Percutaneous radiofrequency ablation approach through the spleen: initial case report for pancreatic tail gastrinoma

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\textbf{Abstract} Gastrinoma has a low incidence, and the pancreas-originated gastrinoma is rare. Pancreatic gastrinoma patients with liver metastases have poor prognosis and short survival. Local treatment to reduce the tumor burden helps to improve symptoms and slows down tumor progression for patients with unresectable tumors. We report a case of pancreatic tail gastrinoma with unresectable liver metastases. The patient received a comprehensive minimally invasive Interventional treatment, that is, chemoembolization and radiofrequency ablation for liver metastases, and percutaneous transplenic radiofrequency ablation combined with radioactive \textsuperscript{192}I seed implantation for pancreatic tail gastrinoma. The patient was followed up for more than 20 months, and showed no clear evidence of tumor recurrence. We explored the safety and feasibility of percutaneous transplenic radiofrequency ablation for unresectable pancreatic tail gastrinoma. This transplenic approach allow more indications for minimally invasive therapy and provides a new treatment option not only for patients with unresectable pancreatic tail tumor but also for patients refusing surgery.

\textbf{Keywords:} Pancreatic neoplasms, gastrinoma, radiofrequency ablation, percutaneous, transplenic

In 1955, Zollinger and Ellison\textsuperscript{(1)} have firstly reported 2 cases of tumor that characterized by high gastric acid secretion, intractable peptic ulcer, watery diarrhea and gastro-esophageal reflux. This is so-called Zollinger-Ellison syndrome. The active substance was extracted from this tumor by Gregory \textit{et al.}\textsuperscript{(2)} in 1961 and identified as gastrin, then the tumor was named as gastrinoma. Gastrinoma is a rare disease, and is seldom originated from the pancreas. The incidence of gastrinoma is 1/1 000 000–3/1 000 000\textsuperscript{(3)}. No more than 100 cases were reported in China. About 20%–30% of patients with invasive growth of gastrinoma have liver metastasis at initial diagnosis. These patients have poor prognosis and short survival. A set of statistical data show that the prevalence of liver metastasis was 36% in patients with the primary tumor larger than 3 cm in diameter, but only 6% while the primary tumor was less than 3 cm. Liver metastasis is a poor prognostic factor of gastrinoma. Currently, there is no uniform standard treatment for gastrinoma with liver metastasis, which is mostly treated with palliative therapy such as chemotherapy and surgery\textsuperscript{(4-6)}. For the patients with localized liver metastases, resection of the primary tumor and metastasis can improve survival and quality of life (QOL)\textsuperscript{(7)}. For the patients with diffused, unresectable liver metastases, reducing the tumor burden can alleviate clinical symptoms and improve QOL. For liver metastases, liver transplantation combined with surgical resection of the primary tumor, or cold/thermal ablation via open or laparoscopic approach can alleviate symptoms and improve QOL\textsuperscript{(8-9)}. Surgery is an effective treatment approach. But for patients who can not tolerate surgery or deny surgery, a minimally invasive therapy with certain effect of reducing the tumor burden can help to alleviate symptoms and inhibit tumor progression. With the advantages of less trauma and pain, rapid recovery, curative effect and repeatability, the image-guided minimally invasive interventional treatment can accurately target tumor, destroy it and improve QOL of the patient.

Here, we reported a case of pancreatic tail gastrinoma with unresectable liver metastases. This patient with the primary tumor larger than 3 cm in diameter refused surgery, received a comprehensive minimally invasive therapy,
including transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) for liver metastases; percutaneous transplenic RFA combined with radioactive $^{125}$I seed implantation for pancreatic tail gastrinoma. Primary tumors and metastases got satisfactory control, and clinical symptoms disappeared. There was no clear evidence of tumor recurrence during the 20-month follow-up. We explored the safety and feasibility of percutaneous transplenic RFA for pancreatic tail gastrinoma with unresectable liver metastases. This therapy is a new treatment option not only for patients with unresectable pancreatic tail tumor but also for patients refusing surgery.

