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Chinese expert consensus on multidisciplinary diagnosis and treatment of pancreatic neuroendocrine liver metastases

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Abstract

Many management strategies are available for pancreatic neuroendocrine neoplasms with liver metastases. However, a lack of biological, molecular, and genomic information and an absence of data from rigorous trials limit the validity of these strategies. This review presents the viewpoints from an international conference consisting of several expert working groups. The working groups reviewed a series of questions of particular interest to clinicians taking care of patients with pancreatic neuroendocrine neoplasms with liver metastases by reviewing the existing management strategies and literature, evaluating the evidence on which management decisions were based, developing internationally acceptable recommendations for clinical practice, and making recommendations for clinical and research endeavors. The review for each question will be followed by recommendations from the panel.

Keywords: pancreatic neuroendocrine neoplasms, liver metastases, clinical diagnosis, treatment

Introduction

Pancreatic neuroendocrine neoplasms (pNENs), especially nonfunctional pancreatic NENs, have a low rate of early diagnosis, and patients are often diagnosed with metastatic disease on their first visit. The liver is the most frequent site for distant metastasis of pNENs, with over 60%[1] of patients presenting with liver metastases at initial diagnosis. Liver metastasis is also the most important adverse prognostic factor, significantly lowering the 5-year survival rate.[2–5]

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Currently, many clinical guidelines or expert consensus have provided regimens for diagnosis and treatments for pNENs patients with liver metastases. For example, the ENENTS guidelines classify liver metastases into 3 types with distinct comprehensive treatment strategies.[6] In general, surgery is the only cure for pNENs patients with liver metastases, and resection of primary and distal sites can significantly improve the overall survival of patients. For patients unsuitable for surgical resection, systemic and topical treatments including somatostatin analogues (SSAs), therapy with cytotoxic drugs, targeted therapy, interventional therapy, and peptide receptor radionuclide therapy (PRRT) may improve prognosis and survival.[7]

In recent years, along with the increased awareness of pNENs, the rapid accumulation of experience in diagnosis and treatment, and the development of clinical studies, new evidence-based knowledge has been collected in this field, which requires up-to-date summaries of recommendations. Furthermore, pNENs, especially those with liver metastases, are highly heterogeneous,[8] thus many uncertainties remain in its diagnostic imaging, pathological diagnosis, and therapeutics, implying a lack of consensus to guide clinical treatment.

In view of the above, experts and scholars in related fields developed this consensus statement based on evidence-based medicine, combined with clinical practice and exploration of the multidisciplinary comprehensive treatment model, aiming to provide a basis and develop a strategy for the diagnosis and treatment of pNENs with liver metastases, in line with China's national conditions.

Methods

A list of topics related to the management of pNENs with liver metastases of particular interest to clinicians was assembled. Many of these topics are areas of controversy or have limited available data. Thirty clinicians (2 radiologists, 3 nuclear medicine experts, 6 pathology experts, 1 endoscope expert, 10 surgical oncology experts, 8 oncology experts) notable for their experience in the management of patients with pNENs with liver metastases were invited to join the consensus. The draft questions were submitted to the group for suggestions and edits, and multiple-choice questionnaires were created. The recommendation for each question was filled out by participants and shared with all participants during the consensus conference.

Prior to the consensus conference, each participant was assigned 2 questions to thoroughly research, which includes identifying the most relevant literature and submitting it to the project library, as well as preparing a presentation for the group meeting. Research results for each question were presented at the conference, followed by a discussion of different viewpoints, to reach an expert consensus based on the most relevant findings from literature and experience. Subsequently, the consensus was edited by the first and senior authors, and distributed to the co-authors and 2 members of the medical group for independent review and approval.

1. What is the clinical application value of conventional or functional imaging examination in the diagnosis and treatment of pNENs with liver metastases?

Various treatments are available for pNENs with liver metastases, including surgery, systemic therapy (SSA, targeted and other drugs), PRRT therapy, interventional therapy, etc, whereas surgery is the only treatment with the possibility of radical cure. Conventional and functional imaging examinations are essential for the diagnosis, staging, resectability assessment, posttreatment efficacy assessment, and follow-up of the primary pancreatic lesions and metastatic lesions, which aids the selection of the appropriate treatments. We proposed the following 4 specific questions and evaluate them one by one, make final recommendations.

