

## Case Report

# Primary perihilar bile duct neuroendocrine tumor: a case report and review of the literature

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**Abstract:** Neuroendocrine tumors represent a rare neoplastic entity, with even rarer occurrences within the biliary tract system. The pathogenesis of such conditions remains enigmatic. Clinical manifestations and radiological evaluations exhibit limited specificity, rendering preoperative diagnoses challenging. As of now, definitive therapeutic modalities remain elusive. Surgical excision stands as the paramount approach for managing biliary neuroendocrine tumors. A thorough preoperative assessment should precede the formulation of a judicious surgical strategy. Postoperative targeted adjuvant therapies hold promise in enhancing therapeutic efficacy and retarding tumor recurrence. This article chronicles a case study detailing a neuroendocrine tumor's diagnostic and treatment course within the perihilar bile duct. Integrating pertinent literature, it encapsulates the clinical attributes and diagnostic and therapeutic advancements in biliary neuroendocrine tumors. The aspiration is to augment awareness of this category of ailments, mitigating the occurrence of both missed and erroneous diagnoses, and furnishing a reference for forthcoming clinical endeavors.

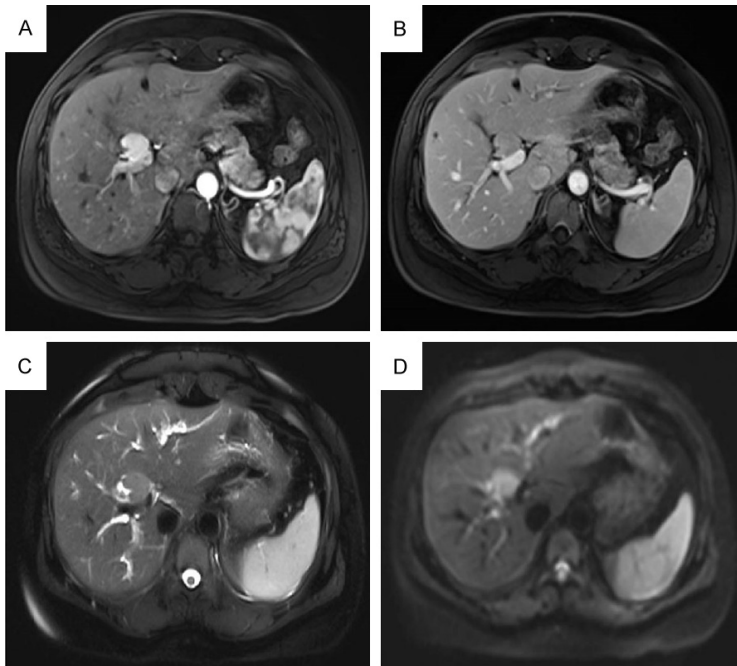
**Keywords:** Bile duct tumor, neuroendocrine neoplasm, perihilar bile duct, PET/CT, immunohistochemical staining

### Introduction

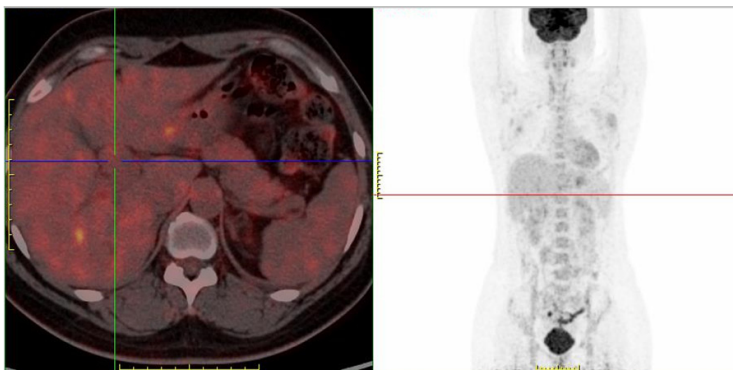
Neuroendocrine neoplasms (NENs), originating from neuroendocrine cells, manifest remarkable heterogeneity. Given the scarcity of neuroendocrine cells within the biliary ducts, biliary neuroendocrine neoplasms (B-NENs) within the biliary tract system are profoundly uncommon, constituting merely 0.2%-2% of all gastrointestinal NENs [1-3]. Recently, we admitted a patient afflicted with a perihilar biliary tract tumor. Adhering to the diagnostic and therapeutic guidelines for perihilar cholangiocarcinoma, curative surgical excision was executed. Postoperative histopathological and immunohistochemical analyses confirmed a neuroendocrine tumor (NET) G2 classification. After the surgery, the patient underwent vigilant outpatient follow-up for twelve months, revealing an absence of tumor recurrence or metastasis. Presented herein is a comprehensive report detailing this clinical case.

