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*Original Article*

# Liver transplantation for a metastasized duodenal gastrointestinal stromal tumor: a case report and review of the literature

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**Abstract:** Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, and it's rare for them to originate from the duodenum. Our report illustrates a 63-year-old woman who underwent pancreaticoduodenectomy (PD) due to a duodenal GIST 13 years ago. After that, the patient experienced unresectable multifocal hepatic metastases. As treatments of sunitinib malate, imatinib mesylate and transarterial chemoembolization (TACE) proved ineffective, she underwent a liver transplantation and finally recovered. Histopathology proved the tumor to be a case of a metastatic GIST. The 12-month follow-up after the transplantation showed that the patient is tumor-free under treatment with immunosuppressant and Stivarga. To the best of our knowledge, this is the only case report published in the English medical literature on an elderly patient with metastasized hepatic GIST after PD due to a duodenal GIST with a 13-year remission, who underwent a liver transplantation successfully. Liver transplantation might be an alternative option with a better prognosis for highly selected patients with unresectable metastatic GIST to the liver.

**Keywords:** Gastrointestinal stromal tumors, liver transplantation, liver metastases

## Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, and they have the unique feature of a high rate of recurrence or metastasis even with radical surgery in a long remission interval [1, 2]. For patients with metastatic GIST, a tyrosine kinase inhibitor (TKI) is recommended, and imatinib mesylate (IM) is the first-line therapy for unresectable GISTs [3, 4], but a single agent therapy often leads to tumor resistance, and only 4.5% of patients with recurrent/metastatic GIST experience tumor shrinkage [5]. In recent years, more and more studies have found that a complete resection of the metastatic lesions combined with IM can prolong survival. Therefore, surgery is generally recommended for a patient with generalized disease progression under treatment and resectable tumors [6, 7]. For those patients with unresectable multiple liver metastases and TKI resistance, treatments remain tremendously challenging [8, 9]. Such cases may bring about serious morbidity, mortality, and complex management issues; no effective therapy is available except for liver transplantation, which might be a chance for cure. There is little information on whether liver transplantation can prolong survival in cases with unresectable multiple liver metastases. However, the exact impact of liver transplantation on prognosis in this setting needs to be determined [10-13].

Herein we report a case of an elderly patient with unresectable, recurrent GIST liver metastases after pancreaticoduodenectomy (PD) due to a duodenal GIST with a 13-year remission interval, who underwent liver transplantation successfully and survived without recurrence for 12 months.

## Case report

In February 2015, a 63-year-old woman presented with mild abdominal discomfort and a history of pancreaticoduodenectomy (PD) due

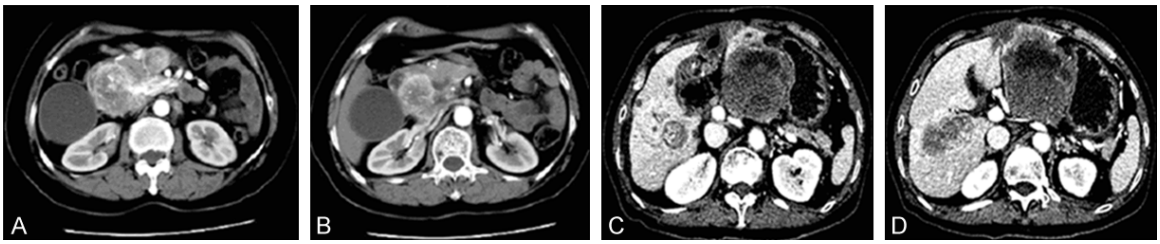


**Figure 1.** A and B: CT scan in 2002 showed the presence of a 5 cm solid tumor located in the descending part of duodenal, which was adjacent to vater's ampullary and enhanced inhomogeneously. C and D: CT revealing multifocal heterogeneous mass in bilateral lobes of liver, ranging from 1-15 cm in diameter in bilateral lobes of liver.