Specific questions:

1.1. Is multiphase-enhanced computed tomography (CT) the preferred examination for staging?

CT is widely used in clinical practice due to its wide range of applications, including good accessibility, large scanning range (brain-cervical-thorax-abdomen-pelvis), high speed, enhanced scanning, and multiple post-processing reconstruction functions. Hypervascular supply is a typical feature of pNETs, the average sensitivity and specificity of CT multiphase enhancement scans for the diagnosis of pNENs is 82% (67%–96%) and 96%, respectively, whereas the average sensitivity and specificity for the diagnosis of liver metastases is 84% (75%–100%) and 92% (83%–100%), respectively.[6] The CT 3D reconstruction-assisted technique can provide information on the proximity of the primary pancreatic focus to the blood vessels, as well as on intrahepatic vessels, bile ducts, and residual hepatic volume, to help guide treatment strategies for the primary pancreatic focus and liver metastases.[9]

1.2. Is multiphase-enhanced magnetic resonance imaging (MRI) the most used examination to evaluate the pancreas and the liver metastases?

MRI is comparable to CT in the overall diagnostic efficacy for pNENs with liver metastases. Multiphase contrast-enhanced MRI has an average sensitivity and specificity of 79% (54%–100%) and 100% for the diagnosis of pNENs, while the average sensitivity and specificity for the diagnosis of liver metastases are 75% (70%–80%) and 98%, respectively.[6] Due to its high resolution for soft tissue, MRI is superior to CT in examining the abdomen, bone, and brain, as well as specific lesions of the pancreas and liver metastases.[10] In addition, diffusion-weighted imaging (DWI) of MRI is an imaging technique that utilizes the diffusion of water molecules. Due to the narrowing of cellular gaps between tumor cells, the diffusion of water molecules is limited, which creates a signal contrast between the lesion and the surrounding normal tissue. Therefore, DWI allows for the detection of primary and metastatic lesions without contrast media administration. This technique is particularly important for patients not suitable for contrast injection.[6]

1.3. Is liver-specific contrast-enhanced MRI advantageous in the evaluation of liver metastases?

Hepatocellular phase imaging with liver-specific contrast agents offers the advantage of excellent lesion to liver contrast and high contrast-to-noise ratio. The successful use of MRI with hepatocellular-specific contrast agents for liver metastatic colorectal cancer has garnered great interest. And more and more studies have shown that MRI with liver cell-specific contrast agents can improve the detection rate of gastroenteropancreatic NENs (GEP-NEN) liver metastasis, liver-specific contrast-enhanced MRI has the advantage of higher sensitivity compared with conventional enhanced MRI.[11]

1.4. Functional imaging examination is only available in limited medical institutions. Which functional imaging examinations are routinely recommended for the clinical diagnosis of liver metastases of pNETs?

Approximately 60%–100% of NETs express somatostatin receptor (SSTR), of which 85% express SSTR2; hence, functional imaging using isotopically labeled somatostatin analogs has become a targeted examination for NETs. The current literature reports that ^{68}Ga-SSA-PET/CT has a sensitivity of 92% (64%–100%) and a specificity of 95% (83%–100%) for the diagnosis of NETs, a sensitivity of 92% and a specificity of 83% for the diagnosis of pancreatic and duodenal NETs,[12] and a sensitivity of 82%–100% and a specificity of 67%–100% for the diagnosis of liver metastases from low-grade NETs. ^{68}Ga-SSA-PET/CT can detect up to 67% of lesions not identified by CT or MRI, particularly helpful for the diagnosis and differential diagnosis of intra- and extrahepatic lesions. Currently it is difficult to diagnose liver metastases smaller than 5.0 mm with either conventional imaging or functional imaging, with a detection rate of less than 50%.[9]

As the Ki-67 index increases, the SSTR expression in tumors gradually decreases, whereas FDG metabolism increases and the usage of ^{68}Ga-SSA-PET/CT and ^{18}F-FDG-PET/CT changes

correspondingly. ^{18}F-FDG-PET/CT is more often used in intermediate to high-grade NETs (Ki-67 index > 10%, ie, some G2 and all G3). For both low-grade NETs and intermediate to high-grade NETs, patients with positive findings on ^{18}F-FDG-PET/CT tend to have a poorer prognosis.[6,12] Therefore, ^{68}Ga-SSA-PET/CT and ^{18}F-FDG-PET/CT may be complementary in the determination of prognosis and can help improve the sensitivity of lesion detection.[6,12]