Materials and Methods

A 64-year-old man was admitted to hospital for recurrent abdominal pain and diarrhea for 3 years, and bloody stools for 12 days. Without obvious incentives, the patient had repeated abdominal pain and yellow watery diarrhea, more than 10 times daily since October 2005. He also complained of sour regurgitation and belching. He was diagnosed as peptic ulcer in another hospital, and the symptoms were alleviated after the acid suppression, fluid infusion, support and symptomatic treatment. However, he began to have dark red bloody stools, with dizziness, fatigue, and palpitations since September 2008, then admitted into the Sun Yat-sen University Cancer Center for further treatment. He had duodenal ulcer for more than 10 years, but no hepatitis and cirrhosis history. He received an intestinal repair surgery in April 2008 due to jejunal perforation. Physical examination revealed no positive signs and Eastern Cooperative Oncology Group (ECOG) physical performance status score was ECOG 1 at the time of hospital admission. Routine blood and biochemistry tests were normal. Gastroscopy showed cardia ulcers and multiple ulcers between the descending duodenum and the upper jejunum. Abdominal MRI scans showed a 4 cm $\times$ 3 cm mass in the tail of pancreas, with heterogeneous moderate enhancement slightly higher than that of normal pancreas after contrast scan, and many diffused liver metastases of multiple sizes (Figure 1A). PET/CT scan also confirmed the lesions (Figure 1B). The largest liver metastasis was about 5.4 cm $\times$ 3.7 cm. The level of fasting serum gastrin (FSG) was 1250 pg/mL. CT-guided liver tumor aspiration biopsy showed that the tumor cells were consistent in size, in adenoid arrangement, and no significant atypia. Immunohistochemical staining showed Gas(+), Syn(+), CD56(+), CK20(+), CK19(+), CK7(+), CEA (-), and CDX2 (-). Pathologic results and clinical symptoms indicated endocrine tumors. The patient was diagnosed with malignant pancreatic tail gastrinoma and multiple liver

Figure 1 Images of the pancreatic tail mass
A, the contrast magnetic resonance images (MRI) shows enhanced signals of a newly diagnosed pancreatic tail mass (arrowhead) with multiple synchronous liver metastases (arrows). B, PET/CT images also show a pancreatic tail tumor (arrowhead) and multiple liver metastases (arrows).
metastases by the multidisciplinary expert panel.

The patient was treated with symptomatic treatment, including proton pump inhibitors and somatostatin, and biological treatment of interferon after admission. Considering that the removal of the tumor burden, including primary and metastatic lesions, can control the gastric acid hypersecretion and eradicate clinical symptoms, we treated multiple liver metastases first to postpone the fatal liver dysfunction caused by the progression of liver tumors. At present, no effect of systemic chemotherapy on gastrinoma with liver metastases is reported, and diffused liver metastases are not suitable for surgery. On MRI, the arterial phase enhancement of liver metastases of this patient indicated sufficient blood supply, suggesting TACE is feasible. The patient received two courses of TACE (Figure 2) with epirubicin, mitomycin, carboplatin, 5-fluorouracil plus lipiodol. Sequential CT-guided RFA on liver tumor was performed 2 times at 3 weeks after TACE. The liver lesions were well controlled with complete inactivation evaluated by CT scan.

Figure 2  CT images show a pancreatic tail mass of 4 cm × 3 cm in size. Contrast CT scan shows heterogeneous enhancement (arrowhead) slightly higher than that of normal pancreas. CT scan also shows multiple liver metastases with irregular lipiodol deposition in the liver after transarterial chemoembolization (arrows)

Then, we selected strategies to treat the primary tumor in the pancreatic tail. Surgical resection of the primary tumor can reduce tumor burden, improve survival and QOL according to the literature, but this patient strongly refused to accept surgery. Therefore, percutaneous transplenic RFA was performed for the primary tumor of pancreatic tail. The

Figure 3  CT-guided transplenic radiofrequency ablation with a cool monopolar loop electrode was carried out to treat the pancreas tail gastrinoma
procedure (Figure 3) is briefly described as follows:

(1) Patient laid in the 60° right oblique position, to fully expose the tumor.

(2) CT scans were performed to determine the level, angle, direction, and depth of the path of the puncture needle.

(3) A water-cooled cycle unipolar RFA electrode needle was punctured to the subcutaneous layer under local anesthesia.

(4) CT scans were performed to reconfirm the level, angle, direction, and depth of the puncture needle. The patient was asked to control breathing. The RFA electrode needle was punctured through the lateral capsule of the spleen to splenic parenchymato avoiding the hilum splenicum.

(5) CT scans were performed to reconfirm the level, angle, direction, and depth of the puncture needle. The RFA electrode needle was punctured through the inboard capsule of spleen to the primary tumor of pancreatic tail. Ablation was performed according to plan by pulsed current to ensure uniform ablation of the temperature rise to 70°C up to 90°C. Ablation time of the individual sites was strictly controlled to ensure complete ablation of tumor, whereas avoiding damage surrounding tissue and resulting stomach and intestinal organ perforation.

