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Case Report

Aggressive Surgical Resection Combined With Imatinib Therapy for Liver Metastases From a Gastrointestinal Stromal Tumor

Mariko Tsukagoshi, Hideki Suzuki, Kenichiro Araki, Norihiro Ishii, Akira Watanabe, Norio Kubo, Satoshi Wada, Fumiyoshi Saito, Hiroyuki Kuwano

Department of General Surgical Science, Gunma University Graduate School of Medicine, Maebashi, Japan

The use of imatinib mesylate has influenced survival in patients with advanced gastrointestinal stromal tumors (GISTs). However, whether a combination of imatinib and surgical resection can further prolong survival in these patients has not yet been fully elucidated. We report a case of a 59-year-old woman with multiple liver metastases from a jejunal GIST. The patient received imatinib therapy after partial resection of the jejunum, and she subsequently underwent right hepatic trisectionectomy. However, liver metastasis was detected again after surgery. Secondary imatinib therapy was started, and the patient underwent partial hepatectomy at the left lateral segment. Postoperatively, the patient underwent imatinib treatment and has survived without recurrence for 3 years. Imatinib is recommended for the treatment of advanced GIST; however, a complete response is rare, and approximately half of all patients develop resistance to imatinib. Aggressive surgical resection combined with imatinib may be effective for the control of advanced GIST.

Key words: Gastrointestinal stromal tumor – Liver metastasis – Imatinib – Surgical resection

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, accounting for approximately 1% to 3% of all gastrointestinal tract neoplasms.[1,2] The most common primary sites of GISTs are the stomach and small intestine,[3] where the tumors are generally treated by surgical resection. However, more than 50% of GIST patients present with locally advanced, recurrent, or metastatic disease,[4] and recurrent tumors develop in approximately 50% of cases even after R0 resection, with the most common site of metastasis being the liver.[5]

Corresponding author: Mariko Tsukagoshi, Department of General Surgical Science, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, 371-8511 Gunma, Japan.
Tel.: +81 27 220 8224; Fax: +81 27 220 8230; E-mail: m13702038@gunma-u.ac.jp

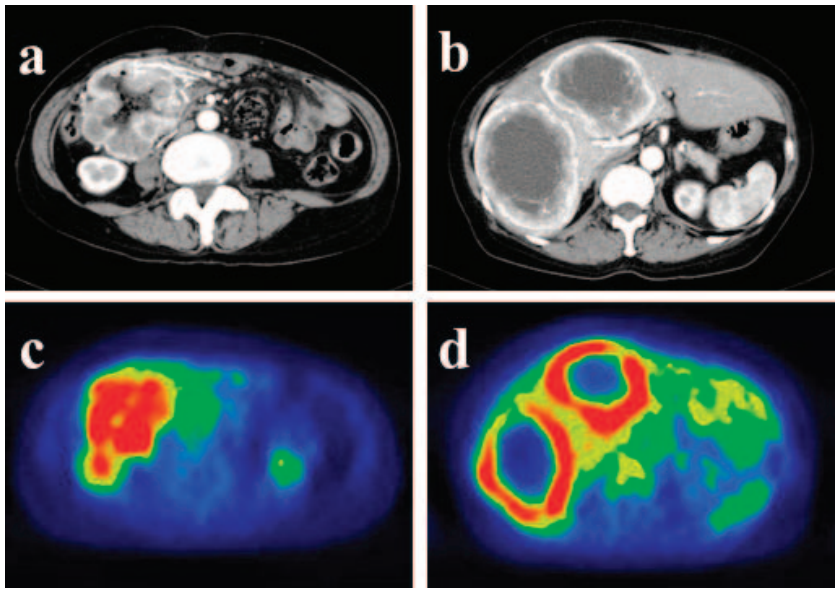

Fig. 1 Abdominal CT and FDG-PET of multiple liver metastases from jejunal gastrointestinal stromal tumor at time of diagnosis. CT scans show a mass arising from the small bowel (a) and multiple liver metastases (b). FDG-PET shows abnormal uptake in the jejunal mass (c) and liver metastases (d).