### Case presentation

A 34-year-old female patient presented with a chief complaint of "icterus of the skin and mucous membranes with concomitant fever lasting 5 days" on April 29, 2022, at the First Affiliated Hospital of Weifang Medical University. The patient had a history of overall good health, with no prior psychological disorders or family history of hereditary ailments. She had not undergone any pertinent systemic diagnostics or treatments before her current visit. Serological assessments revealed hepatic function abnormalities: alanine aminotransferase (ALT) levels (183 U/L, normal range: 0-50 U/L), aspartate aminotransferase (AST) levels (60 U/L, normal range: 0-40 U/L), alkaline phosphatase (ALP) level (253 U/L, normal range: 45-125 U/L), gamma-glutamyltransferase (GGT) level (310 U/L, normal range: 4-60 U/L), total bilirubin (TBIL) level (151.2 umol/L, normal range: 0-23 umol/L), and direct bilirubin (D-BIL) level (111.1 umol/L, normal range: 0-8 umol/L).



**Figure 1.** During the arterial phase of the MRI, conspicuous hypervascularity was observed. The degree of lesion enhancement markedly surpasses that of the surrounding hepatic parenchyma (A); The enhancement magnitude of the tumor during the venous phase exhibited attenuation, closely approximating the signal intensity of the surrounding hepatic parenchyma (B); On T2-weighted imaging, the lesion exhibits a long T2 signal pattern, with the signal slightly elevated compared to the surrounding hepatic parenchyma (C); During the diffusion phase, the lesion demonstrates restricted diffusion, with a signal higher than that of the surrounding hepatic parenchyma (D). Magnetic resonance imaging, MRI.



**Figure 2.** Preoperative <sup>18</sup>F-FDG PET/CT imaging revealed perihilar nodules with slightly increased metabolism.

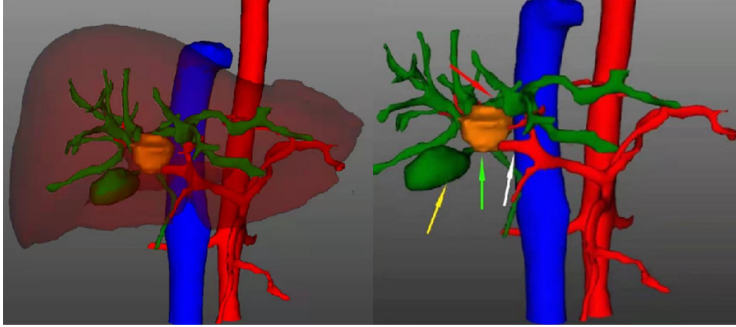
Tumor markers and immunological parameters displayed no discernible anomalies. Abdominal contrast-enhanced MRI findings indicated a nodular lesion in the perihilar region, measuring approximately 2.6 cm × 2.5 cm. The lesion exhibited slightly prolonged T1 and T2 signal

characteristics with restricted diffusion. Significant arterial enhancement was observed during the contrast-enhanced arterial phase, while enhancement decreased during the venous phase (**Figure 1**). <sup>18</sup>F-FDG PET/CT imaging depicted a moderately dense, circular lesion in the perihilar area, measuring about 3.1 cm × 2.6 cm. The lesion displayed clear demarcation from the surrounding hepatic parenchyma and encircled adjacent intrahepatic bile ducts. Radioactive uptake was elevated, with a SUVmax of 3.6, not excluding malignancy (**Figure 2**). The preoperative diagnosis was suggestive of a perihilar bile duct tumor (not excluding perihilar cholangiocarcinoma).

