INTRODUCTION

Although pancreatic neuroendocrine tumors (PanNETs) are rare neoplasms, the incidence and prevalence of PanNET are steadily rising according to the Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2012. PanNET represents heterogeneous biological behavior, most of which the clinical behavior shows indolent feature, however, some PanNETs show rapid progression with poor prognosis. Therefore, the 10-year survival rate of patients with PanNET is only 40%. According to the World Health Organization (WHO) 2010 grading classification, PanNETs are divided into three groups by the proliferative fraction of neoplastic cells, such as low grade (G1), intermediate grade (G2), and high grade (G3). There are other prognostic factors of PanNETs including tumor size, the presence and the site of metastasis, the degree of tumor differentiation, and spontaneous tumor growth rapidly. However, the prognostic factors of PanNET are still debatable because their rarity and heterogeneity of biologic and clinical features. Recently, whole genome sequencing revealed some mutational signatures in PanNETs, and these genetic alterations may predict the prognosis of PanNETs.

GENETIC ALTERATIONS IN PANNETS AND ITS CLINICAL APPLICATION AS A BIOMARKER

PanNET usually appears sporadically, but it can appear as part of three hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome (VHL), and tuberous sclerosis complex (TSC). Therefore, genetic mutations may have roles in the development of PanNETs. Recent large-scale expression profiling and whole exome sequencing discovered several frequently mutated genes, including DAXX (death-domain associated protein, the apoptotic regulator), ATRX (a thalassemia/mental retardation syndrome X-linked, the chromatin modifier), MEN1 (tumor suppressor gene), mTOR (mammalian target of rapamycin) pathway genes, and some germline mutations (MUTYH, CHEK2 and BRCA2).

Jiao et al. reported that 43% of PanNETs harbored inactivating DAXX (25%) or ATRX (18%) mutation. This whole-exome sequence data was a cornerstone in understanding the molecular pathogenesis of well-differentiated PanNETs. These are tightly associated with alternative lengthening of telomeres (ALT, a telomerase-independent mechanism) and chromosomal instability (CIN). CIN also significantly correlated with DAXX or ATRX loss and ALT activation. The presence of DAXX and ATRX mutations is mutually exclusive. Recent studies have suggested that ATRX loss and/or ALT positivity confer in vitro sensitivity to inhibition of the DNA damage mediator, ATR, as well as topoisomerase inhibitors and radiation. According to previous studies involving the majority of Caucasians, ALT was identified in a substantial fraction of PanNETs (48%–61%), unlike this a lower prevalence (15%) was observed in a small Korean cohort, and ALT prevalence may vary by ethnic.

At first, DAXX/ATRX mutations were reported to be associated with better prognosis. Dogeas et al. also reported that ALT activation which is associated with DAXX/ATRX mutation is correlated with improved prognosis in patients with liver metastases of PanNETs. Conversely, Marinoni et al. reported that the loss of DAXX/ATRX are related with CIN and poor survival of patients with PanNETs. Singhi et al. also reported that ALT and DAXX/ATRX loss in PanNETs was associated with shorter disease-free survival and disease-specific survival and likely plays a significant role in driving metastatic disease. The discrepancy between these studies can be explained by different study populations. Patients of the first two studies were metastatic and mostly higher primary tumor stage of PanNETs. In contrast, most of the patients in the latter studies were lower primary tumor stage and nonmetastatic PanNETs. Then, in a large Korean cohort study, ALT activation and loss of ATRX or DAXX expression developed at a relatively late stage of tumor progression, and ALT-positive primary PanNETs displayed aggressive clinicopathologic behavior with poor recurrence-free survival, whereas, ALT activation in patients with metastases was associated with better survival. Recently, another Korean cohort study of PanNETs revealed that negative ATRX/DAXX protein expression was the independent prognostic factor for longer OS and showed significantly longer survival after the recurrence. Therefore, these biomarkers may be used as prognostic markers depending on the context of the disease.
Comprehensive molecular analysis of 102 clinically sporadic PanNETs was conducted recently to define molecular pathology and to identify several novel candidate mechanisms that activate mTOR signaling, including novel gene fusion events. They found five mutational signatures, of which germline MUTYH inactivation was not previously reported and found other unreported germline mutations including CHEK2 and BRCA2. A total of 3,097 somatic mutations were detected in 2,567 genes and MEN1, DAXX, and ATRX were found frequently. Inactivating mutations in negative regulators of mTOR signaling (PTEN and DEPDC5, mTOR pathway genes; TSC1 and TSC2, negative regulators of mTOR signaling) were also present in 12% of their patients. They presented four core pathways of somatic mutations in PanNETs: DNA damage repair, chromatin modification, activation of mTOR signaling, and altered lengthening of telomere. The mutations of mTOR signaling were associated with a poor prognosis in the G2 PanNETs. Previously undescribed three mTOR pathway activation mechanisms including DEPDC5 (encoding a subunit of the GATOR1 complex, a suppressor of mTOR signaling), EWSR fusion genes (previously undescribed EWSR1-BEND2 fusion and EWSR1 exon 7-FLI1 exon 6 fusion genes), and amplification of the PSPN (RET receptor ligand) were also discovered by whole-genome sequencing of PanNETs.2

