

CASE REPORT

Non-Functioning Pancreatic Neuroendocrine Tumor Accompanied With Multiple Liver Metastases: Remorseful Case and Literature Review

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ABSTRACT

Context Pancreatic neuroendocrine tumor (P-NET) is a rare and slow-growing tumor. Unfortunately, there is no clear consensus on the role and timing of surgery for primary tumor and liver metastases, although current reports refer to liver surgery including LT for unresectable liver metastases. **Case report** A thirty nine year-old man was diagnosed with nonfunctioning pancreatic neuroendocrine tumor (P-NET) in the pancreatic head, with multiple liver metastases. The tumor was 2.5 cm in diameter and he was asymptomatic. Small but multiple metastases were detected in the liver, and no extrahepatic metastases were observed. We initially intended to control the liver metastases before resection of the primary tumor. To begin with, transarterial chemoembolization (TACE) and transcatheter arterial infusion (TAI) were repeated. Thereafter, systemic chemotherapy and biotherapy were introduced according to follow-up assessments. Unfortunately, imaging assessment at ~10 months later revealed that liver metastases were partially enlarged, although some were successfully treated. Therefore, these therapies were switched to other regimens, and TACE/TAI, systemic chemotherapies and biotherapies were repeated. Although liver metastases seemed to be stable for a while, the primary tumor was enlarged even after therapy. At 3.5 years after initial diagnosis, the primary tumor became symptomatic (pain and jaundice). Liver metastases enlarged and massive swelling of the para-aortic lymph nodes was observed. Thereafter, palliative therapy was the main course of action. He died at 4.3 years after initial diagnosis. **Conclusion** Our young patient could have been a candidate for initial surgery for primary tumor and might have had a chance of subsequent LT for unresectable metastases. Surgeons still face questions in deciding the best surgical scenario in patients with P-NET with liver metastases.

INTRODUCTION

Pancreatic neuroendocrine tumor (P-NET) is a rare and slow-growing tumor [1]. The American Joint Committee on Cancer stated a new TNM classification in 2009, based on tumor size, including direct invasion and lymphoid and distant metastases [2]. In 2010, the World Health Organization categorized gastro enteropancreatic neuroendocrine tumor (GEP-NET) into three categories (G1, G2 and G3) based on histopathological differentiation, proliferation index (Ki-67), neuroendocrine biomarkers (such as chromogranin A and synaptophysin), hormonal behavior, tumor size, direct invasion, and distant metastasis [3]. These classifications are useful for predicting the prognosis and postoperative recurrence [1]. Curative resection is ideal for this slow-growing tumor [1, 4-6], and postoperative surveillance of at least 10 years is required, because long-term recurrence can occur after surgery [1].

Curative surgery is often difficult, because over 80% of P-NET patients already have unresectable multiple liver metastases and extrahepatic metastasis [1]. Some current opinions suggest an expanded surgical indication for P-NET patients with liver metastases, because survival is improved [1, 6-9]. Aggressive surgery for liver metastases or cytoreductive surgery for over 90% of the visible tumors is important to improve survival [6, 9]. Cytoreductive surgery for liver metastases is indicated to reduce hormone levels and improve clinical symptoms and prognosis [1, 6, 9]. Liver transplantation (LT) was originally conceived as an ideal therapy for unresectable liver metastases [1, 10].

Unfortunately, there is no clear consensus on the role and timing of surgery for primary tumor and liver metastases, although current reports refer to liver surgery including LT for unresectable liver metastases. Here, we reviewed previous studies and present a case of P-NET.

CASE REPORT

A thirty nine-year-old man was diagnosed with nonfunctioning P-NET in the pancreatic head, with multiple liver metastases (Figure 1A and D). Imaging revealed no extrahepatic metastases, and endoscopic fine-needle aspiration and liver needle biopsy showed well-differentiated GEP-NET G1. The tumor was 2.5 cm in diameter (Figure 1A) and nonfunctioning. Small but multiple metastases were detected in the liver (Figure 1D).

Received September 15th, 2014 – Accepted October 25th, 2014

Key words Gastro-enteropancreatic neuroendocrine tumor; Liver Transplantation; Pancreas

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He was asymptomatic at that time. We initially intended to control the liver metastases before resection of the primary tumor, because we considered liver metastases as the most important factor in the prognosis. Initially, transarterial chemoembolization (TACE) and transcatheter arterial infusion (TAI) were repeated. Thereafter, systemic chemotherapy and biotherapy were introduced according to follow-up assessments. Unfortunately, imaging assessment at ~10 months later revealed that the liver metastases were partially enlarged, although some were successfully treated. Therefore, these therapies were switched to other regimens, and TACE/TAI, systemic chemotherapies and biotherapies were repeated. Although liver metastases temporarily seemed to be stable (Figure 1E), the primary tumor was extended, even after therapy (Figure 1B). At 3.5 years after initial diagnosis, the primary tumor caused symptoms of pain and obstructive jaundice (Figure 1C). Selective inhibitor of mammalian target of rapamycin (mTOR) was given, and obstructive jaundice was treated by metallic-stent placement. Liver metastases were enlarged (Figure 1F), and there was massive swelling of the para-aortic lymph nodes. Thereafter, palliative therapy was the principal course of action. He finally died at 4.3 years after initial diagnosis.