(6) At the end of the procedure, the electrode was removed while coagulating the tract preventing tract bleeding.

(7) After 10 days, the radioactive \(^{125}\)I seeds were implanted into the residual lesion area close to the bowel by the same approach.

Results

After the comprehensive minimally invasive therapy, clinical symptoms of the patient disappeared, the level of serum gastrin fell to normal, the primary tumor and metastasis shrank. The patient was followed for more than 20 months, on contrast CT scans no abnormal enhanced lesions were observed in the liver, the pancreatic tail mass showed a low density inactive area with some metal particles of radioactive \(^{125}\)I on the edge (Figure 4).

No serious adverse event occurred during the minimally invasive procedures. Transaminase elevation and grade 1 leukocyte decrease occurred after TACE and RFA for liver metastasis. No complications occurred after RFA and the radioactive \(^{125}\)I seed implantation procedure for primary pancreatic tumor. The patient could get out of bed in the afternoon of RFA procedure and was discharged next day.

Gastrinoma can secrete large quantities of gastrin, stimulate parietal cell hyperplasia and gastric acid secretion, and, in turn, causes refractory ulcers. Therefore, peptic ulcer, stomachache, diarrhea are the most common complaints of these patients. The symptoms of this patient are similar to those of common peptic ulcer disease. Distinguishing and early diagnosing the two diseases by symptoms were difficult. Thus, the patient was misdiagnosed to have peptic ulcer in another hospital. About 60%–70% of gastrinomas locate within the so-called gastrinoma triangle (the confluence of the cystic and common bile ducts as the superior intersection, the junction of the second and third portions of the duodenum as the inferior intersection, and the junction of the neck and body

Discussion

Gastrinoma can secrete large quantities of gastrin,
of the pancreas as medial intersection), 21%–65% locate in the pancreas, and 6%–32% in the duodenum. Gastrinoma was divided into sporadic type and multiple endocrine neoplasia type (MENI type), accounting for 75% and 25% [7,8] respectively. The patients with gastrinoma of MENI type usually have a clear family history, with the tumors grow slowly, and are often small, multiple, distributed in the duodenum and other parts of the digestive system, and may be combined multiple endocrine gland diseases, including lesions of the parathyroid, pituitary, pancreatic islets, and adrenal cortex [9]. Pancreatic gastrinoma usually grow slowly, but some may invade surrounding sites rapidly. Liver metastasis is a poor prognosis factor. Furukawa et al. [10] have found that insulin-like growth factor I (IGF-I) and IGF-I receptor (IGF-IR) were expressed in almost all gastrinomas, and that IGF-II/IGF-IR overexpression was significantly correlated with tumor growth, invasion, and metastasis. Loss of heterozygosity (LOH) in chromosome 1, including 1q31–32 LOH and 1q21–23 LOH, in sporadic gastrinoma may be correlated with aggressive tumor growth and liver metastases [10]. Our patient was diagnosed with malignant pancreatic tail gastrinoma with multiple liver metastasizes. The diagnosis of gastrinoma includes qualitative diagnosis and localization diagnosis. Qualitative diagnosis relies on the biochemical detection. Gastrinoma can be unequivocally diagnosed if FSG is greater than 1000 pg/mL. When FSG is 100–1000 pg/mL, diagnosis depends on a secretin provocative test. Localization diagnosis depends on ultrasound, CT scans, endoscopic ultrasonography, selective digital subtraction angiography, somatostatin receptor scintigraphy, intra-arterial injection of pancreatic endocrine tests, and so on. This patient was diagnosed by FSG detection and radiographic localization, thus ensuring timely treatment. Although the tumor in the pancreatic tail is concealed, MRI and CT can help to localize the disease.

The clinical therapy for gastrinoma aims to inhibit the secretion of gastric acid and alleviate clinical symptoms. Internal medication, including histamine H receptor antagonists, proton pump inhibitors, somatostatin derivatives, can control gastric acid hypersecretion and has an anti-tumor effect, but can not achieve radical cure effect [11]. Surgery resection of primary and metastatic lesions helps to improve survival rates and reduce tumor metastasis [14]. Surgery has certain effect on advanced pancreatic tumor without distant metastasis. For the patients with localized liver metastases, resection of the primary tumor can improve survival and QOL [7]. For those with diffused, unresectable liver metastases, currently, no standard treatment is available. Local treatment on primary lesions can improve clinical symptoms [4–9]. Such patients can benefit from ablation treatment [4, 7, 8]. However, due to the special anatomical location of the pancreas, especially the tail of the pancreas lies in the splenoportal ligament and enters the hilum of the spleen, which is covered by the gastroduodenal ligament, transverse colon and its mesentery, there is no safe puncture path. Transabdominal puncture can easily damage the splenic vessel on the edge of the pancreas. On the other hand, when the RFA electrode needle is punctured through the stomach or intestines and other organs, the risk of gastrointestinal perforation and infection increases. Therefore, reported RFA or cryoablation of pancreatic tumor was mainly intraoperative ablation including ablation via laparotomy and laparoscopic ablation [7, 8, 16]. Currently, image-guided percutaneous transplenic RFA for pancreatic tumor has not been reported yet.

