Long-term survival after comprehensive treatment in a patient with advanced neuroendocrine neoplasm of the pancreas: A case report

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Abstract. Neuroendocrine neoplasms of the pancreas (pNENs) are rare. In February 2021, a 54-year-old woman was diagnosed with pNEN and multiple metastases within the liver. The patient, diagnosed with grade G2 neuroendocrine neoplasm (T4N0M1), underwent an ultrasonography-guided liver biopsy and radiofrequency ablation. After receiving Sandostatin LAR in April 2021, side effects led to its discontinuation after seven cycles. Following two sessions of radiofrequency ablation, the patient's condition was stable. However, disease progression was noted in September 2023, resulting in hemodialysis and closed peritoneal drainage. Surufatinib was administered, stabilizing the tumor by November 2023. The patient underwent transarterial chemoembolization due to a large tumor burden, with subsequent MRCP showing stability from diagnosis in February 2021 to June 2024. The present case report highlights the role of tailored treatment strategies considering patient comorbidities and tumor biology, and the significance of secondary puncture biopsy, which, despite not being pursued by the patient in the present study due to the associated risks, may provide survival benefits for patients with advanced or metastatic pNEN.

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Introduction

As is well documented, neuroendocrine neoplasms (NENs) are rare malignancies that originate from the diffuse neuroendocrine cell system, and are more prevalent in the gastroenteropancreatic (GEP) tract and lung (1). Despite accounting for 1.2% of all pancreatic malignancies (2), the incidence of NEN of the pancreas (pNEN) has notably increased in both the USA and Europe in recent years. In 2018, the age-standardized incidence rate of pNEN reached one case per 100,000 residents, with an average annual growth rate of 110.6% in Europe (3). For pNEN, the estimated 5-year overall survival (OS) has been reported to decrease from 87% at stage I to 71% at stage III and 26% at stage IV (3).

Neuroendocrine neoplasms (NENs) exhibit high heterogeneity and can be classified based on the embryonic origin of the corresponding tissues of the primary tumor into three groups: Foregut (bronchopulmonary, stomach, duodenum, biliary tract and pancreas), midgut (jejunum, ileum, appendix and proximal colon), and hindgut (distal colon and rectum) NENs (4). The rectum and pancreas are the most common sites of occurrence in Asian populations, while in Caucasian populations in Europe and America, the midgut and pancreas are the most common sites (4). In addition, these NENs can be classified into functioning and non-functioning types, with functioning tumors often secreting hormones such as insulin or glucagon, leading to distinct clinical syndromes (5). In the present case, the tumor originated from the pancreas and was non-functional.

The management of pNEN relies on the stage and grade of the tumor at the time of diagnosis. Surgical intervention is the gold-standard treatment for patients diagnosed at an early stage, whereas systemic therapy, such as chemotherapy, and interventional treatment, such as transarterial chemoembolization (TACE), remain the primary treatments for locally advanced disease or for patients with metastatic pNEN who are ineligible for surgery (4). However, the majority of pNENs are diagnosed at locally advanced or metastatic stages (6). Patients with advanced pancreatic NENs may present with

symptoms related to hormone excess, abdominal pain, weight loss and gastrointestinal disturbances. Histologically, these tumors are characterized by a proliferation of uniform cells with granular cytoplasm and may exhibit varying degrees of differentiation. For this population, the role of surgery is therefore often palliative, whereas chemotherapy has limited activity (7-9).

The present case report outlines the case of a patient with multiple metastatic pNEN who underwent numerous sessions of radiofrequency ablation (RFA) and treatment with systemic somatostatin analogs (SSAs). After receiving the targeted therapy surufatinib and TACE, the patient achieved a favorable response.