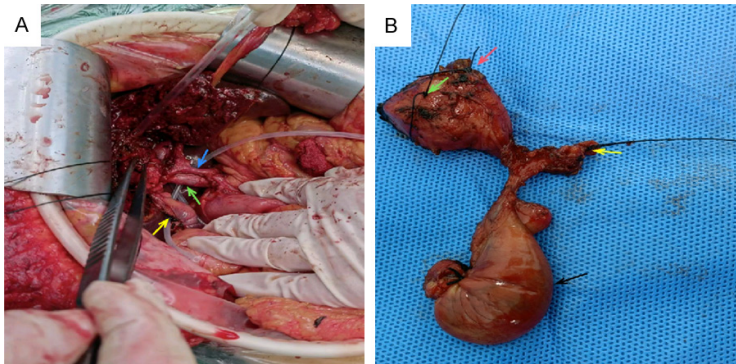
Referring to the Bismuth-Corlette classification for perihilar cholangiocarcinoma, based on radiological assessments, the preliminary determination of the lesion places it within the IIIA category. Before surgery, thorough discussions were held with the patient and her family. Given the indeterminate nature of the tumor and the possibility of malignant biliary neoplasm, the potential for hepatic malignancy could not be excluded. Considering the relatively smaller remnant liver volume after right hemihepatectomy, and with consent from the patient and family, a decision was made to perform resection of the perihilar bile duct tumor, cholecystectomy, and hepaticojejunostomy with a Roux-en-Y anastomosis to the jejunum. Preoperative planning included meticulous three-

dimensional reconstructions (**Figure 3**). The surgical procedure unfolded as follows: Palpation of the perihilar bile duct revealed a firm mass measuring approximately 3.0 cm × 3.0 cm. Resection encompassed segments S4b and S5 of the liver, with a 5 mm distance

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**Figure 3.** The three-dimensional model was meticulously crafted through preoperative CT imaging. The neoplasm is indicated by the green arrow, the gallbladder by the yellow arrow, the right hepatic artery by the white arrow, and the left hepatic duct by the red arrow.



**Figure 4.** The comprehensive excision alongside meticulous dissection of regional lymph nodes surrounding the hilum was performed for the masses afflicting the bile ducts (The blue arrow designates the hepatic artery, the green arrow signifies the portal vein, the yellow arrow denotes the gallbladder, while the forceps are directed towards the tumor within the hilum bile duct) (A). Surgical resection of perihilar bile duct masses (The left hepatic duct is delineated by the red arrow, the right hepatic duct by the green arrow, the distal bile duct by the yellow arrow, and the gallbladder by the black arrow) (B).

from the tumor's edge. The left hepatic duct and the right anterior and posterior hepatic ducts were individually ligated at a 5 mm margin from the tumor. A comprehensive lymph node dissection was conducted at the perihilar (**Figure 4**). Rapid intraoperative pathological analysis indicated residual tumor components at the cut end of the right hepatic duct. To ensure clear margins, a 5 mm expansion of the resection was performed at the proximal end of the right hepatic duct, with subsequent rapid pathological analysis confirming negative margins. Ultimately, a hepaticojejunostomy with a Roux-en-Y anastomosis was meticulously conducted.