Pancreatic neuroendocrine carcinomas (PanNECs) are usually more aggressive, however, their clinicopathologic and genetic features are largely unknown. Yachida et al. reported that 57% of the cases had inactivating mutations of the TP53 gene and 71% had inactivating mutations of the RB1 gene in 19 cases of PanNECs.9 The targeted sequencing data for 593 cases of small cell lung cancer (SCLC) and 274 GEP-NECs reported by Bergsland et al. included 123 cases of PanNECs.10 Mutations in TP53 (18%) and RB1 (10%) are less common in PanNECs than in SCLC, colon NEC and other types of gastrointestinal NECs, whereas mutations in MEN1 (33%) and DAXX (20%) are more common in PanNECs.10 These results are consistent with a previous study that presented higher inactivating mutation rate of DAXX/ATRX and MEN1 in advanced PanNETs.5 In addition, the proportion of K-ras mutation was lower in PanNEC (7%) than PDAC, which means genetically different entities each other.

CONCLUSIONS

Based on the recently published genome analysis, we improved our understanding for PanNETs. DAXX/ATRX and MEN1 mutations may be promising biomarkers predicting the prognosis of PanNETs. Understanding of the molecular mechanisms leading to the development of PanNETs can be invaluable for a more personalized treatment approach. The mutations in PanNETs may provide a way to prioritize patients for molecular targeted therapy including mTOR inhibitors. Future studies in genetic alterations of PanNETs may give us insights to discover strong prognostic markers for survival and therapeutic response and will provide a breakthrough in conquering diseases with high mortality such as PanNECs.

REFERENCES


A case of gastric neuroendocrine tumor with multiple hepatic metastases

**CASE DESCRIPTION**

A 35-year-old man was admitted to a local hospital for intermittent right upper quadrant pain. He had no history of underlying disease. Abdominal computed tomography (CT) revealed three arterial enhancing and delayed wash-out lesions in hepatic S5 (2.8 cm) and hepatic S6 (6.0 cm, 3.0 cm) (Figure 1). Hepatic adenoma was suspected and the S5 lesion was removed. The frozen section was diagnosed as neuroendocrine carcinoma. The patient was referred to our hospital for further surgery.

At admission, his vital signs were stable and routine laboratory tests were normal. However, NSE (neuron specific enolase) was elevated (32.76 ng/mL, normal range 0–16.3 ng/mL). Upper endoscopy was performed and a 2 cm sized, dumbbell shaped subepithelial tumor was found in the greater curvature of the proximal antrum (Figure 2). Endoscopic biopsy revealed a large cell neuroendocrine carcinoma. PET-CT showed no metastases other than the liver metastasis (Figure 3). The final diagnosis was gastric neuroendocrine carcinoma with multiple hepatic metastases.

For the purpose of neoadjuvant chemotherapy, octreotide (30 mg, intramuscularly) was started at monthly intervals on an outpatient basis. After three cycles of octreotide treatment, the size of the largest tumor decreased slightly from 6.0 cm to 5.5 cm by follow-up CT. An additional three cycles of octreotide were administered. However, no change in tumor size was observed by follow-up abdominal CT (Figure 4). Surgery was decided and the gastric lesion was removed by wedge resection, and the S5 and S6 lesions by segmentectomy. Follow-up CT findings at one month after surgery revealed a new focal attenuated lesion in the hepatic S4 surface (1.5 cm) (Figure 5), which was subsequently treated by radiofrequency ablation (RFA).