Case report

Patient case. A 54-year-old woman hospitalized at The First Affiliated Hospital of Xinxiang Medical University (Xinxiang, China) without prior medical history was originally diagnosed with moderately differentiated pNEN during a routine physical examination in February 2021. Fig. 1 depicts the timeline of the present case report. In February 2021, the patient underwent ultrasonography-guided liver biopsy, liver lesion RFA and pancreatic lesion RFA. The results of the morphological analysis on the pNEN revealed a Ki-67 proliferation index of 10%, with 5 mitotic figures/2 mm^2 and the absence of necrosis. Postoperative pathology delineated that the liver lesions were NENs (grade G2, stage IV, T4N0M1), according to the American Joint Committee on Cancer 8th edition (10). Immunohistochemistry results of the pNEN (Fig. 2A-H) showed that the tumor had the following characteristics: CK19(+), SYN(+), HEP(-), somatostatin receptor (SSTR)2(+), E-cadherin(+), β-catenin(membrane +), P504S(-) and Ki67(+ 10%). Furthermore, histopathological examination of the tumor (routine hematoxylin and eosin staining) depicted that tumor cells were arranged in a cribriform pattern (Fig. 2I). Additionally, the cells exhibited atypia, with marginally abundant cytoplasm, oval nuclei of different sizes, deeply stained nuclei and few mitoses. The nuclear membranes and nucleoli were difficult to visualize. Notably, metastases were not detected outside of the liver. According to the National Comprehensive Cancer Network guidelines (11), the patient was administered Sandostatin LAR (20 mg intravenously; q4w) to suppress tumor growth in April 2021. Following the seventh cycle in October 2021, the patient self-discontinued Sandostatin LAR due to side effects, such as dizziness, outside the hospital setting.

After an imaging evaluation (including assessment of the target, non-target and new lesions) according to the Response Evaluation Criteria in Solid Tumors version 1.1 (12), the condition of the patient was considered stable. To further reduce the tumor burden, the patient underwent two sessions of percutaneous RFA under ultrasound guidance for liver lesions in July and October 2021. Between November 2021 and September 2023, the patient declared that they self-administered traditional Chinese herbal medicine, and they did not attend the hospital for a follow-up appointment. Notably, no other information was provided regarding the traditional Chinese medicine taken, including the composition, dosage and administration.

In September 2023, the patient presented with abdominal distension and generalized itching, prompting her to be re-hospitalized to undergo abdominal paracentesis and drainage. Subsequently, magnetic resonance cholangiopancreatography (MRCP) dynamic enhancement imaging (Fig. 3A and D) indicated that the range and number of pancreatic tail and liver lesions had increased compared with in June 2022, reflecting disease progression. Notably, the right kidney was displaced and rotated due to compression. Subsequently, the patient underwent three sessions of temporary hemodialysis to mitigate renal dysfunction induced by right kidney compression, and closed peritoneal drainage to relieve abdominal discomfort due to ascites. After a multi-disciplinary treatment (MDT) consultation and considering the associated high risk, no further ultrasonography-guided biopsy was performed to reassess the pathological staging of the lesion progression. Meanwhile, the patient was treated with surufatinib (300 mg orally, qd) and received two doses of the short-acting SSA octreotide (0.05 mg subcutaneous injection, q12 h) to enhance treatment effectiveness.

Treatment efficacy was assessed based on subsequent MRCP reevaluations compared with the initial MRCP result (Fig. 3A and D; September 2023). After 2 months, MRCP dynamic enhancement imaging demonstrated a decrease in the size of the pNEN and multiple metastatic lesions (Fig. 3B and E; November 2023), indicative of stable disease progression. After that, the patient underwent TACE, a procedure involving chemotherapy (ethiodized poppyseed oil, 4.8-g injection) and embolization through the hepatic artery, in November 2023. After 3 months of targeted therapy, neuron-specific enolase (NSE) levels had decreased to within the reference range (0-17.5 ng/ml) (Fig. 4). The MRCP reevaluation in June 2024 revealed a stable condition (Fig. 3C and F). The latest follow-up visit was in mid-June 2024.

By June 2024, the progression-free survival (PFS) time of the patient was 12 months, and a total of 41 months had passed since the initial diagnosis of pNEN. The patient had achieved stable disease following evaluation.