DISCUSSION

Resection of primary tumor

Approximately half of P-NETs are nonfunctioning [11], and tumors < 10–30 mm are not indications for surgery [1, 6].

Functional P-NET should be removed even if the tumor is < 10 mm [1, 6], because functional P-NET has malignant potential despite a small tumor size [1]. Some factors, such as young age, hormonal function, and surgical resection, are important for overall survival [6, 12]. Seventy to ninety percent of enlarging P-NETs have malignant potential [1], and the aim of surgery for primary nonfunctioning tumor is to avoid malignant change and subsequent distant metastasis [6]. Although endoscopic ultrasonography with fine-needle aspiration biopsy is useful for determining the malignant potential and predicting prognosis [13–15], there are no definitive criteria regarding whether P-NET should be removed or observed based on tumor size [1,6]. Curative resection is considered as standard therapy in well-differentiated GEP-NET G1/G2 with a Ki-67 index of < 10% [1, 4]. Cytoreductive surgery for primary tumor is indicated to reduce hormone levels and improve clinical symptoms [1, 6, 16], although the effects on prognosis are still controversial [1, 5]. Overall, surgery for primary tumor should be curative resection [1, 4–6], although palliative therapy may be indicated if there is a possibility of improvement of clinical symptoms, such as endocrine symptoms, oppression on surrounding organs by primary tumor, jaundice and oral passage disturbance [6, 17].

Resection of liver metastases

Curative surgery is often difficult, because over 80% of P-NET patients already have unresectable multiple liver

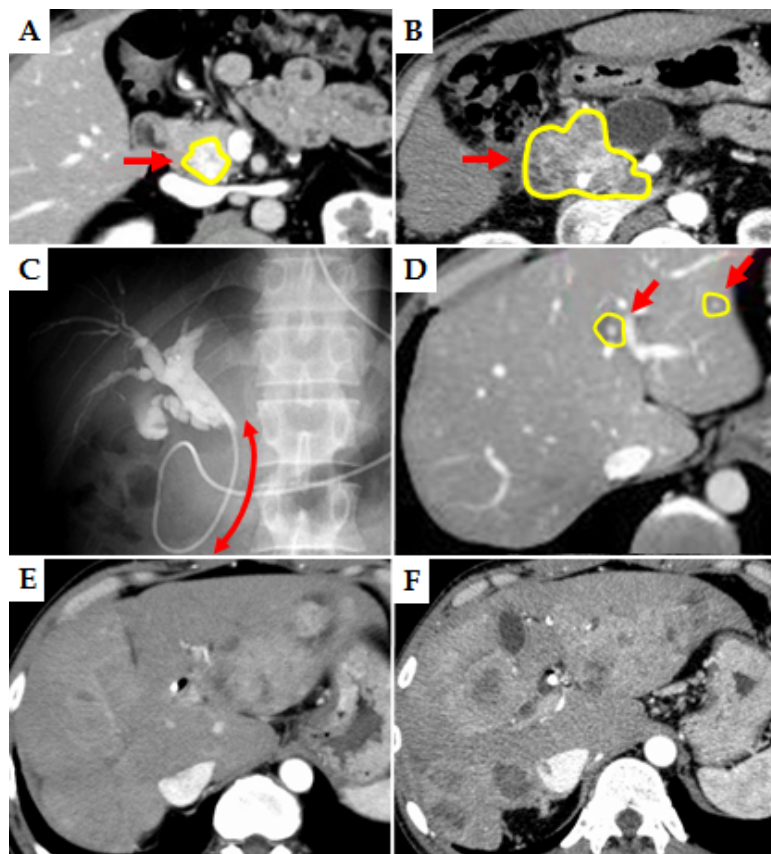


Figure 1. Enhanced computed tomography and endoscopic retrograde cholangiography. A: A nonfunctioning P-NET in the pancreatic head (2.5 cm in diameter) was observed (yellow circle and red arrow); B: Primary tumor grew, even after therapy (yellow circle and red arrow); C: Obstruction of bile duct due to enlarged primary tumor (red arrow) at 3.5 years after initial diagnosis; D: Small but multiple liver metastases were detected at initial diagnosis (yellow circle and red arrow). E; Liver metastases temporarily seemed to be stable, although continuous and repeated therapies (TACE/TAI, systemic chemotherapies and biotherapies) were required; F: Liver metastases enlarged again at 3.5 years after initial diagnosis.