Thereafter, the patient was administered octreotide 4 weekly at our outpatient clinic, and underwent abdominal and chest CT every three months. Fortunately, at one year after RFA treatment and on-going treatment at the outpatient clinic, no recurrence was encountered.

**DISCUSSION**

Gastric neuroendocrine tumor (GNET) is classified into three types. Type 1 GNET is related to chronic atrophic gastritis and type 2 GNET to Zollinger-Ellison syndrome or multiple endocrine neoplasia. Both type 1 and type 2 GNET have multiple gastric lesions and are associated with hypergastrinemia. Metastasis from type 1 GNET is rare and from type 2 GNET has been reported to be 10-30%. On the other hand, type 3 GNET is not related to any associated disease, has a normal gastrin level, and presents a solitary lesion. Notably, type 3 GNET has a poor prognosis because of its high metastatic potential (>50%). The described case was classified as type 3 GNET because this was only one primary lesion, no associated disease, and multiple hepatic metastasis. Little evidence-based data is available regarding the optimal management of patients with hepatic metastasis from a neuroendocrine tumor. In one study of 172 patients, hepatic resection of metastatic neuroendocrine tumors achieved long-term survival in some patients (a 10-y ear overall survival rate of 50.4%), and a recent meta-analysis reported a 5-y ear overall survival rate of 41% to 100% in patients with neuroendocrine tumors that underwent hepatic resection. However, most patients with resected metastatic disease will eventually experience recurrence. If metastatic lesions are resected, future treatment with octreotide or lanreotide may be anticipated. Residual disease may be effectively controlled postoperatively with long-acting somatostatin analogues, which inhibit tumor growth and tumor progression. In addition, the somatostatin analogue octreotide is an important adjunct for regulating carcinoid syndrome and preventing perioperative carcinoid crisis. For patients with clearly unresectable disease, transarterial chemo (radio) embolization may be considered with the primary palliative goal of reducing hormonal symptoms or delaying liver failure. In summary, in the described case of type III GNET with multiple hepatic metastases, successful curative treatment was achieved by aggressive surgery and RFA. Long-term octreotide treatment is needed to prevent recurrence for this patient.


A 35-year-old female, who began to suffer repeated palpitation, tremor, and sweating 1 year ago, was sent to a local hospital because of aggravated symptoms and unconsciousness. Blood test showed glucose of 1.4 mmol/L and insulin greater than 300 μU/mL. The patient was transferred to our hospital due to refractory hypoglycemia. The laboratory findings on admission were as follows: blood glucose was 2.4 mmol/L, serum CgA was 45.38 ng/ml, and serum NSE was 35.11 ng/mL. 18F-FDG PET/CT and 68Ga-DOTA-somatostatin analog-PET/CT showed a mass in the head of pancreas, enlarged peripheral lymph nodes, and multiple lesions in liver, which showed high uptake of FDG and positive somatostatin receptor imaging findings. Biopsy on hepatic metastasis confirmed that they were grade II neuroendocrine tumors with a ki-67 proliferation index of 15% and positive staining for Insulin, CgA, Syn, MGMT and SSTR2. The diagnosis was malignant insulinoma with metastasis in peripheral lymph nodes and liver (G2, T1N1M1, stage IV).

Diazoxide (100 mg q12h) was applied to control glycaemia. Then six cycles of chemotherapy with temozolomide/capecitabine (Captem) regimen (capecitabine 1 g bid, D1-D14; temozolomide 300 mg qd, D10-D14, q4w) was conducted, during which three cycles of transarterial embolization (TAE) procedures were performed. Blood glucose level and serum insulin level were successfully controlled in the normal range during the first stage of treatment. CT scan was performed 1 month after every TAE procedure and showed constant shrinkage of tumor size and decrease in tumor quantity and density in liver. In the second stage of treatment, octreotide LAR (30 mg IM, q4w) was applied for maintenance therapy, accompanied with Diazoxide (100 mg q12h). Blood glucose level and serum insulin level were under control all the time. However, new metastatic lesions were found in liver by CT scan after 2 cycles of octreotide LAR treatment.