Pathology

Hematoxylin and eosing staining. Tissues were fixed in 10% neutral buffered formalin at room temperature for 24 h before being sectioned into 4-μm thick slices. The sections were then deparaffinized at 45˚C for ~5 min. Next, the slides were immersed in hematoxylin at 25˚C for 5-10 min, differentiated in hydrochloric acid alcohol at 25˚C and then stained with eosin at 25˚C for 1-3 min, followed by rinsing with water. Finally, the sections were mounted with neutral gum sealant. The quality of staining was evaluated using a LEICA DM1000 LED microscope (Leica Microsystems GmbH) at a magnification of x200.

Immunohistochemical staining. The tissue sections were deparaffinized at 45˚C for 5 min, followed by immersion in an immunohistochemical antigen retrieval solution (neutral pH) at 95˚C for 20 min. The sections were then respectively immersed in distinct primary antibody solutions (diluted 1:100), including those for CK19 (cat. no. ZM-0074), SYN (cat. no. ZA-0506), HEP (cat. no. ZM-0131), somatostatin receptor 2 (cat. no. ZA-0587), E-cadherin (cat. no. ZA-0565), β-catenin (cat. no. ZA-0646), P504S (cat. no. ZA-0227) and

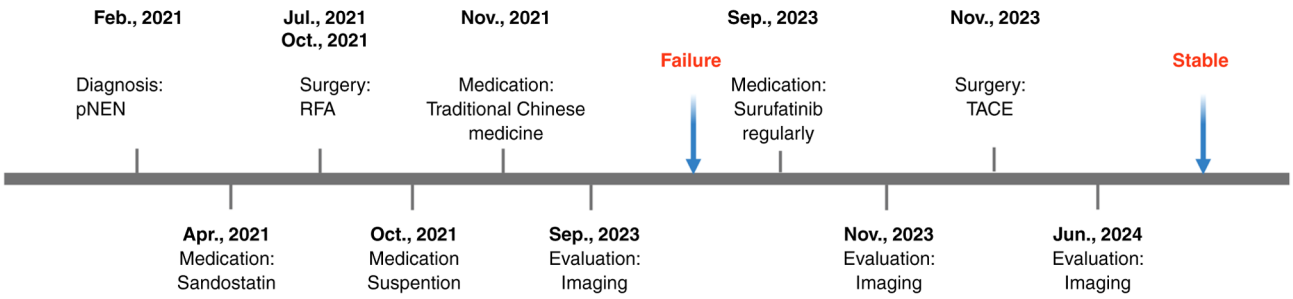

Figure 1. Timeline of the case report. pNEN, neuroendocrine neoplasm of the pancreas; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