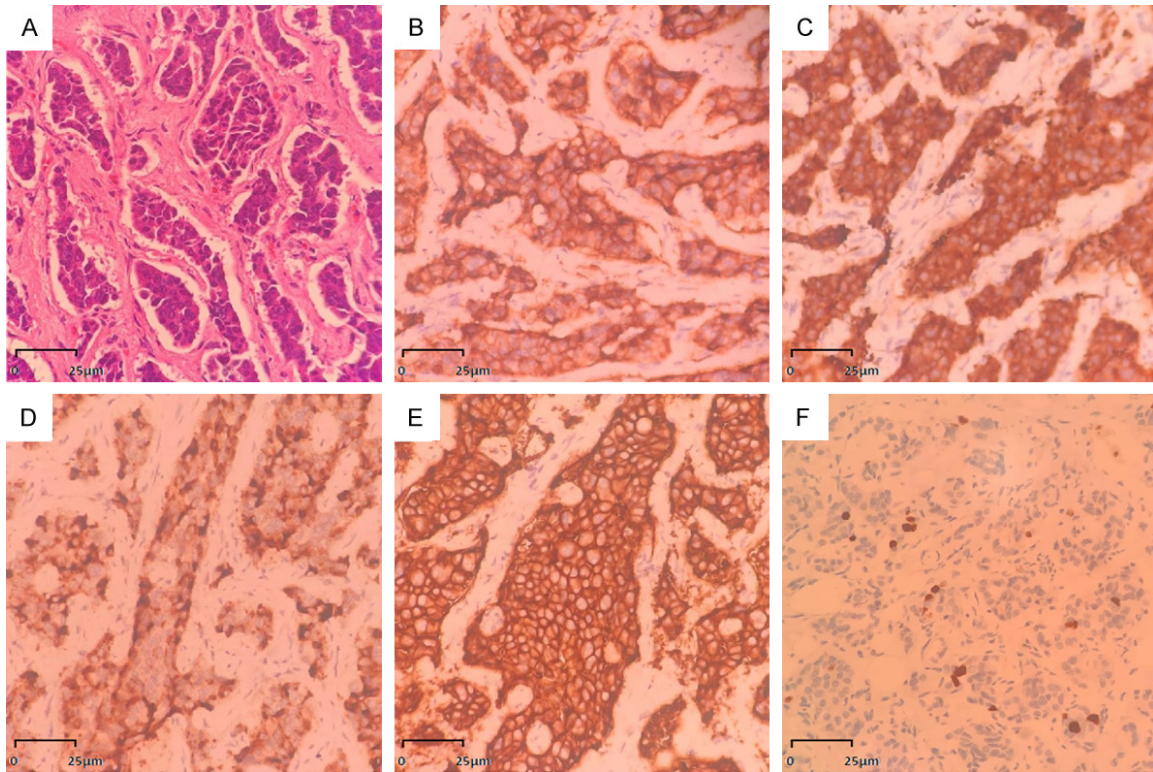
The postoperative pathological findings unveiled the nature of the lesion as a neuroendo-

crine tumor (NET, Grade 2), situated in the perihilar bile duct. The tumor measured 3.3 cm × 2.5 cm × 2.2 cm and exhibited infiltration across all layers of the bile duct wall, along with the involvement of the surrounding adipose tissue. Intra-vascular tumor emboli were identified, along with encroachment upon nerves and serosal surfaces (+). The immunohistochemical analysis yielded the following results: Broad-spectrum cytokeratin (CKs) (+), synaptophysin (Syn) (+), chromogranin A (CgA) (+), Somatostatin receptor 2 (SSTR2) (+), CK7 (+), CD56 (+), partial CK19 (+), occasional CK20 in isolated cells (+), partial CDX2 (+), CEA (-), and a Ki-67 index of approximately 5% (**Figure 5**). On the 7th day post-surgery, the <sup>18</sup>F-SSTR PET/CT scan was performed, ruling out the possibility of metastatic lesions. The patient was discharged successfully on the 10th day post-surgery. Following discharge, the patient's postoperative ALT and TBIL levels gradually returned to within the normal range (**Figure 6**). Close monitoring over 12 months revealed no signs of recurrence or metastasis.

