considered to be the drug of choice[1, 2]. However, approximately 12%-14% of GIST patients treated with imatinib, showed no effect after the initiation of treatment (primary resistance), and half of the patients who initially respond developed resistance (secondary resistance) after receiving the treatment for approximately two years. Thus, cases of radical cure are extremely rare[3]. In addition, continuous administration may be impossible in some patients because of adverse effects.

Two paths of action can be considered for imatinib-resistant GIST: (1) increased dosage of imatinib, and (2) change to sunitinib. However, sunitinib tends to be ineffective to tumor cells which possessed mutations on exon17 or 18, which is the activation loop domain, and its efficacy in the

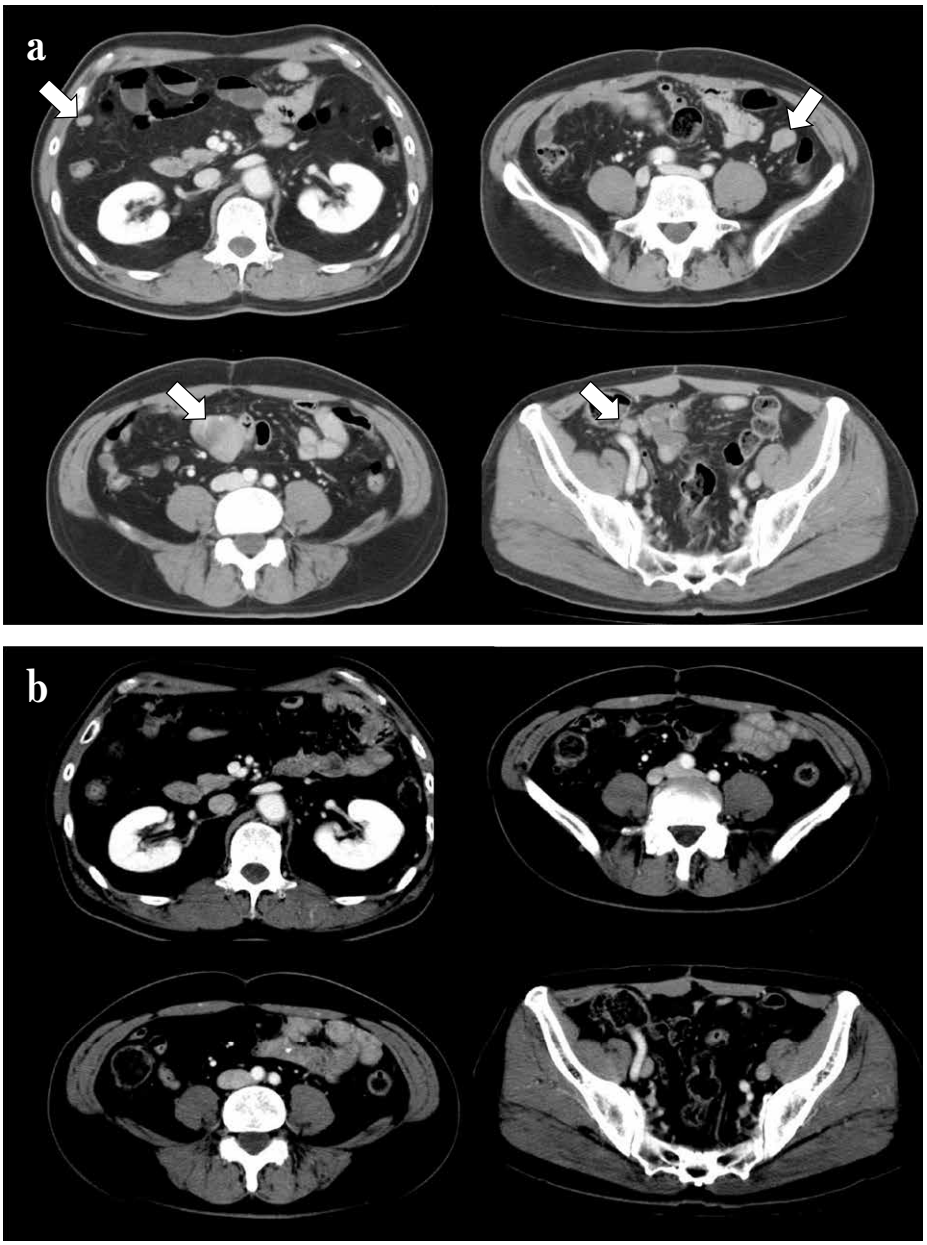

Fig. 7. (a) 17 months after operation, another disseminated tumors (white arrows) was detected by follow-up CT. (b)The dissemination was diminished after three months re-chalenged imatinib therapy.

