

# Combined associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) followed by left trisectionectomy and Whipple operation for PNET

Ren Ji<sup>1</sup>, Shi Zuo<sup>1</sup>, Siyuan Qiu<sup>1</sup>, Ping Li<sup>2</sup>, Albert Chan<sup>1</sup>, William Sharr<sup>1</sup>, Chung Mau Lo<sup>1</sup>

<sup>1</sup>Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, <sup>2</sup>Division of Pathology, University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China

Correspondence to: Ren Ji, MS. Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, University of Hong Kong-Shenzhen Hospital, Shenzhen 518053, China. Email: jir@hku-szh.org.

**Abstract:** Pancreatic neuroendocrine tumor (PNET) is slow-growing, and account only for 2% of all pancreatic primary tumors. Surgical resection is still the only curative treatment for PNET patients. Unfortunately, most of PNETs was found with unresectable multiple liver metastases and extrahepatic metastasis as their characteristics of non-functional and asymptomatic. With advances in liver surgery in these years, especially combined associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), provide a new curative surgical treatment for PNET with liver metastases patient. Here we report a PNET with multiple liver metastases case underwent ALPPS (followed by left trisectionectomy) and Whipple operation within one-stage.

**Keywords:** Neuroendocrine tumor; liver metastases; surgical resection

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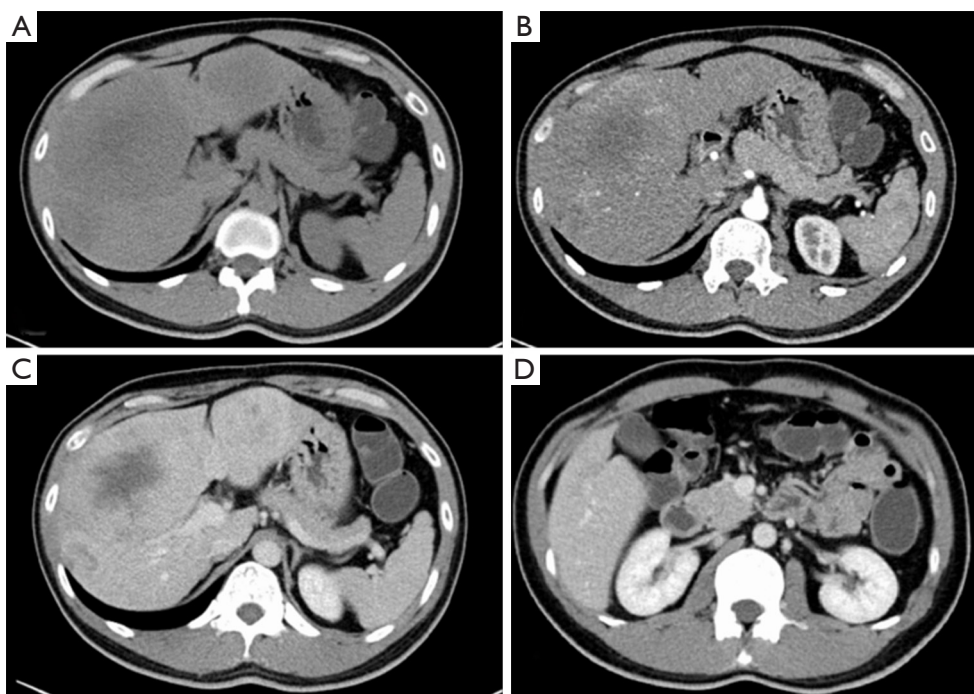
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## Introduction