metastases and extrahepatic metastasis [1]. Current opinions suggest extended surgical indications for P-NET patients with liver metastases, because survival is improved and P-NET is a slow-growing tumor [1, 6-9]. For liver metastasis without extrahepatic metastasis, standard/aggressive surgery is the first choice for well-differentiated P-NET categorized as GEP-NET G1/G2 [1, 7, 8]. Aggressive surgery for liver metastases and cytoreductive surgery for > 90% of the visible tumors are important to improve survival [6, 9]. Cytoreductive surgery for liver metastases is indicated to reduce hormone levels and improve clinical symptoms and prognosis [1, 6, 9]. For metastatic poorly-differentiated P-NET categorized as GEP-NET G3, cisplatin-based combination therapy is considered as the first-line therapy. Radiofrequency ablation, TACE/TAI, and selective inhibitor of mTOR are available as optional treatments [1]. Systemic biotherapy, such as somatostatin analog and interferon- α , is indicated for functional P-NET and postoperative recurrence [1].

LT for unresectable liver metastases

LT was originally conceived as an ideal therapy for advanced hepatic malignancy, because it eliminates the liver tumors and the potential for recurrence in the liver remnant [1, 10]. LT for unresectable metastases has essentially been abandoned [10]. Several attempts to implement this strategy between 1960 and the 1980s showed poor results, although LT for early hepatocellular carcinoma has been established [18]. It is well known that highly selected P-NET patients with liver metastases may be candidates for LT [10, 19-21]. The only prospective study recommended strict selection criteria for LT with curative intent (i.e., low grade, removal of primary tumor, liver involvement < 50%, age < 55 years, and stable disease for $\geq$ 6 mo before LT) [21], and a study reported 96% overall survival and 80% disease-free survival [22]. However, it was also reported that P-NET patients with liver metastases who received LT had a follow-up term of no longer than 5.8 years, and the longest tumor-free survival was 5.1 years [23], and a high rate of tumor recurrence was reported at almost 60% [20].

Use of LT for extended indications always presents an ethical dilemma [10]. The United Network for Organ Sharing has generally held that LT for malignancy should be considered only when results are essentially equivalent to results with standard indications, generally requiring a 5-year survival rate of 60–70% [10]. Previous results that indicate LT for P-NET [20-22] must be interpreted cautiously [10], especially given the global scarcity of liver grafts available [10]. These results should not justify LT at this time [10]. Current studies suggest a growing consensus concerning LT for liver metastases of P-NET as follows [20, 24-28]. (1) Liver metastases of symptomatic or asymptomatic P-NET are unresectable. (2) Disease is confined to the liver, and extrahepatic metastases are ruled out. (3) LT is indicated for well-differentiated P-NET categorized as GEP-NET G1/G2. Poorly differentiated P-NET categorized as GEP-NET G3 is considered as a contraindication for LT. Ki67 index

< 10% is recommended. (4) LT should not be associated with major extrahepatic resection. Primary tumor should be removed before LT.

Our case

We understand that P-NET patients often have unresectable liver metastases at initial diagnosis [1], and that surgical indications for P-NET with liver metastases should be determined individually in each case [6]. Resection of the primary tumor in metastatic nonfunctioning P-NET patients with unresectable liver metastases does not significantly improve survival [4]. Presence of liver metastases is a major prognostic factor for P-NET patients [1, 20], and surgical management of liver metastases remains controversial [9]. In our case, we initially intended to control the liver metastases before resection of the primary tumor, because we considered liver metastases as the most important prognostic factor. Our decision at that time may have been consistent with previous opinions [1, 4, 6, 9, 20].

Currently, classification of GEP-NET is useful for evaluating malignancy, predicting prognosis, and determining therapeutic strategies [1, 2]. Surgical indications for primary tumor [1, 4-6, 16] and hepatic surgery, including LT for liver metastases [1, 10, 20, 24-28] have already been stated. However, it seems to be not easy to decide optimal timing of surgery for primary tumor and liver metastases. In our case, aggressive surgery for liver metastases seemed to be difficult even during a period of stable liver metastases and resection of primary tumor is required before LT. We retrospectively regret that aggressive surgery for primary tumor and subsequent LT for unresectable liver metastases may have provided a better course in our case. Currently, surgical procedures and devices are well developed, and the question is whether Pancreato duodenectomy or distal pancreatectomy is risky. We believe that pancreatic surgery is safe and beneficial for patients, if indicated. We retrospectively speculate that a negative approach to aggressive surgery for primary tumor may have resulted in poor quality of life and deprived our patient of the opportunity of LT for unresectable liver metastases. Our young patient could have been a candidate for initial surgery for primary tumor and might have had a chance of subsequent LT for unresectable metastases. Surgeons still face questions in deciding the best surgical scenario in patients with P-NET with liver metastases.

Conflict of Interest

Authors declare to have no conflict of interest.

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