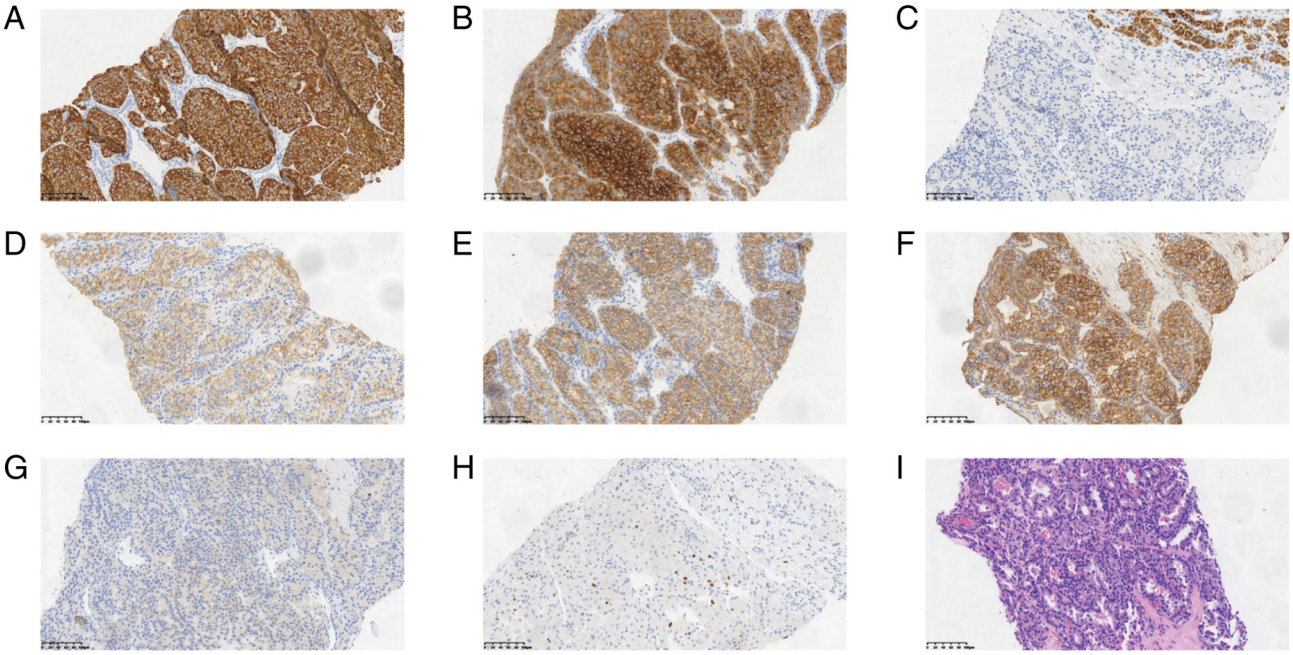

Figure 2. Immunohistochemistry and H&E staining of the pNEN. (A) CK19(+); (B) SYN(+); (C) HEP(-), strongly positive cells are normal hepatocytes adjacent to pNEN; (D) somatostatin receptor 2(+); (E) E-cadherin(+); (F) β-catenin(membrane +); (G) P504S(-); (H) Ki67(+ 10%). (I) Histopathological examination (routine H&E staining). Magnification, x200. H&E, hematoxylin and eosin.

Ki67 (cat. no. TA500265) (all Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.), and incubated at room temperature for 1-2 h. After washing, the sections were incubated with a suitable secondary antibody (horseradish-conjugated goat anti-rabbit/mouse IgG; diluted 1:200; cat. no. PV-8000; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.). Finally, the substrate solution DAB (cat. no. ZLI-9017; Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd.) was added, and the color development reaction was observed.

NSE detection. Fasting venous blood was collected and centrifuged at x1,170 g (25˚C for 10 min) to separate the serum. The level of NSE was then detected using the Chemiluminescent Immunoassay with the Roche Cobas e602 (both Roche Diagnostics GmbH), following the manufacturer's instructions.

Discussion

The complexity and heterogeneity of NENs pose numerous challenges in their treatment. Surgical management is the preferred option for patients with early-stage tumors and achieves satisfactory outcomes (13,14); however, the prognosis of patients with advanced and metastatic pNEN remains suboptimal (15,16), with comprehensive treatment being the mainstay approach (1). The present case report provides valuable insights into the challenges and implications for the diagnosis and treatment of this specific subgroup of patients.

In the present study the patient was diagnosed with advanced pNEN with liver metastases. Notably, hepatic metastatic lesions pose a greater risk due to compression of abdominal organs compared with the primary tumor, and removing the primary tumor provides relatively minimal improvement in treatment effectiveness or survival time for the patient (11). The classification of neuroendocrine neoplasms (NENs) into functional and non-functional types is based on hormone secretion. In the present case, it was classified as non-functional. In addition, for G1/G2 non-functional pNENs, radical surgery should be pursued. If the tumor involves adjacent organs or tissues, radical resection of both the primary tumor and the affected organs or tissues is recommended. If the tumor is associated with liver metastases, the surgical plan should be based on the resectability of the primary tumor and the classification

