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MINIREVIEWS

Pancreatic neuroendocrine tumor accompanied with multiple liver metastases

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Abstract

Pancreatic neuroendocrine tumor (P-NET) is rare and slow-growing. Current classifications predict its prognosis and postoperative recurrence. Curative resection is ideal, although often difficult, because over 80% of patients have unresectable multiple liver metastases and extrahepatic metastasis. Aggressive surgery for liver metastases is important to improve survival. Aggressive or cytoreductive surgery for liver metastases is indicated to reduce hormone levels and improve symptoms and prognosis. Liver transplantation was originally conceived as an ideal therapy for unresectable liver metastases. Unfortunately, there is no clear consensus on the role and timing of surgery for primary tumor and liver metastases. Surgeons still face questions in deciding the best surgical scenario in patients with P-NET with unresectable liver metastases.

Key words: Gastroenteropancreatic neuroendocrine tumor; Pancreas; Liver metastasis; Liver surgery; Liver transplantation

Core tip: Pancreatic neuroendocrine tumor is rare. Current classifications predict its prognosis and postoperative recurrence. Curative resection is often difficult, because over 80% of patients have unresectable multiple liver metastases and extrahepatic metastasis. Aggressive or cytoreductive surgery for liver metastases is indicated to reduce hormone levels and improve symptoms and prognosis. Liver transplantation was originally conceived as an ideal therapy for unresectable liver metastases. However, there is no clear consensus on the role and timing of surgery for primary tumor and liver metastases.

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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 gastroenteropancreatic 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 cur-

rent 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 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]. 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. Surgeons still face questions in deciding the best surgical scenario in patients with P-NET with unresectable liver metastases. Here, we reviewed previous studies about therapeutic strategies for P-NET, with our regretful case.

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 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].

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 ⩾ 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]. LT in selected GEP-NET patients has shown a 5-year recurrence-rate as low as 30%[21]. 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]. The Milan Criteria is maybe a better definition of selection criteria for LT[21]. In the last decade, selection criteria based on clinical presentation have been integrated with a proper histopathologic classification and diagnostic techniques[21]. In particular, Ki67 expression has been considered as a prognostic factor of risk of recurrence[21,24-28]. A Ki67 proliferation index of < 10% is a characteristic of well-differentiated tumor, which we have adopted as a cut-off value to consider GEP-NET patients for LT candidates[21,24]. 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; and (4) LT should not be associated with major extrahepatic

resection. Primary tumor should be removed before LT.

As described above, primary tumor should be removed before LT. However, optimal timing for LT in patients with stable versus progressive disease remains unclear[20]. In previous report, 83% of patients had undergone surgical treatment for primary tumor, and a 5-year overall survival has increased to 59% in relation with fewer patients presenting poor prognostic factors[20]. Favorable outcomes in cases of unknown primary tumor might suggest that a failure to detect the primary tumor before LT should not be considered as an absolute contraindication[20].

MANAGEMENT OF UNRESECTABLE LIVER METASTASES

For metastatic poorly-differentiated P-NET categorized as GEP-NET G3, cisplatin-based combination therapy is considered as the first-line therapy. Radiofrequency ablation, transarterial chemoembolization (TACE), transcatheter arterial infusion (TAI) and selective inhibitor of mammalian target of rapamycin 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].

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogs is a novel treatment in patients with somatostatin receptor-expressing, well-differentiated and metastatic neuroendocrine tumors[29-31], and the PRRT with yttrium and/or lutetiumis a potent therapeutic approach. On the other hand, transarterial radioembolisation [*i.e.*, selective internal radiotherapy (SIRT)] is an innovative therapy in liver-limited unresectable, neuroendocrine liver metastases[32-34]. SIRT is an effective treatment option for patients with metastatic liver disease in a salvage setting with acceptable toxicity.

OUR REGRETFUL CASE

A 39-year-old man was diagnosed with nonfunctioning P-NET in the pancreatic head, with multiple liver metastases. The tumor was 2.5 cm in diameter, and was histopathologically well-differentiated with a Ki-67 expression of < 10%. 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, TACE/TAI were repeated. Thereafter, 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. 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. 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]. However, 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.

DISCUSSION

Currently, classification of GEP-NET is useful for evaluating malignancy, predicting prognosis, and determining therapeutic strategies[1,2]. Though this report focused surgical options for P-NET with liver metastases, novel managements (*i.e.*, PRRT and SIRT) are currently available for unresectable liver metastases, with acceptable side effects[29-34]. Effective and beneficial treatment options for P-NET patients with liver metastases should be carefully considered. From the viewpoint of surgical option, 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. Currently, surgical procedures and devices are well developed, and the question is whether pancreatoduodenectomy or distal pancreatectomy is risky. We believe that pancreatic surgery is safe and beneficial for patients, if indicated.

In LT for P-NET patients, previous excellent reports focused on a prognostic factors for overall survival, a post-transplant risk of recurrence, a better selection criteria, a difference between P-NET and others, and an importance of the post-transplant surveillance[21,24,28]. There is a difference in behaviors between P-NET and the other tumors, the indication for LT for unresectable liver metastases is unique for P-NET[21,24]. Also, an importance of careful surveillance after LT due to the risk of recurrence was documented[21,24]. Tumor re-staging should be scheduled at least 4 times per year for the first two years and continued thereafter with progressively longer follow-up intervals[21].

Though we understand that any decisions cannot be made based on a single patient experience, we retrospectively speculate that a negative approach to aggressive surgery for primary tumor may have resulted in poor quality of life and deprived patient of the opportunity of LT for unresectable liver metastases. P-NET patient with

liver metastases 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.

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