Taking tumor progression into account, chemotherapy with Captem regimen was reused, combined with Diazoxide and 1 cycle of TAE procedure in the third stage of treatment. After 2 cycles of chemotherapy, primary tumor and hepatic metastases were found stable by CT scan, but the patient suffered intermittent hypoglycemia again. Lowest blood glucose level reached 2.2 mmol/L.

Everolimus was used instead of Captem and Diazoxide in the fourth stage of treatment, with the dose of 5 mg/d in the beginning. The dosage was adjusted to 7.5 mg/d 7 days later and increased to 10 mg/d after another 7 days. Meanwhile, 1 cycle of TAE procedure was performed. CT scan revealed that the lesions both in liver and pancreas were stable after 3 months. Blood glucose level and serum insulin level were in the normal range. However, stomatitis and skin rash occurred 2 weeks after everolimus was administered. The patient’s condition is still being followed up until present.
Insulinomas, which derive from insulin-secreting pancreatic beta cells, are the most common functional neuroendocrine tumors (NETs) originating in pancreas, accounting for 93.1% of functional p-NETs in South China. About 90% cases of insulinomas are benign, while others present malignant characteristics, such as local invasion into the surrounding soft tissue, lymph nodes or liver metastasis. Clinical manifestations resulting from hypoglycemia caused by high secretion of insulin include palpitation, tremor, sweating, etc. and unconsciousness in some severe cases. The key treatments for patients with insulinoma are controlling hypoglycemia and suppressing tumor growth.

Diazoxide, a benzothiadiazine derivative, is regarded as first-line treatment for glycemic control in patients with insulinoma. By opening ATP-dependent potassium channels in pancreatic beta cells to inhibit insulin secretion and potentially increasing hepatic glucose production and inhibiting glucose uptake, Diazoxide is able to increase blood glucose level effectively. In this case, Diazoxide was applied to control the symptoms of hypoglycemia from beginning, until everolimus was used. An effective result of glycemic control was achieved. Blood glucose level of the patient was controlled in normal range for 8 months.

Somatostatin analogs (octreotide, lanreotide) are known for their ability to exert both anti-prliferative and symptom-controlling effect by activation of somatostatin receptors (SSTR), and are thus commonly used in treatments for neuroendocrine tumors. The hyperglycemic effect of somatostatin analogs relies mainly on activation of the SSTR2. However, in the cases that SSTR2 is low expressed or not expressed at all in insulinoma, more severe hypoglycemia could be paradoxically caused by somatostatin analogs due to inhibition of glucagon secretion. Therefore, somatostatin analogs should be applied with caution in treating patients with insulinoma.

Everolimus, a mTOR-targeted drug, suppresses tumor proliferation by inhibiting mTOR, which is a component of signaling pathways regulating cell survival and growth, as well as angiogenesis. Two randomized clinical studies showed that everolimus was effective in the treatment of advanced pancreatic NET. Stomatitis, rash, diarrhea and fatigue were commonly observed as adverse effects of everolimus, but most adverse events were grade 1 or 2. Another observed side effect in clinical studies of everolimus was hyperglycemia, which can be taken advantage of to increase blood glucose level in treatment of insulinoma.

For malignant insulinomas with liver metastasis, metastatic lesions in liver comprise the main tumor burden in most cases, and most metastatic NETs are highly vascular, deriving their blood supply mainly from the hepatic arterial circulation. It is necessary to reduce tumor burden in liver through interventional therapies so as to control refractory neuroendocrine symptoms. Interventional therapies, including liver-directed embolotherapies and thermal ablation, have demonstrated efficacy for tumor burden reduction and symptom relief. Although thermal ablation can destroy hepatic lesions completely, the majority of patients with metastatic NETs, who have diffused liver metastasis, are not suitable for ablation therapy which requires single or few lesions with diameters no more than 3 cm. Therefore, trans-arterial chemoembolization (TACE) and trans-arterial embolization (TAE) are commonly chosen as regional therapy for liver metastasis of NETs. As no significant superiority of TACE over TAE was observed in treatment efficacy and chemotherapeutics might cause additional toxicities, TAE is regarded as an appropriate approach for tumor burden reduction. In our experience, it is important to perform super-selective embolization. The catheter should be super-selectively guided to second arterial branches or further to inject embolization agents. Solid embolization agents such as microspheres, PVA and gelfoam particles, instead of lipiodol, should be used in TAE procedures for more complete embolization effect.