Our department is one of the earliest research departments which carried out RFA in China. We have accumulated more than 10 years experience of image-guided percutaneous ablation. RFA works by transmitting a high-frequency electrical current through an electrode placed directly into the target ablation region to raise the temperature of the ablation region quickly to 70°C –90°C, thus RFA can kill tumor cells thoroughly. There are mainly three different ways that a RFA procedure may be performed: RFA via laparotomy, laparoscopic RFA, and image-guided percutaneous RFA. Currently, RFA is the most mature technique to treat liver tumor, and has been used to treat the tumors of many other regions or organs including the lungs, bone, adrenal, kidney, and retroperitoneum [17]. However, due to the special anatomical location of the pancreas, currently, RFA via laparotomy is mainly used to treat pancreatic tumors. We first reported a case with pancreatic tail gastrinoma treated with percutaneous transplenic RFA without the complications of bleeding and pancreatic leakage.

Our experience indicate that the following points deserve special attention: (1) According to previously reported experience of RFA via laparotomy for pancreatic tail tumor, advanced pancreatic tail tumor destroys the exocrine and endocrine glands, resulting in the corresponding main pancreatic duct occlusion [18]. Therefore, using RFA to treat pancreatic tail tumor reduces the occurrence of pancreatic leakage and pathoglycemia. (2) Interventional radiologists with skilled puncture technology should have extensive experience of percutaneous transplenic biopsy and splenic embolization. (3) The position of patients and the angle, direction, and depth of the puncture needle should be accurately planned according to the size and shape of tumor. Route design of ablation should ensure radiofrequency energy being applied in the tumor, while avoiding damage surrounding vital organs. (4) Mastering electrode ablation apparatus and the physical properties helps to control the ablation area precisely. During the RFA procedure, CT scans can be used to monitor the ablation scope and avoid complications. (5) The
clinicians should be familiar with the anatomy and imaging of the pancreas and surrounding organs, and follow the principles of “from shallow into the deep” to prevent tumor implantation. Three-dimensional imaging helps to ensure overlapping ablation without blind zone. (6) Let patient awakening and breathing controlled, the RFA electrode needle should be gradually punctured to avoid damage to the hilum splenicum and other important organs. (7) To avoid complications such as intestinal perforation, pancreatic leakage, and splenic vessels damage, the radioactive $^{125}$I seeds were implanted into the residual lesions after percutaneous transsplenic RFA can inactivate most tumor tissues. (8) After the treatment, the electrodes should be retracted slowly to ablate the needle track, thus preventing tract bleeding. (9) Preoperative preparation includes blood transfusion preparation. If severe intraoperative bleeding occurs, digital subtraction angiography-guided embolization of the branches of splenic artery should be performed.

Because the patient who was diagnosed with pancreatic tail gastrinoma and unresectable multiple liver metastases refused surgery for the primary tumor, we treated him with comprehensive minimally invasive therapy. The comprehensive treatment improved the QOL and got nearly radical cure effect. The minimally invasive therapy in this case is the key to successful treatment. With the advantages of accurate localization, less trauma and pain, rapid recovery, exact efficacy and repeatability, the image-guided minimally invasive therapy avoid surgical trauma-induced immune injury. Thus, it is consistent to the modern medical pattern of Biology-Social-Psychology. With the continuous development of high technologies and constant renewal of the concept of social medicine, the concept that minimally invasive therapy should gradually replace the treatment with great damage to physiological and immune function will be widely accepted. In addition, our experience shows that percutaneous transsplenic RFA, apart from surgery or RFA via laparotomy, is worthy of further accumulating experience, especially for patients with unresectable pancreatic tail tumor or refusing surgery.

Minimally invasive therapy has been gradually explored and used in the palliative treatment of advanced cancers. Although the special anatomic location of the pancreatic tumor causes great difficulties to RFA procedure, percutaneous transsplenic RFA is feasible with careful preoperative assessment and preparation.

References