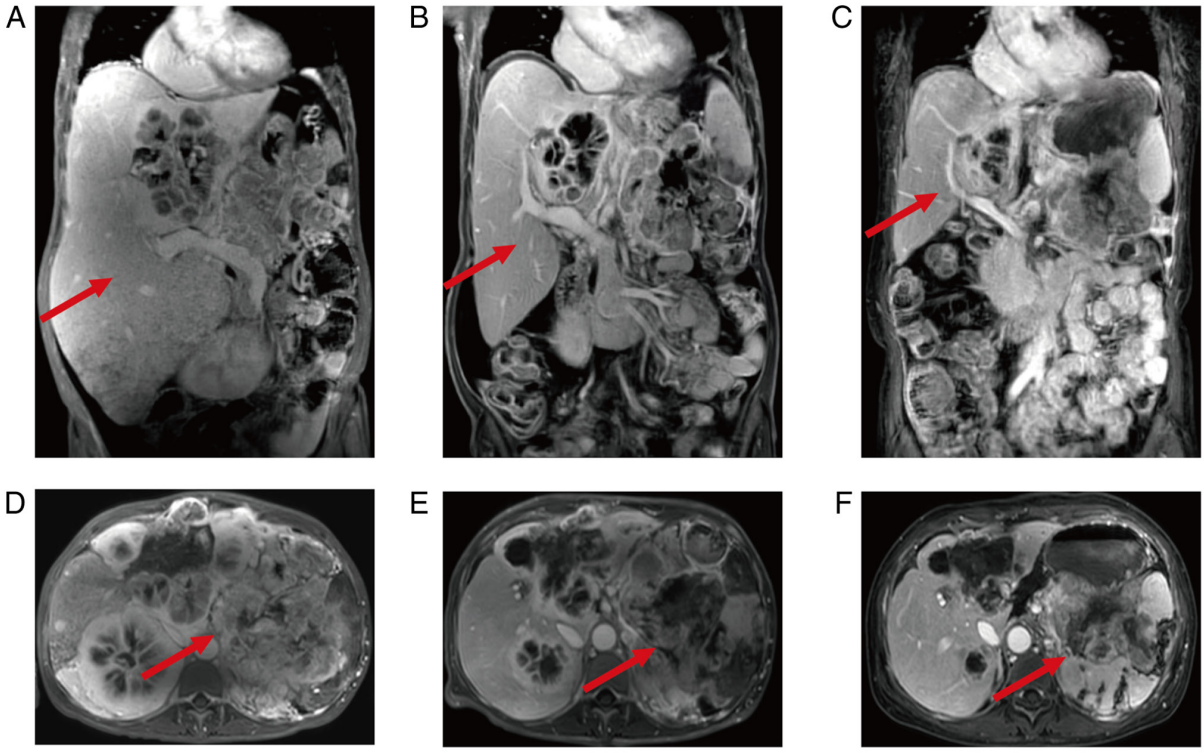

Figure 3. Magnetic resonance cholangiopancreatography dynamic enhancement imaging demonstrated tumor changes in the patient undergoing targeted therapy. (A, B and C) Coronal sections, with the liver location indicated by arrows. (D, E and F) Transverse sections, with the pancreatic location indicated by arrows. After the first [(B and E) November 2023] and second [(C and F) June 2024] rounds of targeted treatment, the size of lesions in the liver and pancreas were markedly decreased compared with that pre-treatment [(A and D) September 2023].

of the liver metastases (4). Generally, resection of the primary tumor helps improve symptoms, and liver metastases can also be managed through surgery combined with interventional treatments. Specifically, when both the primary and metastatic lesions are resectable, radical surgery should be attempted; if the primary tumor is resectable but resection of the metastases is difficult, effective debulking surgery (with ≥70% debulking) combined with interventional treatment for liver metastases is recommended. When metastases cannot be resected, resection of the primary tumor may offer some benefit, which requires a comprehensive evaluation of the primary tumor size, overall tumor burden and any complications from local compression (4). When the primary tumor cannot be resected but metastases can be, resection of the metastases alone is typically not recommended (17). Imaging evaluation revealed that the patient in the present study did not meet the criteria for curative resection of the primary tumor and metastatic lesions. Therefore, the initial treatment plan included multiple sessions of RFA combined with medical therapy to reduce tumor burden including the liver metastases and the primary tumor and alleviate symptoms, followed by a liver biopsy to confirm the pathological grade of the tumor.