Two to four cycles of TAE should be performed to ensure ischemia inside tumors, leading to tumor necrosis to a maximal extent, thus achieving a relatively long-term control of tumor growth and neuroendocrine symptoms in the presence of combined systemic therapies.
FIGURE 1
A. $^{68}$Ga-DO TA-somatostatin analog-PET/CT showed the primary tumor in the head of pancreas (red arrow) and metastases in liver (yellow arrow).
B. $^{18}$F-FDG PET/CT showed the primary tumor in the head of pancreas (red arrow) and metastases in liver (yellow arrow).

FIGURE 2
A. CT scan for hepatic metastases (arrow) on admission.
B. CT scan for hepatic metastases after 3 cycles of TAE.

FIGURE 3
Skin rash after administration of everolimus

FIGURE 4
A. Digital subtraction angiography (DSA) showed metastatic lesions and arterial branches in liver before embolization.
B. Angiography after embolization by 40-120 μm microspheres and 100-300 μm PVA.
<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
</table>
A case of vasoactive intestinal polypeptide tumor (VIPoma)

Authors
Heli Gao, Kaizhou Jin, Xianjun Yu

E-mail
yuxianjun@fudanpci.org

Institute
Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, P.R. China; Shanghai Pancreatic Cancer Institute; Pancreatic Cancer Institute, Fudan University

City/Nationality
Shanghai, China

Category
Case

CASE DESCRIPTION

A 30-year-old man was admitted to this hospital in October 2016 because of a six-month history of diarrhea and fatigue. The patient had been in his usual state of health until 6 months before admission to this hospital, when he developed watery diarrhea with frequency of more than 10 times per day, with no abdominal pain, blood or mucus, nausea or vomiting. He also noted fatigue and weight loss of 5 kg. He had no family history of cancer. Two months later, the patient was admitted to a local hospital. He was treated with Berberine and levofloxacin, but symptoms were not relieved.

Six months later, the patient was admitted to our hospital. The laboratory test results were as follows: the serum potassium was 2.1 mmol/L (normal range 3.5-5.5 mmol/L), serum calcium was 3.17 mmol/L (normal range 2.11-2.62 mmol/L), serum sodium 130 mmol/L (normal range 137-147 mmol/L). Serum chloride and phosphorus was normal and urinary potassium and calcium were normal, and serum calcitonin was 0.948 pmol/L (normal range 1.575-6.825 pmol/L). Serum alkaline phosphatase, glucose, amylase, lipase, total protein, and albumin were normal. Tumor markers of serum CEA was 10.2 ng/mL (normal range 0-52 ng/mL), serum CA125 was 48.62 U/mL (normal range 0-35 U/mL), CA199, AFP, NSE, and ProGRP were in the normal range. Such as thyroid hormones, growth hormone, ACTH, serum cortisol, serum metanephrine and methoxy norepinephrine were all in the normal range. Abdominal CT scanning revealed abnormal thickness in the intestinal wall of duodenal decreased segment, and the structure of head of pancreas was unclear. There were multiple low-density lesions in the liver. Findings suggested of duodenal carcinoma invading the head of pancreas with liver metastasis (Figure 1). Somatostatin receptor scintigraphy showed abnormal radioactive uptake of the intestinal wall of duodenal descending segment, head of pancreas and multiple intra-hepatic lesions, which are both considered high expression of somatostatin receptor (Figure 2). The histopathology of the liver biopsy confirmed the diagnosis of neuroendocrine tumor, positive staining for CK, Syn and VIP.

The patient was treated with short-acting octreotide and potassium supplement, after which the symptom of diarrhea was significantly relieved, and serum potassium was maintained in range of 3.5-5.5 mmol/L. On November 11, 2016, the patient underwent pancreaticoduodenectomy plus hepatic multiple nodular resection and intraoperative radiofrequency ablation. The pathological section of pancreatic duodenum and liver was performed. The primary tumor was neuroendocrine tumor, 5×3 cm, located in the head of pancreas and invaded in the duodenum, with no vessel and nerve invasion. Lymph node metastasis was 2/18. Immunohistochemistry (IHC) showed positive staining for CgA, Syn and SSTR2, and VIP positive, Ki-67 proliferation index was 3%. Then the diagnosis of this patient was confirmed as neuroendocrine tumor (VIPoma) with lymph node and liver metastasis (G2, T3N1M1, stage IV).