Imatinib mesylate, a selective tyrosine kinase inhibitor, has been demonstrated to influence the survival of patients with advanced GIST, and it is now regarded as a first-line treatment for locally advanced or metastatic GIST.[6,7] Moreover, imatinib is also currently under evaluation as an induction and adjuvant therapy.[4]

Although imatinib has been shown to be highly effective for the treatment of metastatic GIST, complete responses are rare, and approximately half of all patients will develop imatinib resistance.[7,8] The efficacy of surgical resection for tumors resistant to imatinib is still under investigation, and whether surgical resection combined with imatinib can improve clinical outcomes in patients with metastatic GIST has not yet been fully elucidated.

Here, we report our experience with a patient who underwent aggressive surgical resection of liver metastases combined with imatinib therapy, and we review the current literature on the topic.

Case Report

A 59-year-old woman presented with an upper abdominal growth, and she was found to have a malignant tumor in the jejunum as well as multiple liver metastases (S4, S4/5, S6, and S8). A computed tomography (CT) scan showed that the tumor of the jejunum was 8 cm in size, whereas the largest liver tumor was 11 cm (Fig. 1a and 1b). ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) showed abnormal uptake in the jejunal mass and liver tumors (Fig. 1c and 1d). The patient was diagnosed with multiple liver metastases arising from the jejunal GIST and underwent partial resection of the jejunum. Pathologic examination after surgery revealed spindle cells positive for the proto-oncogene c-Kit and CD34, with 27 mitoses per 50 high-power fields and an MIB-1 labeling index of 30%. Retrospective mutational analysis of the *KIT* gene was performed, and a 51-bp deletion was detected, located between codons 560 and 576 in exon 11.

The patient received 400 mg of imatinib to treat the liver metastases after the surgical resection of the jejunal GIST. One month after commencing imatinib treatment, a follow-up abdominal CT scan showed a partial response, with a reduction in the size of all liver tumors and a thinning of the solid masses; the central necrosis had increased in size (Fig. 2a). However, 6 months into imatinib treatment, abdominal CT revealed that all of the liver tumors had developed (Fig. 2b). The response to imatinib treatment was thus evaluated as progressive disease.

Subsequently, the patient was referred to our hospital for surgical treatment of the GIST liver metastases. FDG-PET imaging revealed that all of the liver tumors were metabolically inactive (Fig. 2c). After portal vein embolization, right hepatic trisectionectomy was performed, and 4 metastatic lesions were resected. Immunohistochemical staining revealed positive expression of c-Kit and slightly positive expression of CD34 (Fig. 3), confirming a diagnosis of metastatic GIST. The tumor cells were viable, but no mitosis was observed. Moreover, no