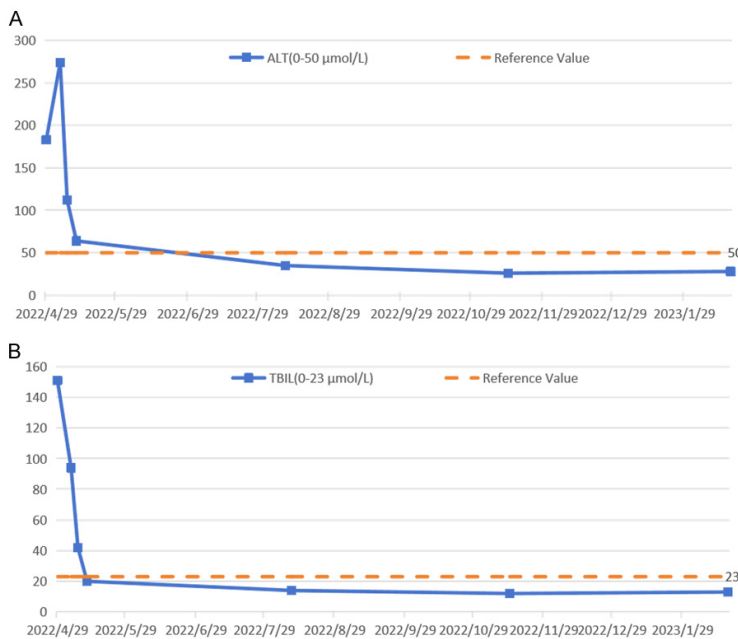
### Discussion

Neuroendocrine neoplasms (NENs) manifest as heterogeneous growths originating from peptidergic neurons and neuroendocrine cells. These tumors can secrete an array of peptide hormones and biologically active amines. Characterized by sluggish proliferation, certain instances of malignancy are evident. Given the absence of neuroendocrine cells within the biliary tract, neuroendocrine neoplasms within the biliary system (B-NENs) stand as exceedingly infrequent occurrences, constituting merely 0.2% to 2% of all gastrointestinal NENs, with the majority lacking endocrine functionality [1-3]. Predominantly, B-NENs arise within the hepatic duct and distal common bile duct (19.2%), followed by the middle portion of the

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**Figure 5.** Pathological images and immunohistochemistry staining were conducted as follows: (Magnification: 10 × 40). Tumor tissue sections stained (H&E) depicting adenoid or nest-like arrangements of tumor cells with infiltrative growth. The nuclei are rounded, eosinophilic, and display visible mitotic figures (A); CD56 immunohistochemical staining exhibited diffuse positivity (B); Syn immunohistochemical staining displayed diffuse positivity (C); CgA immunohistochemical staining showed diffuse positivity (D); SSTR2 immunohistochemical staining demonstrated diffuse positivity (E); Ki-67 sporadically displayed positivity with a positive index of approximately 5% (F).



**Figure 6.** The alteration trends of ALT (A) and TBIL (B) before and after the surgical procedure.

common bile duct (17.9%), the cystic duct (16.7%), and the proximal common bile duct (11.5%) [4]. Morphologically, they present as intraductal, nodular, or periductal infiltrative subtypes [5]. Following the most recent World Health Organization (WHO) classification from 2019, these tumors are categorized as highly differentiated neuroendocrine tumors (NETs), poorly differentiated and aggressively invasive neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs). The NETs are subcategorized based on nuclear division features and the Ki-67 index: G1 (Ki-67 index < 3% or mitotic rate < 2 per 2 mm<sup>2</sup>), G2 (Ki-67

index 3-20% or mitotic rate 2-20 per 2 mm<sup>2</sup>), and G3 (Ki-67 index > 20% or mitotic rate > 20 per 2 mm<sup>2</sup>). NECs (Ki-67 index > 20% or mitotic rate > 20 per 2 mm<sup>2</sup>) are classified into large-cell and small-cell types. Mi-NENs involve tumors wherein both neuroendocrine and non-neuroendocrine components account for more than 30% of the neoplasm [6]. An examination conducted by Zhou et al [7] at Peking Union Medical College Hospital scrutinized 446 B-NENs patients from the Surveillance, Epidemiology, and End Results (SEER) database. Their statistical analysis revealed that 39.2% were well-differentiated NETs and 58.1% were poorly differentiated NECs. Conversely, Zheng et al [8] at Peking Union Medical College Hospital conducted a study involving 28 Chinese B-NENs cases, indicating that high-grade G1 and G2 NETs constituted merely 14.2% of all cases. This proportion closely resembles the 14.3% reported in a Korean study [9], suggesting potential racial variations between Western and Asian populations. In this specific case, the patient's tumor was located within the hepatic duct, extending into the right hepatic duct. Referencing the Bismuth-Corlette classification, it is categorized as type IIIA, and pathologically identified as NET G2 stage. Clinically exceptional, we extensively reviewed all relevant literature on PubMed and have yet to encounter detailed case reports of this specific type.