The objectives of medical treatment for functional NENs (the pNEN in this case was non-functional) are to attenuate symptoms caused by hormone release and to delay tumor growth. Antitumor therapies for NENs include biological agents, targeted drugs, cytotoxic chemotherapies and immunotherapy. Systemic chemotherapy is typically not recommended as the first-line treatment for G1/G2 grade gastrointestinal neuroendocrine tumors (GI-NETs), and is only reserved for

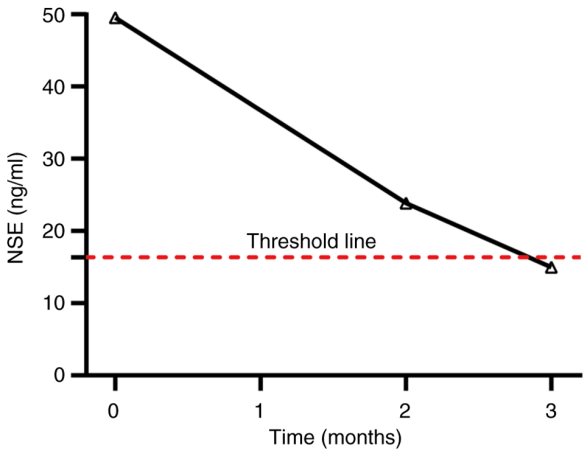

Figure 4. Changes in NSE levels in the patient undergoing targeted therapy. After 3 months of targeted therapy, NSE levels decreased to within the reference range (0-17.5 ng/ml). NSE, neuron-specific enolase.

cases where other therapeutic approaches, including biologics, tyrosine kinase inhibitors, and peptide receptor radionuclide therapy (PRRT), have failed (1).

In recent years, immune checkpoint inhibitors (ICIs), particularly those targeting PD-1/PD-L1, have shown clinical efficacy across various types of cancer (18-20). However, their use in NENs remains at an exploratory stage (21). A systematic review evaluating the role of ICIs both as single agents and in combination in NENs reported a pooled overall response rate (ORR) and a disease control rate of 10 and 42%, respectively.

In addition, the median PFS was 4.1 months, while the median OS was 11 months (21). Notably, the ORRs from existing clinical trials of ICIs (21) are generally low.

PRRT involves labeling radioactive isotopes that emit α or β particles onto tumor-targeting peptides (22). The results of a phase III (NETTER-1) trial indicated that the estimated PFS at 20 months was 65.2% in patients with advanced midgut neuroendocrine tumors treated with the PRRT 177 Lu-DOTATATE and 10.8% in the same patients treated with octreotide (23). However, due to the heterogeneity and complexity of pNENs, the effectiveness of PRRT warrants further prospective clinical studies to validate its efficacy (24).

Extensively used SSAs, such as long-acting octreotide and lanreotide autogels, exert anti-proliferative and pro-apoptotic effects by binding to SSTR (25). Notably, the PROMID phase III clinical trial corroborated the efficacy of SSAs in delaying tumor progression (26). Clinical research on metastatic patients demonstrated that, in pNEN, lanreotide significantly prolonged PFS compared with the placebo, with a median PFS of 18.0 months versus not reached, and the estimated rates of PFS at 24 months were 65.1 and 33.0% in the lanreotide group and placebo group, respectively (27). The European Society for Medical Oncology consensus recommends SSAs as the first-line treatment option for advanced GEP-NETs and NENs with unknown primary sites that are SSTR-positive, have slow growth rates and a Ki-67 proliferation index of 10% (1). Therefore, SSAs were administered in the present case to further prevent tumor growth, given the stable postoperative condition of the patient. The patient received seven cycles of an SSA (Sandostatin LAR 20 mg, q4w) from April 2021 to October 2021, and self-discontinued Sandostatin LAR due to dizziness, a known adverse reaction associated with SSAs, outside the hospital setting. According to the Chinese Society of Clinical Oncology (CSCO) guidelines, long-acting SSAs include long-acting octreotide (Sandostatin LAR) and lanreotide (28). However, lanreotide was only officially approved for the treatment of GI-NETs and pNENs in China on March 29, 2024. Prior to this, due to the drug availability, it could not be considered a first-line option.