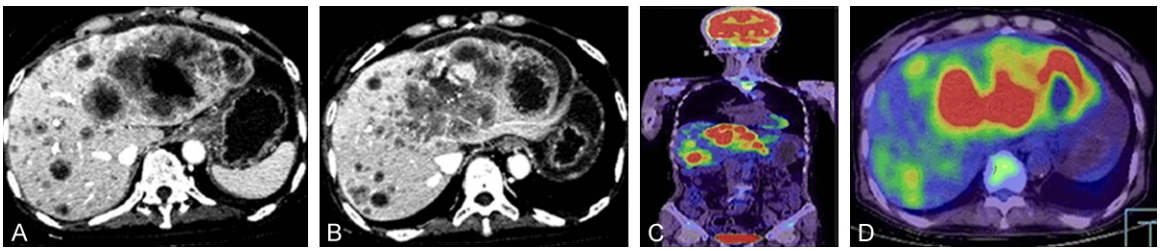


**Figure 2.** A and B: CT showing a significant increase in tumor size and number, ranging from 2-18 cm in diameter; and a large gas-bearing capsular space (5 cm) with peripheral enhancement in hepatogastric space after treatment with IM and TACE; C and D: Preoperative PET/CT showing multiple hepatic hotspot, no sign of extrahepatic recurrence or metastasis.

to a duodenal GIST 13 years ago. The computer tomography (CT) scan done in 2002 showed the presence of a 5 cm solid tumor in the descending part of the duodenum, which was adjacent to vater's ampullary and was enhanced inhomogeneously (**Figure 1A**, **1B**). A physical examination showed a soft abdomen and slight pain in the epigastric area without any resistance. The liver was palpable with non-tender and hard masses. No abnormality was found on digital rectal examination. The tumor markers included carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), prostate specific antigen (PSA), and cancer antigen 19-9 (CA19-9), and routine laboratory tests showed no abnormal findings except for hypoproteinemia (albumin, 28 g/L) and a mild elevation in alkaline phosphatase (ALP, 155 U/L) and gamma-glutamyl transpeptidase (GGT, 185 U/L). Ultrasonography and computer tomography (CT) scans disclosed the presence of a multifocal heterogeneous mass ranging from 1-15 cm in diameter in the bilateral lobes of the liver (**Figure 1C**, **1D**). Upper and lower endoscopy revealed no tumors of the gastrointestinal (GI) tract. A core liver biopsy demonstrated atypical spindle cells with a positive expression of CD117 and DOG-1 in immunohistochemical stains, which is consistent with metastasized GIST based on the previously primary duodenal GIST.

Due to the irresectability of the metastatic tumors, the patient was treated with IM by multidisciplinary recommendation, which was administrated at a dose of 600 mg per day (a larger dose was intolerable). In the 3-month follow-up, the tumor size increased gradually. The treatment was adjusted to sunitinib malate (50 mg, once a day, SM, Sutent ®, Pfizer, New York, NY, USA) and transarterial chemoembolization (TACE) (once a month). In the next 6 months, the patient developed nausea, vomiting, abdominal distention, anorexia, anemia (Hemoglobin 108 g/L), and a 10-kg weight loss, and the abdominal CT scans showed a significant increase in tumor size and number, ranging from 2-18 cm in diameter (**Figure 2A**, **2B**). Further examinations and a reevaluation were carried out with the help of a CT scan and 18-Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ($^{18}$F-FDG-PET/CT). Except for multiple hepatic hotspots and a large gas-bearing capsular space (5 cm) with peripheral enhancement in the hepatogastric space (**Figure 2C**), no sign of