The etiology of biliary neuroendocrine neoplasms (B-NENs) remains elusive. Certain investigations propose an association with chronic inflammation induced by cholelithiasis and congenital biliary anomalies. Prolonged chronic inflammation is believed to progressively transform biliary epithelial cells into NENs [10]. Clinically, jaundice predominates, often accompanied by pruritus and epigastric pain, with only a minority of patients displaying neuroendocrine symptoms [3, 11]. Due to the lack of specific clinical manifestations, preoperative diagnosis is exceedingly challenging. Since the first reported case in 1959, a mere 5.1% of patients have achieved preoperative definitive diagnoses [3]. B-NENs frequently exhibit distinctive MRI characteristics: on T1-weighted images, tumor signals are lower than those of hepatic parenchyma, while on T2-weighted images, signals tend to surpass hepatic parenchymal signals. During the diffu-

sion phase, tumor signals surpass those of the liver parenchyma [5]. In this case, the patient's MRI demonstrated hypervascularity in the arterial phase, with marked enhancement in the arterial phase and decreased enhancement in the venous phase (**Figure 1**). B-NENs manifest abundant arterial-phase vascularity on magnetic resonance imaging, offering a certain degree of distinction from biliary adenocarcinoma. Frequently employed tumor markers in clinical practice often exhibit no significant elevation. In this instance, the patient's preoperative tumor markers were within the normal range, which corroborates this standpoint. However, for patients with B-NET G3 stage and B-NECs, CA19-9 and CA125 levels often exceeded normal levels [12]. Serum CgA, Syn, and neuron-specific enolase (NSE) demonstrate a relatively high positivity rate in NENs, providing a certain diagnostic value. We posit that in patients displaying symptoms of obstructive jaundice combined with carcinoid syndrome, refinement of the aforementioned laboratory assays, coupled with imaging characteristics, holds promise for enhancing preoperative diagnostic accuracy.

Preoperatively, obtaining relatively precise histopathological diagnoses can be achieved through biliary brush cytology specimens. Techniques such as endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) might contribute to preoperative diagnoses. However, due to the frequent submucosal location of the tumors, cytological brush sampling exhibits a notable false-negative rate. Hence, the definitive diagnosis of the majority of B-NENs relies on postoperative histopathology and immunohistochemical findings [13].

Somatostatin receptors (SSTR), which reside upon the surfaces of NEN cells, exhibit particularly pronounced expression in NET G1 and G2 subclasses [14, 15]. Employing SSTR PET/CT imaging stands as a sophisticated and NEN-specific diagnostic modality, characterized by a sensitivity and positive predictive value of 81%, and a specificity and negative predictive value of 90%. This technique proves valuable in locating primary foci, facilitating staging, and guiding treatment stratagems [16]. For individuals

under suspicion of NEN pathology, the augmentation of  $^{18}\text{F}$ -ALF-NOTA-SSTR or  $^{68}\text{Ga}$ -DOTA-SSTR PET/CT imaging can expound upon the primary site, facilitating staging to serve as a foundation for subsequent therapeutic decisions. Regrettably, in this presented instance, the patient did not undergo preoperative SSTR PET/CT imaging. Postoperatively, we conducted an enhanced  $^{18}\text{F}$ -ALF-NOTA-SSTR PET/CT, dispelling the possibility of metastatic lesions, thereby culminating in the definite diagnosis of primary B-NET.

B-NET harbors a malignancy potential, and radical surgery excision stands as the paramount therapeutic strategy for non-metastasized tumors. The surgical approach adheres to the treatment principles applicable to biliary tract cancer, guided by considerations encompassing the lesion's preoperative radiological localization, regional vascular involvement, lymphatic infiltration, and extent of dissemination. The surgical scope entails resection of the affected bile duct in conjunction with regional lymph node clearance while ensuring negative surgical margins during the procedure. Perihilar B-NETs should be managed akin to perihilar cholangiocarcinoma, involving intraoperative rapid pathological assessment of surgical margins to achieve R0 resection. Conforming to tumor location, curative resection is executed concomitantly with regional lymph node dissection, which can maximize patient prognosis. In cases with concomitant liver metastasis, concerted efforts are directed toward excising the primary focus alongside hepatic metastatic lesions. For patients with distant metastasis where curative resection is unfeasible, tumor reduction surgery can moderately impede tumor progression and heighten survival rates [17]. Preoperative evaluation and tailored surgical planning are imperative for perihilar-associated B-NETs.