treatment of imatinib-resistant GIST shows a clinical benefit response (CBR) of 53% and an intermediate PFS value of approximately 34 weeks[4], which makes it inefficient. We believe that resectable partially-resistant GIST should be surgically resected to preserve sunitinib as a future alternative. The 2009 National Comprehensive Cancer Network (NCCN) guidelines state that, if unresectable, metastatic, recurrent GIST can be controlled by administration of imatinib, surgical intervention should be considered at an appropriate time. Bauer *et al.* also reported that if administration of imatinib

can control unresectable, metastatic GIST, surgical intervention tends to extend the survival period to a greater degree than continued therapy with solely imatinib[5]. At the American Society of Clinical Oncology (ASCO) in 2010, Nguyen *et al.* reported a better prognosis for patients whose metastatic GIST was, in principle, treated with imatinib followed by surgical intervention. According to Ford SJ *et al.*[6], surgery may have a limited favorable impact on progression-free survival and overall survival for those patients whose disease is responding to imatinib or those with limited focal progression. Patients with imatinib resistant disease should not be offered surgery unless as an emergency where palliative intervention may be justified[6]. Furthermore, a randomized comparison study (EORTC 62063) is currently being conducted in Europe and Australia to review the utility of surgical intervention in patients with metastatic, recurrent GIST controlled by imatinib therapy. With regard to the timing of surgical intervention, a retrospective study by Mussi *et al.* in unresectable, recurrent, metastatic, GIST patients treated with imatinib revealed that surgery performed when the best clinical response was obtained yielded a significantly better two years- progression-free survival (PFS) and five years- disease-specific survival (DSS) than surgery conducted when local progression had already been diagnosed[7].

A single- facility retrospective study of patients with unresectable, metastatic GIST conducted in the USA showed a significantly better prognosis when resection of the residual tumor was performed under the control of tyrosine kinase inhibitory agents, such as imatinib, compared with surgical intervention at an aggravated stage[8]. In other words, if surgical resection is performed on the GIST during the efficacious stage when imatinib resistance emerges or in the early stages of partial resistance, an excellent prognosis may be obtained, such as in the patient described here. Thus, the efficacy of imatinib in the treatment of GIST and the early discovery of resistance are considered to be important factors in its prognosis.

Generally, the efficacy of treatment of a solid tumor is assessed on the basis of RECIST criteria, and more than 30% reduction in tumor diameter is judged to be a partial response. However, a change in CT value in GIST due to reduced blood flow or cystic changes of the tumor is known to reflect a treatment effect. Therefore, to evaluate the efficacy of imatinib in the treatment of GIST, Choi criteria that included tumor diameter and changes in CT value have been used[9]. Furthermore, 18FDG-PET enables the evaluation of viable cells in GIST by identifying metabolic changes in the tumors. Stroobants *et al.*[10] and Antoch *et al.*[11] reported that, after the administration of imatinib, changes in uptake in PET are a good reflection of a treatment effect and is well correlated with prognosis in GIST. In our patient, reduction in tumor diameter stopped 8 months after the onset of administration of imatinib; however, the SUV value was as low as 2.5. Therefore, administration of imatinib was continued and a reduction in disseminated lesion was observed for 3 years. Furthermore, Gayed *et al.*[12] reported that PET-CT was useful in assessment of the effect of imatinib on recurrent GIST; therefore, PET-CT is believed to be valuable in the early evaluation of resistance to imatinib in unresectable, metastatic, recurrent GIST.

Unresectable, metastatic, recurrent GIST is primarily treated with molecular-targeted therapeutic agents, such as imatinib and adjuvant surgery, if the tumor became resectable, is one of the most effective therapeutic strategies. Even when the partial resistance to imatinib is observed, combined modality therapy that involves surgical intervention is expected to improve the treatment outcome.

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