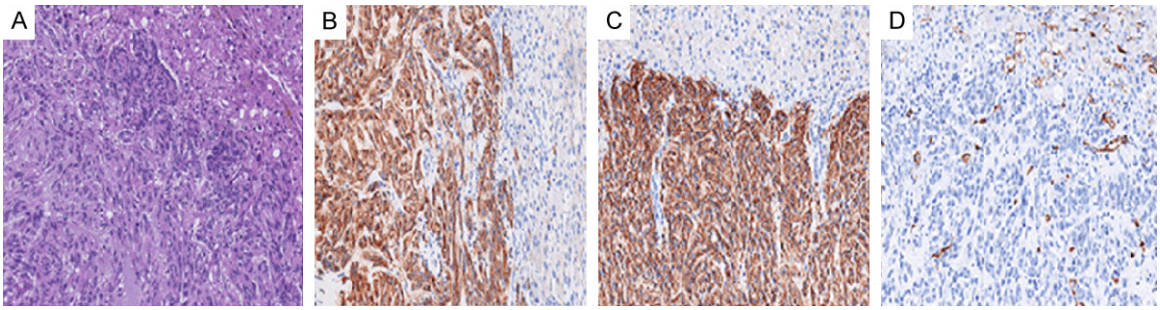


**Figure 3.** (A): Histopathologic findings of HE (hematoxylin-eosin) staining (×200) revealed a bilateral multifocal tumor, mainly consisting of spindle cells and cells with heterogenic nucleui, in which there were more than 20 cells per 10 high-power fields undergoing mitosis. (B-D): Immunohistochemical study (×200) showed the diffusive positive expression of c-kit (CD 117) (B), and DOG-1 (C), negative expression of CD34 (D).

extrahepatic recurrence or metastasis was found (**Figure 2D**).

In the setting of rapid disease progression and a gradually deteriorating general condition with a poor response to the TKIs, there was no alternative therapy but liver transplantation, as determined by our multidisciplinary consensus. After two weeks of supportive treatment and the discontinuation of TKI, the patient's nutrition and general condition were improved. Classic orthotropic liver transplantation was performed with a marginally deceased donor soon afterwards in January 2016. An abscess in the hepatogastric space resulting from an intestinal fistula was explored and resolved simultaneously. Due to severe vascular adhesions and scarring of the hilum, hepatectomy was performed with mass clamping of the hilar structures, and no extracorporeal venovenous bypass was used. The histopathologic findings revealed a multifocal tumor in the bilateral lobes of the liver mainly consisting of spindle cells and cells with a heterogenic nucleus (**Figure 3A**), and there were more than 20 cells per 10 high-power fields undergoing mitosis. The immunohistochemical study showed a diffusely positive expression of c-kit (CD 117) and DOG-1, a weak positive expression of SMA (smooth muscle actin) and desmin, but CD34 and S100 were negative (**Figure 3B**, **3D**). Even though the previous pathologic data were lost and cannot be provided in this paper, these findings confirmed the diagnosis of metastatic GIST based on standard immunohistochemical criteria and the past history of duodenal GIST [14]. Further examinations showed KIT N822K gene mutation in exon 17.

The postoperative course was uneventful except for a relative longer mechanical ventilation (5 days) and transient arrhythmia in the ICU (intensive care unit). The patient received treatment with tacrolimus (FK506; 0.1 mg/kg per day) and was discharged from the hospital 3 weeks after transplantation. Regorafenib (160 mg once daily, brand name Stivarga, Bayer, Germany) was given two months after transplantation. At the last follow-up at the time of writing in December 2016, 12 months after LT, the patient is in excellent condition under continuous regorafenib treatment and with a stable FK506 concentration without untreatable severe side effects. No evidence of metastasis or recurrence was found by PET/CT (**Figure 4A**, **4B**).

## Discussion

GISTs are the most common gastrointestinal mesenchymal tumors, but they are quite rare in gastrointestinal (GI) tumors, which account for 0.1 to 3%. The interstitial cell of Cajal (ICC), an intestinal pacemaker cell, has been recently proposed as the origin of GISTs. They can be present anywhere in the GI tract but most frequently affect the stomach (50%-60%), followed by the small intestine (20%-30%). Only 4-5% involve the duodenum, and they account for less than 5% of all duodenal tumors [15, 16].