The present patient was medicated with Sandostatin. After 3 months of recovery and follow-up, imaging assessments revealed that the disease remained stable, and the patient underwent two sessions of percutaneous RFA targeting the hepatic lesions in July and October 2021. RFA is a local ablative technique used to treat liver metastases from NENs in patients who are not eligible for curative surgical resection (29) by delivering high-frequency electrical currents to generate heat, which destroys tumor tissue. This procedure can assist in managing the size and number of liver metastases, alleviate symptoms and potentially extend survival (30). For patients with a limited number of liver metastases, hepatic resection or ablative therapies, such as RFA or microwave ablation, may be promptly performed in conjunction with systemic treatments (1). Notably, a systematic review and meta-analysis involving 292 patients with pNENs documented a pooled complete radiological response of 87.1% and a pooled partial response of 11.4% (30).

In the present study, the patient developed ascites and generalized itching 2 years after the last RFA, attributed to portal hypertension from liver metastasis and malignant effusion. In September 2023, the patient underwent MRCP dynamic enhancement imaging, which revealed disease progression, with an increase in the range and number of pancreatic tail and liver lesions compared with in June 2022. The patient used traditional Chinese herbal medicine treatment between November 2021 to September 2023, which may not have effectively inhibited tumor progression. Despite earlier studies (31,32) reporting that Chinese herbal medicine can delay the progression of NENs, these were largely single-center studies with limited sample sizes. Therefore, the efficacy of traditional Chinese herbal medicine in the treatment of NENs requires further exploration.

To determine progression in the pathological grading of the tumor, a second biopsy is necessary; however, after thoroughly discussing the risks (including infection, bleeding, pain, tissue damage and the possibility of more serious complications) associated with a second biopsy with the MDT, the patient declined to undergo the procedure. Additionally, the patient experienced abdominal distension due to tumor progression, with compression-induced right kidney displacement leading to renal function abnormalities, rendering them unable to tolerate RFA.

Surufatinib is a small-molecule inhibitor targeting vascular endothelial growth factor receptor and fibroblast growth factor receptor 1 (33). The SANET-p phase III clinical trial revealed that the median PFS was 10.9 months in the surufatinib group and 3.7 months in a placebo group (34). In June 2021, the Chinese National Medical Products Administration approved surufatinib for the treatment of individuals with locally advanced or metastatic, progressive, non-functional, well-differentiated (G1, G2) pNENs, offering a novel treatment option for patients with NENs. Accordingly, the patient described in the present study was treated with surufatinib to diminish the tumor burden. According to the CSCO guidelines, everolimus and surufatinib are both recommended as optional medications (28). In the RADIANT-3 study, for the treatment of advanced pNENs, the median PFS for the everolimus group versus the placebo group was 11.0 versus 4.6 months ($P<0.01$) (35); for the surufatinib group versus the placebo group, it was 10.9 versus 3.7 months ($P=0.0011$). The ORR was 5% for the everolimus group and 19% for the surufatinib group (34). Due to the higher ORR of sunitinib, this medication was chosen for treatment in the present case.

Recently, a phase II clinical trial (TALENT) investigating the efficacy of lenvatinib for the treatment of advanced NENs highlighted an ORR of 29.9%, with 44.2% in pancreatic neuroendocrine tumors and 16.4% in gastrointestinal neuroendocrine tumors at 23 months. Furthermore, the median (range) duration of response was 19.9 (8.4-30.8) and 33.9 (10.6-38.3) months in the panNET and GI-NET groups, respectively. The median PFS was 15.7 months (27). Lenvatinib has demonstrated the highest ORR among targeted therapies for GEP-NETs to date.