The necessity of adjuvant therapy for patients following curative resection remains a subject of substantial contention. We posit that patients presenting with high-risk recurrence factors warrant consideration for postoperative prophylactic utilization of prolonged octreotide. In instances where surgical excision proves unattainable or R0 resection remains unrealized among advanced or metastatic perihilar-associated B-NET patients, a tailored approach to adjuvant therapy aligned with the guidelines

for gastrointestinal or pancreatic NETs could be adopted to retard tumor progression. Somatostatin analog octreotide also emerges as a frontline therapeutic modality for patients with NET G1 and G2 (Ki-67 index < 10%) in advanced stages [18, 19]. Peptide receptor radionuclide therapy (PRRT), involving the substitution of imaging isotopes with therapeutic isotopes, directly targeting tumor cells through the connection of radioactive isotopes to somatostatin analogs (SSAs), has witnessed advancement in recent years. The radioactive isotopes  $^{111}\text{In}$ ,  $^{90}\text{Y}$ ,  $^{68}\text{Ga}$ , and  $^{177}\text{Lu}$  have successively been employed in PRRT for NETs. In January 2018, the U.S. Food and Drug Administration (FDA) recommended  $^{177}\text{Lu}$ -DOTATATE therapy for SSTR-positive NET patients (earlier approved in Europe in September 2017) [20]. Interferon shares similar antitumor properties with somatostatin analogs. When resistance to somatostatin analogs develops, interferon treatment may be contemplated, albeit accompanied by notable adverse reactions and limited tolerability [21]. Presently, there exists no unified chemotherapeutic regimen for B-NETs. Currently, chemotherapy approaches for G1 and G2 stage pancreatic NETs encompass alkylating agents (e.g., streptozotocin, temozolomide), used individually or in conjunction with antimetabolites (5-fluorouracil, capecitabine). These regimens have demonstrated relatively favorable therapeutic outcomes [22].

Targeted therapy commonly serves as the second or third-line treatment paradigm for NENs. Numerous investigational agents with targeted mechanisms are currently under scrutiny; however, they rarely progress to the advanced stage of phase III clinical trials. Noteworthy among these agents are sunitinib, everolimus, surufatinib, and lenvatinib, each sequentially exhibiting a discernible degree of therapeutic efficacy within the realm of gastrointestinal and pancreatic NENs [23]. Regrettably, reports pertaining to targeted therapeutic interventions for B-NENs remain conspicuously scarce. In recent epochs, the domain of immunotherapy has witnessed a gradual surge in its utilization. Immune checkpoint inhibitors directed against programmed cell death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) have demonstrated commendable clinical effectiveness across an array of tumor types. However, their application within the context of NENs continues to dwell within the exploratory clini-

cal phase. The aggregate efficacy rate witnessed in the current body of clinical trial results remains notably modest. Consequently, immunotherapy does not garner endorsement as a standard modality for NEN treatment. For individuals afflicted by metastatic NENs who persistently advance despite undergoing standardized multimodal therapies, the contemplation of embarking upon immunotherapeutic interventions emerges as an avenue worth exploring.

The prognosis of B-NEN is influenced by a multitude of factors. Approximately one-third of patients present with metastasis at the time of diagnosis. The 5-year survival rate spans from 60% to 100%. For patients with B-NEC, about 40% to 50% exhibit metastasis at diagnosis, resulting in an exceedingly low 5-year survival rate [24]. Noteworthy prognostic determinants encompass age surpassing 65 years, absence of curative resection, advanced SEER staging, tumor size (> 2 cm), and the presence of poorly differentiated pathology (NEC). These elements collectively contribute as pivotal factors influencing patient prognosis [7].

### Conclusion

In light of the aforementioned exposition, B-NENs stand as an exceptionally uncommon occurrence within the clinical realm. The paucity of distinct clinical symptoms, specific laboratory markers, and imaging manifestations renders the task of preoperative diagnosis notably intricate. We posit that a comprehensive therapeutic approach centered around surgery holds the potential to bestow favorable long-term prognostic outcomes upon patients grappling with B-NENs. The formulation of surgical strategies should encompass a holistic consideration of the tumor's functional attributes, dimensions, location, resectability, staging, pathological classification, and grading, while meticulously evaluating the surgical risks and benefits. Presently, our comprehension of the etiopathogenesis, disease progression, and biological characteristics of biliary neuroendocrine tumors remains somewhat limited, underscored by a dearth of genetic and molecular-level exploration. In the future landscape, targeted therapy and immunotherapy may conceivably emerge as novel trajectories in the treatment of NENs.

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Informed consent to participate in this study was obtained from this patient.

### Disclosure of conflict of interest

None.

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