The postoperative recurrence of high-risk GIST is very common, even after a long period of remission. For recurrent and/or metastatic GISTs, IM has been recommended as the first line of treatment, and the two-year progression-free survival was 77%, but only 4.5% of patients

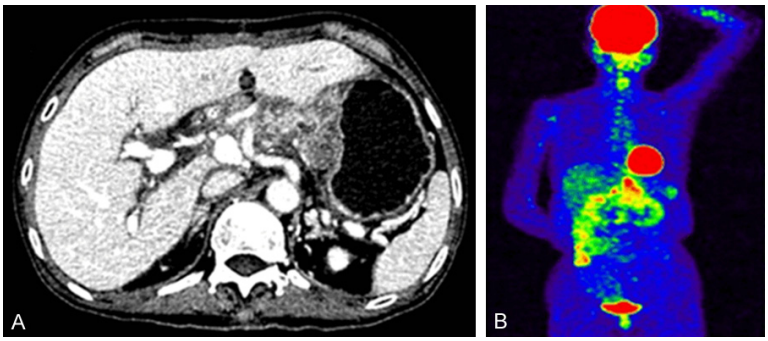


**Figure 4.** (A, B): Postoperative PET/CT showing no sign of intrahepatic or extrahepatic recurrence or metastasis at one year after transplantation.

had tumor shrinkage, as described for the patients in many reports [5]. In recent years, more and more reports revealed that the complete resection of liver metastases combined with IM achieved better survival rates than simple treatment with IM. Chen et al. [17] reported significantly prolonged survival in patients with complete resections of hepatic metastasis, in which five of six patients were alive after a median follow-up period of 53 months. Similarly, DeMatteo et al. [18] reported a series of 56 patients with hepatic metastases of sarcomas, 61% of which were GISTs, who underwent complete resections in half of the cases; they noted that the 5-year survival rate after complete resection was 30% versus 4% in patients who did not undergo resection. So, they recommended that complete resection of hepatic metastases should be considered for metastatic resectable GISTs to the liver. Nowadays the challenge lies in the effective treatments for unresectable metastatic GISTs with liver unresponsive TKIs. Considering the promising results of surgery for metastatic resectable GISTs and the poor efficacy of palliative treatments such as chemotherapy, ablation and TACE, liver transplantation might be a treatment option for unresectable metastatic GISTs [19].

There are limited studies of liver transplantation for metastatic hepatic GISTs in the English medical literature. Husted et al. [10] reported a study of 13 patients with metastatic sarcoma, and they found that patients with post-transplantation had an earlier tumor recurrence and a shorter median survival (only 10.8 Months) in 2006, but only 8 patients with metastatic GISTs who have high risk characteristics are included in their study. Cameron et al. [15, 18] reported 2 patients who underwent liver transplantation with disease-free survivals of 48 and 69 months respectively. Meanwhile, the case described by Bompas et al. [20] presented a 24-month disease-free interval after liver transplantation, and a stable tumor recurrence with IM. The recent report by Frilling et al. [14] was more encouraging, in which a patient with metastatic hepatic EGIST (17 years after primary tumor resection) is symptom-free with 2-cm stable para-rectal metastases in a 10-year follow-up after a living donor liver transplantation.

The report we present here is the first case of an elderly patient with unresectable and recurrent GIST liver metastases originating from duodenum. It is unique not only because of the long remission interval of 13 years, but also because of the difficulties in transplantation caused by former PD and abdominal abscess due to an intestinal fistula. The decision to perform a liver transplantation on this patient by our multidisciplinary group was based on meticulous preoperative evaluations and selection criteria: the definite irresectability and the poor-response to palliative treatments of liver metastases, control of the primary tumor, absence of extrahepatic tumor manifestations, the long remission interval to hepatic metastases, good overall health after supportive treatment, extraordinary compliance and ability for subsequent treatment of immunosuppressive agents and molecularly targeted drugs. Many of the selection criteria were also recommended by Frilling et al. [21]. Strict selection of cases for liver transplantation is crucial for satisfactory postoperative survival. Of all the above-mentioned criteria, a time interval from the primary tumor to the occurrence of liver metastasis greater than 2 years has been identified as the only predictor of survival after a complete resection of a sarcoma, including GIST, metastatic to the liver, which was emphasized by the multivariate analyses of many reports [18, 20]. Thus, Frilling et al. [21] postulated a longer-than-2-year time to liver metastases should be adopted also for transplantation candidates. Considering the shortage of donor organs, a marginally deceased donor was distributed and used for liver transplantation in our case.