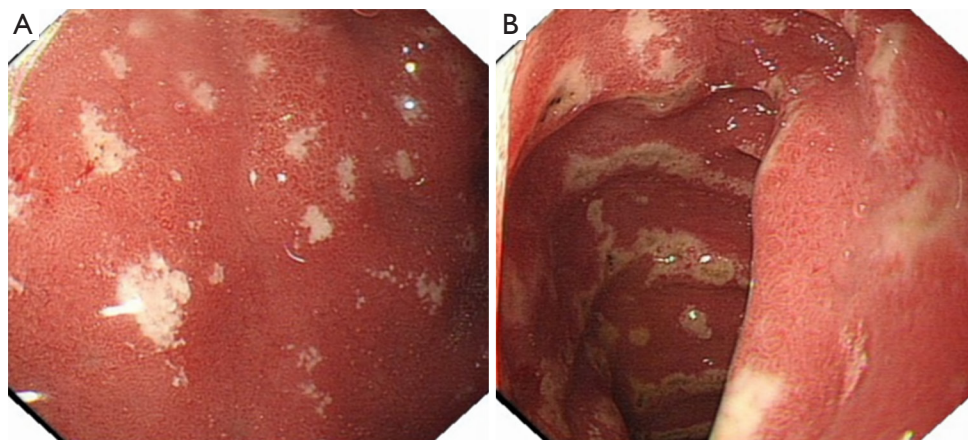
Pancreatic neuroendocrine tumor (PNET) is slow-growing (1), and account only for 2% of all pancreatic primary tumors. Surgical resection is still the only curative treatment for PNET patients. Unfortunately, most of PNETs was found with unresectable multiple liver metastases and extrahepatic metastasis as their characteristics of non-functional and asymptomatic. With advances in liver surgery in these years, especially combined associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), provide a new curative surgical treatment for PNET with liver metastases patient. Here we reported a case of a 36-year-old man who was diagnosed PNET with liver metastases and underwent ALPPS (followed by left trisectionectomy) and Whipple operation within one-stage.

## Case presentation

We report on a 37-year-old male patient (176 cm, 68 kg, good past medical history) who presented uncharacteristic symptoms (i.e., epigastric pain, diarrhea, weight lost) 2 months prior to admittance, which led to the initiation of diagnostic procedures by a gastroenterologist and included an esophagogastroscope, abdominal computed tomography (CT) (*Figure 1*) and PET-CT. The esophagogastroscope revealed multiple ulcers of the gastric antrum and duodenum (*Figure 2*). Based on the CT imaging studies bilobular hepatocellular carcinoma (HCC) was diagnosed, although the HBVs Ag is negative and the serum tumor marker alpha fetoprotein is normal. Other suspicious for metastatic disease (i.e., pancreas, prostate, colon), were excluded by CT and PET-CT. In addition, the serum tumor marker CEA, CA19-9, and prostate-specific antigen



**Figure 1** Upper abdominal computed tomography. (A) Plain phase; (B) arterial phase; (C) portal vein phase; (D) portal vein phase: no suspicious of pancreatic head.



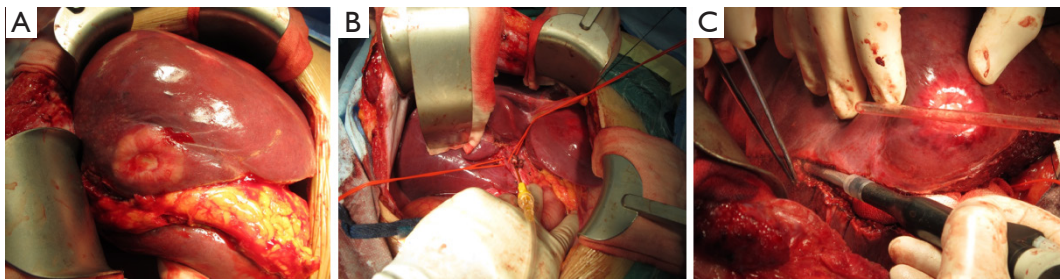
**Figure 2** esophagogastroscopy photos. (A) Multiple ulcers of the gastric antrum; (B) multiple ulcers of duodenum.

were within normal reference range. Besides the patient was feeling fine with no clinical symptoms of diabetes, hypoglycemia, hypopituitarism, hypoparathyroidism.