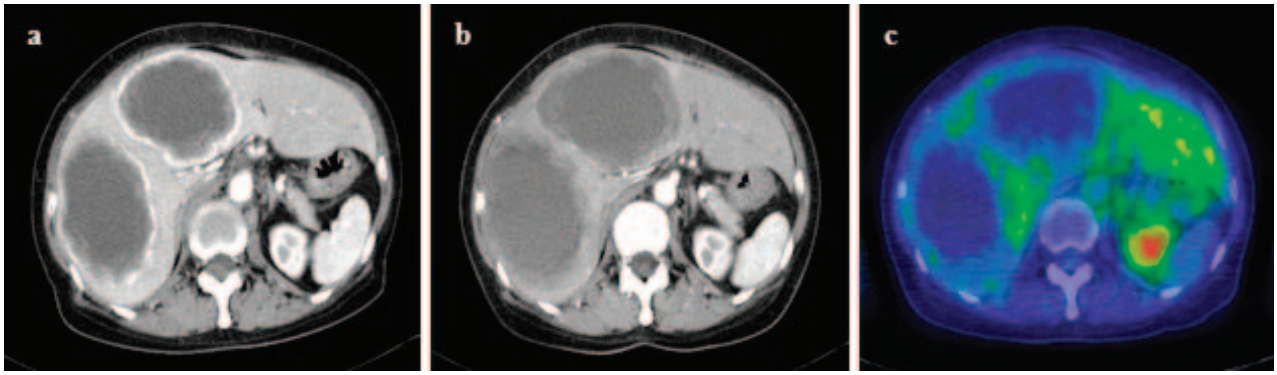

Fig. 2 Abdominal CT scans and FDG-PET after primary resection. CT performed 1 month after the initiation of imatinib treatment shows a reduction in the size of all liver tumors (a). CT performed after 6 months of imatinib treatment shows that all liver tumors have redeveloped (b); simultaneous FDG-PET imaging indicates that the liver tumors were metabolically inactive (c).

secondary mutations were observed at exons 13, 14, and 17 of the *KIT* gene.

After the surgical resection, the patient was followed up without imatinib treatment. For 6 months, no recurrence was observed (Fig. 4a). However, 7 months after the hepatic trisectionectomy, a follow-up CT revealed a 2.5-cm liver metastasis (Fig. 4b). Because the tumor was near the left branch of the portal vein, treatment with 400 mg of imatinib was initiated. Three months later, abdominal CT showed a reduction in the tumor size (2 cm; Fig. 4c), and there was no remarkable interval change for 6 months. Nine months after the imatinib treatment was reinitiated, CT showed increased contrast enhancement of the wall of the metastatic tumor, and a viable tumor was suspected (Fig. 4d). Ultrasonography revealed another 3 metastatic tumors. Accordingly, the patient underwent partial hepatectomy at the left lateral segment. Pathologic examination revealed that almost all tumor cells were viable, with 30 mitoses per 50 high-power fields. No secondary mutations were observed at exons 13, 14, and 17 of the *KIT* gene.

After surgery, treatment with 400 mg of imatinib was reinitiated. No tumor recurrence was observed 3 years after the partial hepatectomy (Fig. 5), and the imatinib treatment consequently ceased. At the latest follow-up (3 months after imatinib termination), no recurrence was observed.

Conclusion

Therapy for advanced GIST has changed significantly with the introduction of imatinib mesylate,