In the transplantation we used the technique of mass clamping of the hilum to facilitate the difficult hepatectomy. This technique was first reported by Starzl et al. in 1976 and then recommended by Nikolaos Pararas et al. [22] as an effective procedure in the management of complicated liver transplants. There has been no patient mortality, graft loss, or technical complications attributed to this technique. In our case, there were severe vascular adhesions and scars in the ligamentum hepatoduodenale due to the previous PD and nearby abdominal abscess, which resulted in extreme difficulty and potentially excessive bleeding by classic dissection. We clamped the hepatic hilum structures en mass, then dissected the triad structures after transection. Though the anhepatic phase was longer (89 min), there were no severe coagulopathy, visceral venous stasis or intimal dissection of the hepatic artery attributed to this technique. Mass clamping of the hepatic hilum can be an effective alternative to classic hilum dissection in cases with severe vascular adhesions, scars or varicosity in the hilum.

The high rate of recurrence after surgeries for primary and metastatic GIST implies a systemic disease and the need for perioperative adjuvant therapy. It's difficult to predict metastatic risk due to its variable nature. It is also difficult to determine the exact place and ideal duration of adjuvant TKIs after transplantation. Generally, IM treatment can be initiated as soon as the patients recover from surgeries and should continue for 2 years, especially for high-risk cases [23, 24]. In addition, the molecular test for kinase mutations is important for the selection of adjuvant drugs. The mutations are mostly located on KIT exon 11 (70%), KIT exon 9 (10%), and PDGFR (platelet derived growth factor receptor alpha) exon 18 (5%). KIT N822K gene mutation in exon17 was detected in our case, which many studies found to be responsible for the resistance of IM and sunitinib imalate [25-27]. Regorafenib is a multityrosinekinase inhibitor that has been shown to be active in patients with IM-resistance and KIT N822Kgene mutation in a phase III trial [28]. Our patient has been treated with Stivarga at a dose of 120 mg once daily for two months after transplantation, which was recommended by our multidisciplinary group and tolerated without interruption. Additional attention should be paid to the interaction of these drugs with immunosuppressive agents in the context of post-transplantation, as both drugs are mainly metabolized in the liver by cytochrome P450, which can increase or decrease concentrations reciprocally. Thus, surveillance of liver function tests and concentration measurements of immunosuppressants are more vital and strict for this type of case. Unfortunately, the pharmacokinetic analysis of regorafenib cannot be carried out in our center; we cannot study the interaction of the two drugs in post-transplantation patients.

This case, to the best of our knowledge, represents the first report in the English medical literature describing liver transplantation for unresectable metastatic GIST to the liver with a former pancreaticoduodenectomy. We attribute the success of this case to the well-done perioperative evaluations and the optimization of the patient's general status and a well-planned multidisciplinary approach. This patient we present underwent liver transplantation successfully and survived without recurrence for 12 months, so these data show that liver transplantation can be performed safely with a prolonged survival and a better quality of life, and they also provide new insights into the treatment of metastatic hepatic GIST. However, the impact of liver transplantation on long-term survival remains unclear; more studies are needed to assess the value of liver transplantation for patients with unresectable metastatic GIST of the liver.

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## Disclosure of conflict of interest

None.

## Abbreviations

GISTs, gastrointestinal stromal tumors; PD, pancreaticoduodenectomy; TACE, transarterial

chemoembolization; TKI, tyrosine kinase inhibitor; IM, imatinib mesylate; CT, computer tomography; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; PSA, prostate specific antigen; CA19-9, cancer antigen 19-9; GI, gastrointestinal; ICC, interstitial cell of Cajal.

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