A total of 1 month after initiating treatment with surufatinib, MRCP imaging indicated that the tumor was stable. In November 2023, the patient underwent TACE, taking into account the high tumor burden. Local treatment of unresectable liver metastases is crucial, and various methods can be adopted, encompassing transcatheter arterial embolization (TAE), TACE and transarterial radioembolization (TARE) through the hepatic artery (36). Considering that the majority

of the blood supply of NEN liver metastases (NENLMs) originates from the hepatic artery, the hepatic artery approach is regarded as an effective treatment for whole-liver involvement. In a previous study, the median PFS and OS were 18.4 and 40.7 months, respectively, for patients with NENs who underwent liver embolization (37). According to another study, the median survival time of patients with liver metastases secondary to NENs who underwent TARE was 28 months, with 1-, 2- and 3-year survival rates of 72.5, 57 and 45%, respectively (38). Overall, multiple sessions of interventional therapy are recommended for patients with a tumor burden exceeding 50% to minimize the risk of complications (1).

To date, studies have established that the efficacy between TAE and TACE is comparable (39). Drug-eluting beads (used in TAE and TACE) used in patients with NENLM can significantly increase the risk of hepatic and biliary damage, and increase the risk of hepatic abscess by 6.6 times (40); therefore, they are not recommended for use in patients with NENLM.

There are limitations to the present study. The first limitation is regarding the methods used to monitor the conditions of the patient. We encourage patients to undergo any nuclear imaging examinations, since they provide detailed functional, metabolic and molecular information about the lesions, including very small lesions. However, due to the high cost of 18F-PET-CT and its exclusion from medical insurance coverage in China, the patient did not undergo this examination. Other radiotracer PET-CT scans are not widely available in most hospitals in China; therefore, the patient did not receive any nuclear imaging examinations. Second, the level of SSTR expression may be of guiding significance for the applicability and efficacy of PRRT. Currently, since PRRT is not offered at our institution or nearby medical facilities, SSTR testing was not performed for the present patient. Third, NENs exhibit high spatiotemporal heterogeneity, with potential variability in metastases at different sites and times. Therefore, the pathological characteristics of lesions in the advanced stage may change, thus affecting the choice of treatment. It is therefore advisable to perform a second biopsy; however, the patient in the present case report did not undergo a secondary biopsy due to the risk of puncture. Additionally, the potential interference of the traditional Chinese herbal medicine with the patient outcomes cannot be overlooked.

Despite challenges in selecting treatments for patients with advanced pNEN, it is vital to conduct a comprehensive analysis of factors, such as tumor location, functional status, differentiation level, proliferation index, SSTR expression, tumor burden and disease progression, to formulate the most appropriate treatment schedule for each patient. In the present case report, a patient with advanced multiple metastatic pNEN was successfully managed via multiple sessions of RFA, TAE and targeted therapy. The present case emphasizes the role of tailored treatment strategies considering patient comorbidities and tumor biology, and the significance of secondary puncture biopsy despite the high risk involved, which may provide survival benefits for patients with advanced or metastatic pNEN.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LZ contributed to writing the original draft, investigation and methodology. XC was responsible for conceptualization, investigation, methodology, generated figures, and writing, reviewing and editing the manuscript. HoZ contributed to investigation, obtaining resources and data validation. HaZ was involved in investigation, obtaining resources and data validation. WD also participated in investigation, obtaining resources and data validation. ZM handled conceptualization, investigation, methodology, funding acquisition, supervision, and writing, reviewing and editing the manuscript. ZM and XC confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The patient provided written informed consent to participate.

Patient consent for publication

The patient provided written informed consent for publication of this report and the associated images.

Competing interests

The authors declare that they have no competing interests.

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