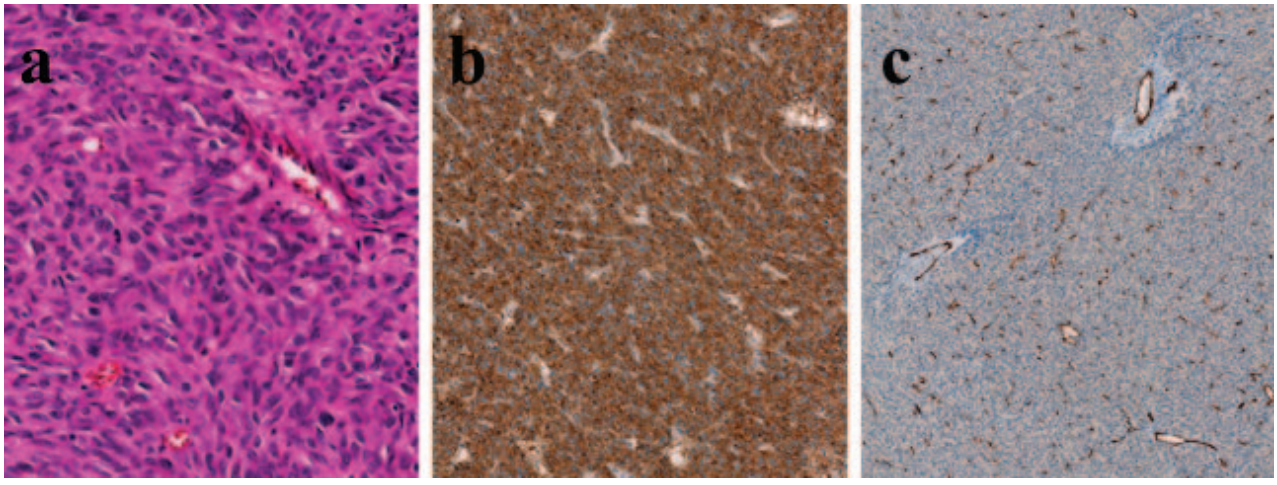

Fig. 3 Histologic findings of the liver metastatic gastrointestinal stromal tumors. Hematoxylin-eosin stain shows a stromal tumor (a), and immunohistochemical stain reveals positive expression of proto-oncogene c-Kit (b) and slightly positive expression of CD34 (c).

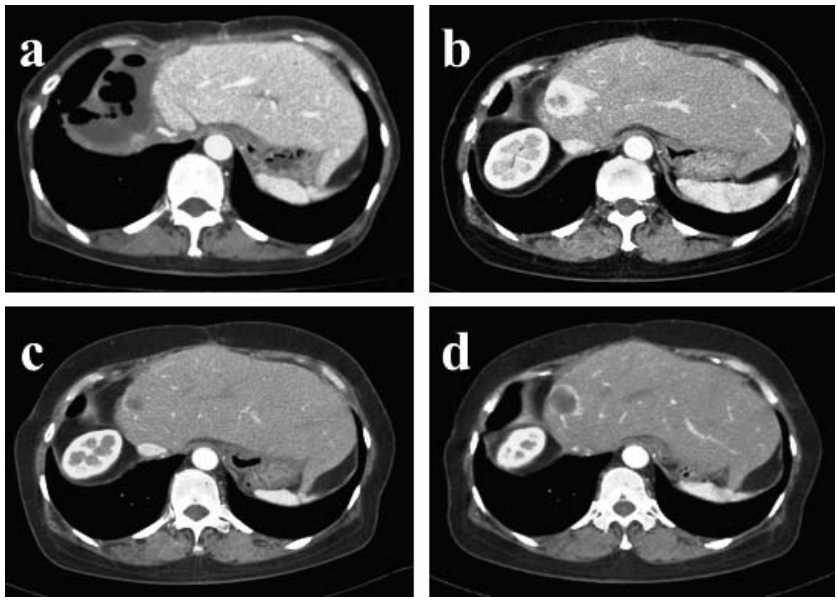

Fig. 4 Abdominal CT scans after the right hepatic trisectionectomy. No recurrence was observed 2 months after the hepatectomy (a). CT performed 7 months after the hepatectomy reveals a 2.5-cm liver metastasis (b); imatinib was initiated thereafter. CT performed 3 months later shows a reduction in the size of the liver tumor (c). CT performed 9 months after imatinib treatment shows increased contrast enhancement of the wall of the metastatic tumor (d).

which has greatly improved the survival of patients with metastatic or locally advanced GIST. The European Organisation for Research and Treatment of Cancer phase 3 trial on imatinib treatment of metastatic GIST demonstrated complete response, partial response, and stable disease rates of 5.84%, 50.70%, and 32.39%, respectively.[9] Imatinib is now regarded as a primary treatment for advanced GIST,[6,7] and the effects of adjuvant and neoadjuvant imatinib therapy are under evaluation. Several studies have investigated the effects of adjuvant therapy with imatinib, and decreased recurrence rates and improved patient prognoses have been reported.[10] The Radiation Therapy Oncology Group phase 2 trial evaluated neoadjuvant imatinib treatment administered 8 weeks prior to surgery and found that the 2-year progression-free survival rate was 77% in patients with advanced GIST.[11]

In the present case, we diagnosed multiple liver metastases from a jejunal GIST. After partial resection of the jejunum, the patient was treated with 400 mg of imatinib mesylate for the liver metastases. The patient initially responded well to imatinib; however, 6 months after treatment was initiated, abdominal CT showed progression of the liver tumors.