The serum potassium was back to normal after the operation, and the patient no longer had diarrhea or fatigue. Long-acting octreotide was then injected every 4 weeks for 6 months, and a follow-up one year post operation showed normal serum potassium and stable disease in liver metastasis on abdominal MRI (Figure 3). The patient was symptom free. After six cycles of long-acting octreotide, the patient refused to receive further treatment because of financial issue. The patient was still under positive follow-up.
VIPoma (vasoactive intestinal peptide tumor), also known as Vemer-Morrisson syndrome, is a rare neuroendocrine neoplasm with the incidence rate of one per 10,000,000 per year. Its clinical feature is diarrhea-based disease, caused by the secretion of vasoactive intestinal peptide (VIP). VIP is a vasodilator; the biological activity of VIP is activating VIP receptor of intestinal epithelial cells, promoting intestinal C-AMP synthesis, causing intestinal secretion of water and electrolytes, and bile secretion. 80%-90% of VIPoma occurs in the pancreas, especially the tail of the pancreas, so it is also known as “pancreatic cholera”. 1/3 to 1/2 of VIPoma is malignant, and liver is the major metastasis organ. 

The clinical manifestations of VIPoma are as follows: ① prolonged watery diarrhea, with fasting stool volume > 750-1,000 mL/day. The diarrhea is not septic, the onset is slowly and gradually increased for a duration of up to several years, and diarrhea begins as episodes and then gradually becomes persistent to more than 10 times per day. Severe diarrhea can lead to dehydration and uncontrollable electrolyte imbalance and acidosis; ② hypokalemia due to severe diarrhea, VIPoma can lead to potassium loss from the stool (150~500 mmol/L). ③ No or low stomach acid: VIP can inhibit gastric acid secretion. Other syndromes include muscle weakness, nausea, vomiting and achlorhydria. The lab test of VIPoma includes blood chemistry tests (electrolyte and comprehensive metabolic panel), stool examination for the cause of diarrhea, and electrolyte and VIP levels in the blood. CT or MRI scan and somatostatin receptor scintigraphy are used to localize the tumor site, which is usually metastatic at diagnosis. In this case, we failed to test the VIP level in blood because of the examination limitation. However, the patient’s signs and symptoms made the clinical team consider the extremely rare diagnosis of VIPoma. Somatostatin receptor scintigraphy and abdominal CT showed the primary site of pancreas and liver metastasis. And the IHC of tissue showed the positive of VIP staining.

The treatment for localized VIPoma is surgery to remove the tumor. If the tumor has not spread to other organs, surgery can often cure the condition. For patients who do not accept surgery or are not suitable for surgery, somatostatin analog can also slow the diarrhea and control the disease progression. Octreotide blocks the action of VIP, and relieves 80%-88% of VIP-caused syndrome, including diarrhea and hypokalemia. For metastatic disease, traditional hepatic-directed therapies, including resection, ablation, hepatic artery embolism, and liver transplantation, are used for liver metastasis. New therapies such as peptide receptor radionuclide therapy (PRRT) can be highly effective, and combined chemotherapy of capecitabine and temozolomide seems to show response for some VIPoma patients. Sunitinib and everolimus are also the most promising treatments for metastasis disease. Other treatments include correcting dehydration; fluids are often given through a vein (intravenous fluids) to replace fluids lost in diarrhea. There is no report of surgery in VIPoma patients with liver metastasis. In this case, the patient was diagnosed as VIPoma with type II liver metastasis. Our multidisciplinary team considered the metastasis sites to be resectable. With the resection of primary site and metastasis sites, the patient recovered well from related syndrome. We need more cases to study the role of surgery in stage IV VIPoma.

FIGURES

**FIGURE 1** Abdominal CT scan before operation A. Mass in the head of pancreas and duodenum, B. Metastases of the liver, C. Metastases of the liver

**FIGURE 2** Somatostatin receptor scintigraphy showed the metastases in the liver (arrow)

**FIGURE 3** Abdominal MRI scan after operation A. Liver metastases after six months (T2), B. Liver metastases after one year (T2)
<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
</tr>
</thead>
</table>