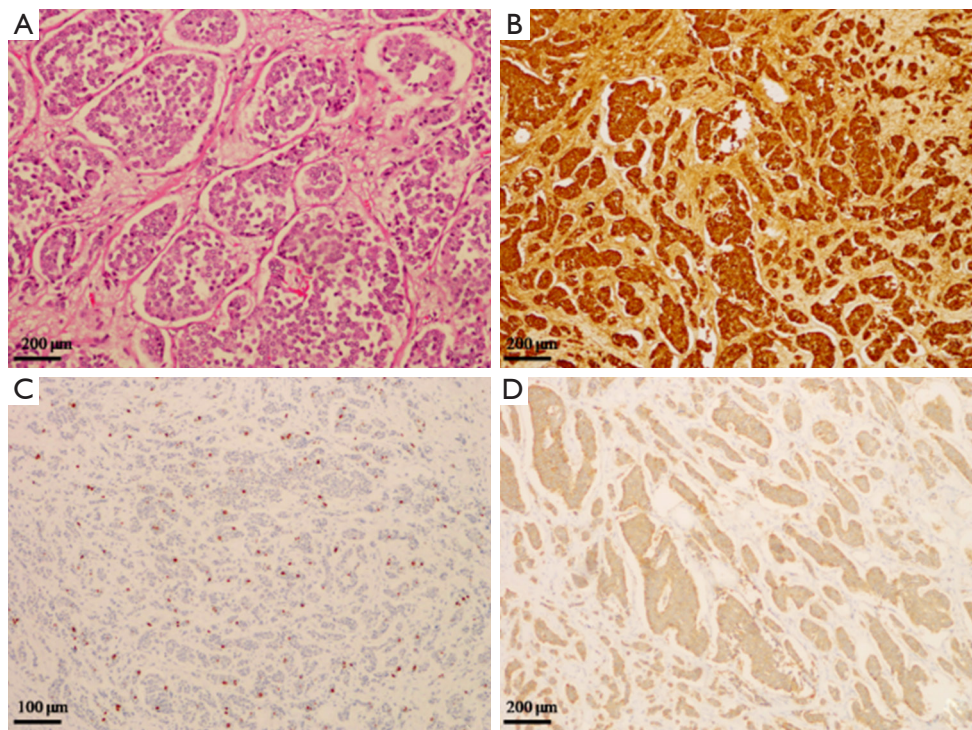
#### **Clinical course—hepatic surgery (ALPPS stage 1)**

After routine exploration for abdominal surgery, we fully mobilized the liver and performed intraoperative

ultrasound (IOUS) in order to evaluate resectability of the hepatic lesions. The hepatic lesions identified by IOUS were resected by multiple sub-segmental resections (n=6, S1/II/III/IVa/IVb/V/VIII). As calculating the future liver remnant (FLR)/estimated standard liver volume (ESLV) ratio just 24%, significant lower than our standard of 30% (no cirrosis). ALPPS stage 1 was performed, during the operation we ligated the left portal vein and partition the



**Figure 3** Intraoperative photos. (A) Tumor; (B) anatomy of right pedicle; (C) CUSA partition the SVI/VII from SV/VIII. CUSA, Cavitron Ultrasonic Surgical Aspirator.



**Figure 4** Microscopically, pancreatic tumor consists of relative uniform cells forming solid nests. (A) HE staining showed small sized tumor cells with bland feature ( $\times 20$ ); (B) immunohistochemically, the tumor cells were positive for chromogranin ( $\times 20$ ); (C) Ki-67 staining (proliferation) showed a lower proliferation rate with index about 5% ( $\times 10$ ); (D) immunohistochemically, the tumor cells were positive for synaptophysin ( $\times 20$ ).

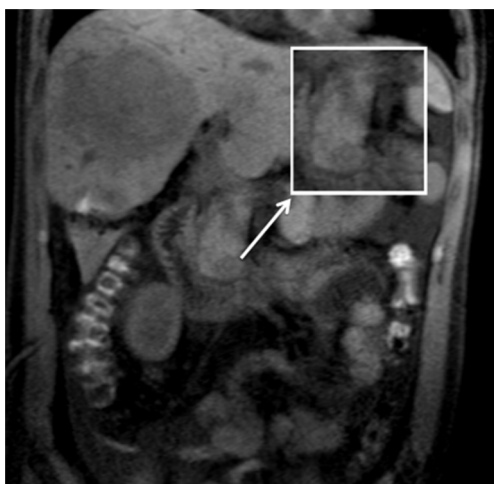
SVI/VII from SV/VIII by CUSA (Cavitron Ultrasonic Surgical Aspirator, Valleylab, Boulder, CO, USA). One additional lesion (2 cm) in SIVb and some enlarged lymph nodes in ligamentum hepatoduodenal was resected for pathologic diagnosis (*Figure 3A-C*).