Although imatinib is effective for the treatment of metastatic GIST, it rarely results in complete response.[12] Consistent with what was observed in our case, DeMatteo *et al*[13] reported that the response of GIST to imatinib generally plateaus after 6 months of therapy. Primary resistance to imatinib is rare, but approximately half of all patients become resistant 2 years after initiation of treatment. In a recent study, initial resistance and late resistance to imatinib were found to occur in 12% and 42% of advanced GIST cases, respectively.[14] The most common mechanism of acquired resistance is a secondary *KIT* mutation.[8,15] For the management of imatinib-resistant GIST, several treatment options are recommended. Sunitinib is known to inhibit c-Kit and has been used as a second-line therapy for imatinib-resistant GIST.[16] Increasing the dose of imatinib is another therapeutic option; however,

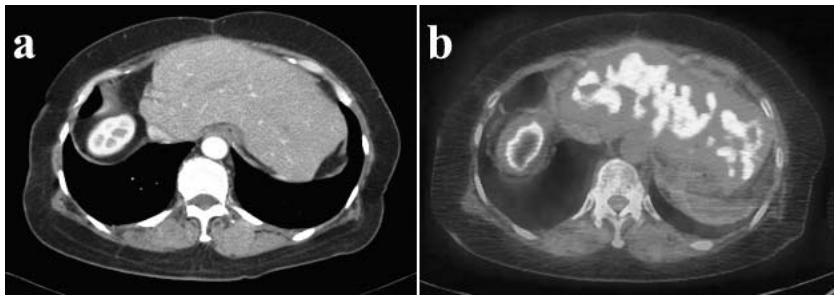

Fig. 5 Abdominal computed tomography (CT) scans and FDG-PET 3 years after the partial hepatectomy. No recurrent lesion was observed on CT (a) or FDG-PET (b).

this is not approved in Japan. The surgical approach is also limited to investigational studies. Therefore, careful selection of patients is required for surgical intervention.

In our case, we performed aggressive surgical resection after 6 months from the initiation of imatinib, and all of the liver metastases were completely removed before a secondary *KIT* mutation appeared. Accordingly, Bonvalot *et al*[17] pointed out that surgical resection should always be considered after 6 to 12 months of imatinib among responders, because of the high risk of secondary resistance.

Although the efficacy of surgical treatment for advanced GIST has not been established and it remains controversial, the present case indicated that combination therapy including repeated surgical resection and imatinib might be an effective management method in selected patients. Maehara *et al*[18] reported that repeated surgical resection and medical treatments for liver metastases from gastric GIST improved overall survival. In the present case, the primary tumor specimen carried a *KIT* exon 11 deletion mutation. Moreover, no secondary mutation was found in resected liver metastases. It is known that GISTs with a *KIT* exon 11 deletion mutation are the most sensitive to imatinib treatment.[19] Because the patient had received the first course of imatinib therapy only for a limited period until surgical intervention, secondary imatinib therapy was found to be effective, and it facilitated complete tumor resection.

The timing of surgical resection is important in combination therapy for the patients with recurrent or metastatic GIST. We propose that a rapid treatment response assessment using CT or PET should be performed from the initiation of imatinib therapy, and it is advisable that patients be followed up closely. If the medical condition of the patient permits, surgical resection should be considered before secondary resistance appears. Considering the present case, surgical resection is recommended between the sixth and ninth months of imatinib treatment. Although we experienced a good clinical outcome in this case, it remains a single case. Further large-scale studies are necessary to determine the role of surgical resection combined with imatinib for advanced GIST.

In summary, we report a case of advanced GIST with liver metastases where the patient underwent aggressive surgery combined with imatinib therapy. Although imatinib has improved the survival of patients with metastatic or locally advanced GIST, a complete response seldom occurs, and resistance to imatinib commonly develops during chronic imatinib therapy. However, aggressive surgical resection combined with imatinib may be effective for the control of metastatic GIST.

Acknowledgments

The authors declare that they have no conflict of interest.

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