#### Clinical course—diagnosis correcting

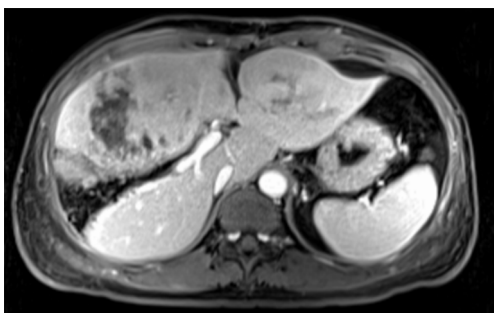
The ALPPS stage 1 hepatic surgery postoperative course was uneventful, with no evidence of bleeding, bile

leakage and liver failure. On day 10, the histopathological examinations of the resected liver specimen and the lymph nodes in ligamentum hepatoduodenal revealed metastases of a NET. Microscopically, both the specimen showed small-sized ovoid cells arranged in nests separated by broad fibrous bands and glandular duct formation. They displayed poorly differentiated with large nuclei. Immunohistochemically, the tumors were positive for chromogranin A, synaptophysin, Ki-67 (with index about 5%), but negative for CD56 (*Figure 4*).





**Figure 5** MRI revealed a lesion (size 1.6 cm × 2.3 cm) in pancreatic head. The arrow indicates the tumor of pancreatic head.



**Figure 6** Hypertrophy of right posterior lobe (from 328 to 504 cm<sup>3</sup>).

As the primary liver NET is rare, and most primary NET come from pancreas. We performed an emergency MRI examination which identified a small size lesion located at the pancreatic head (*Figure 5*). In general, corresponded to the resected metastatic liver NET, the lymph nodes in ligamentum hepatoduodenal and the MRI image, we corrected the diagnosis with PNET with liver metastases.

### Clinical course—stage 2 surgery (ALPPS stage 2 combine Whipple procedure)

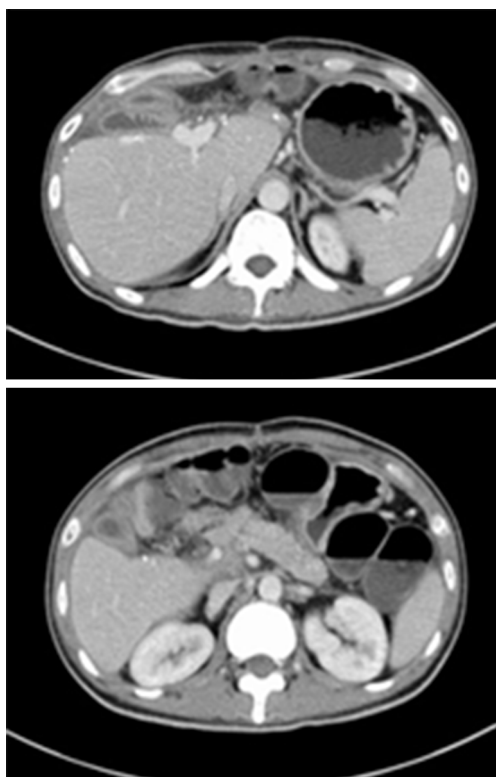
As the patient is young, and recover very smoothly from the stage 1 operation, the SVI/VII volumetry (FLR/ESLV) from 24% increase to 38% (*Figure 6*), we performed ALPPS stage 2 (left trisectionectomy) combine Whipple procedure at the same time (*Figure 7A*). During operation pancreatic head tumor identified by IOUS and frozen biopsy section. The histopathological examinations of the resected liver specimen (*Figure 7B*) revealed metastases of a NET, that, in general, corresponded to the resected primary lesion in the pancreatic head (*Figure 7C*). Both the primary pancreatic tumor and the liver metastases showed the same typical neuroendocrine tumor.

### Follow up

Four years passed, the patient did not accept chemotherapy as patient's personal reasons. There was no evidence for NET recurrence within the liver or pancreas by CT or MRI



**Figure 7** Intraoperative photo of stage 2 operation and the specimens. (A) specimen removed during stage 2 operation; (B) bilobed multiple solid tumor; (C) Pancreatic head solid tumor, size about 2.0 cm × 1.8 cm. The arrow indicates the tumor of pancreatic head.



**Figure 8** Recently CT scan: no evidence for tumor recurrence within the liver and pancreas.

(once per 6 months) (*Figure 8*), the patient general condition is good, diarrhea symptom also improved obviously.

## Discussion

At present, operation performing to resect the primary pancreatic tumor and all the metastatic hepatic tumor is the only curative treatment for PNET with liver metastases (2), gives 5-year survivals of 76% (nonresectable 5-year survivals are 30–40%) (3). Typically, CT is the first line imaging choice for most patients with suspected PNET with liver metastases. Most liver metastases of PNET is characterized by rich blood supply from the hepatic artery, so it presents markedly enhancement in the arterial phase. As be lack of the portal vein blood supply, it also present phenomenon of “wash out”, which make it difficult to distinguish PNET with liver metastases from other diseases such as primary liver cancer. In this case, we also misdiagnose it primary HCC at first. On the other hand, in about 11–14% of liver metastases, the primary lesion is hard to even cannot be identified as their small size or location (i.e., pancreas, small

bowel, prostate) (4). Just like this case we report, NETs are often present in an advanced stage with an unknown primary or initial diagnosed with metastasis (5,6). For the PNET liver metastasis patients, besides the resection of liver metastatic lesions, it is more important to find the primary site of pancreas, because it has great impact on the patient’s outcome by resection of the primary pancreatic tumor (4). We should be aware of, primary liver-NET, is an extremely rare occurrence, and until 2015, there were only less than 150 reported cases in the English literature (7). So, once we detected PNET in liver, ought to try to identify the primary for an optimal therapy. Over the last few years the detection rate of primary NET in the pancreas by MRI diffusion weighted imaging (DWI) has been improved (8). Recently, somatostatin receptor PET/CT scan technique was one of topics of most concern, as studies reported it can detects about 59% unknown NET primaries. However, which means, even by using such a sensitive technique, more than 1/3 of patients’ primaries could not be found (9).

Liver transplantation (LT) for unresectable metastases has essentially been abandoned as its high rate of tumor recurrence (10). Without exception, several reports showed poor results on LT apply to PNET patients with liver metastases between 1960 and the 1980s. In the present critical situation of donor shortage, LT apply to PNET patients with liver metastases should be strictly controlled. It has been wildly accepted that only highly selected PNET patients with liver metastases may be candidates for LT (11-13). The only prospective study recommended strict selection criteria (i.e., low grade, removal of primary tumor, liver involvement <50%, age <55 years, and stable disease for  $\geq 6$  months before LT) for LT with curative treatment (13). These strict selection criteria have strongly limited the surgical treatment for PNET patients with liver metastases until ALPPS was reported as a novel surgical technique liver resection in traditionally nonresectable primary intrahepatic tumors or metastatic liver tumors since 2012 (14-16).

For those patients with hepatic mass and small-size FLR, ALPPS provide a novel resolution. The procedure is consisted of two staged hepatectomy by which rapid significant hypertrophy of the remnant is induced by transecting the parenchyma while there is not enough time for the development of collateral formation (16-21). The technique is relied on portal vein ligation and *in situ* splitting through parenchyma so that the two parts are just connected through hilar structures in the first step. Partitioning will be completed after an interval of 7 days if FLR hypertrophy is satisfactory (15,19). Particularly worth

mentioning is the NET patients' liver is normal, which always contribute a rapid increase of FLR hypertrophy, are good cases for this procedure.

Only very few literatures compare the outcome of one-stage or two-stage hepatectomy for metastatic liver tumor in patients undergoing Whipple operation, a dual center analysis showed the advantage of less abscess incidence (7%) in one-stage operation group (22). To our knowledge, by retrieving literatures, we find no literature on the ALPPS combine Whipple operation for PNET within one-stage.

In conclusion, combined ALPPS and Whipple operation within one-stage appears to be a valuable option for patients with advanced pancreatic NETs metastatic to the liver, thus facilitating curative liver surgery.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Informed Consent:* Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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