In some special types of NETs, such as insulinomas, the positive rate of SSTR expression is only approximately 50%–60%; hence, the sensitivity of SSTR imaging in insulinoma diagnosis is low. Currently, the clinical diagnosis of insulinomas is highly reliant on GLP-1 receptor and DOPA receptor imaging, that is, ^{68}Ga-Exendin-4 and ^{18}F-DOPA, respectively, achieving a diagnostic accuracy of more than 90%.[13] As for routine imaging techniques, compared with conventional contrast-enhanced CT, pancreatic perfusion CT and DWI technique of MRI have higher sensitivity and specificity for the diagnosis of insulinoma. Furthermore, MRI can help determine the relationship between the tumor and the adjacent pancreatic duct.[14]

Expert consensus

Multiphasic contrast-enhanced abdominal/pelvic CT + chest CT with or without contrast is recommended as the preferred examination for the diagnosis and staging of pNENs with liver metastasis. Multiphasic contrast-enhanced MRI of the abdomen, especially with liver-specific contrast agents, may help detect more liver lesions. The overall diagnostic efficacy of functional imaging is better than conventional imaging, and the combined use of functional and conventional imaging can help diagnose and differentially diagnose intra- and extrahepatic lesions, as well as exclude extrahepatic metastases. Functional imaging techniques can be used alone or in combination depending on the therapeutic needs (initial diagnosis and staging, restaging, prognosis, etc). ^{68}Ga-SSA-PET/CT is indicated for NET G1, G2, and NET G3, whereas ^{18}F-FDG-PET/CT is indicated for intermediate to high-grade NETs (some G2 NETs, G3 NETs, and NECs). For patients with insulinomas, ^{68}Ga- Exendin-4 and ^{18}F-DOPA- PET/CT is often used. Combined imaging of ^{68}Ga-SSA-PET/ CT and ^{18}F-FDG-PET/CT is more helpful in detecting lesions, determining prognosis, and guiding treatment.

2. NENs are highly heterogeneous. In clinical practice, inconsistencies in pathological grades between primary and metastatic foci are common in patients with pNENs with liver metastases. In response to this situation, how should we carry out tumor grading to guide clinical treatment?

NENs have strong temporal and spatial heterogeneity among individuals and even between different tumor foci of the same individual. Previous studies have observed an increased Ki-67 index in liver metastases compared with the primary foci in 35.3%–63.0% of patients with metastatic gastroenteropancreatic NENs,[15–17] wherein 7.5%–39% showed a higher pathological grade in the liver metastases.[18–20] Zhang et al observed that in 103 patients with pancreatic neuroendocrine liver metastases, 23.3% had inconsistent pathological grades between liver metastases and the primary foci, of which 17.5% had a higher pathological grade in liver metastases.[21]

At present, there is no guideline recommendation for the above situation. Since pathological staging is closely related to prognosis, theoretically speaking, biopsies should be done in as many sites and as many times as possible, but this faces difficulties and uncertainties in clinical operation and implementation. Re-biopsy of the primary foci is generally not recommended when the metastases can provide adequate pathological information.[22] In the case of tumor progression, the literature recommends performing biopsies of both the primary and the metastatic foci. Re-biopsy can confirm the diagnosis and simultaneously help observe disease progression.[9] If the grade of the metastasis differs from the primary tumors, the higher grade is usually used as the basis for clinical treatment. However, it should be noted that when patients experience rapid clinical progression during treatment or when the clinical presentation is inconsistent with the pathological grade, a re-biopsy is recommended to determine the pathological changes and to guide clinical decisions. Regarding the selection of biopsy sites for multiple intrahepatic metastases, multi-site biopsy guided by combined ^{68}Ga-SSA-PET/CT and ^{18}F-FDG-PET/CT imaging is recommended when conditions allow.[23,24] Selecting sites with high ^{18}F glucose metabolism for puncture biopsy can better reflect foci with high tumor proliferative activity.

Expert consensus

In patients with pancreatic neuroendocrineliver metastases, if conditions permit, biopsies of both the primary and the metastatic foci are recommended to clarify the pathological diagnosis and observe pathological progressions. If the pathological grades of the primary and metastatic foci are inconsistent, it is recommended to guide clinical treatment based on the higher grade.

3. What are the clinical applications of molecular diagnosis in pNENs with liver metastases? Should O6-methylguanine-DNA methyltransferase (MGMT) detection be used to guide the treatment of pNENs patients with liver metastases?

Molecular diagnosis has significant clinical applications in pNENs patients with liver metastases. First, molecular diagnosis helps to identify the tumor's tissue of origin. For example, DAXX/ATRX gene mutations or protein expression defects suggest pancreatic origin, tumors expressing CK20/CDX2 suggest gastrointestinal origin, while TTF1 positivity suggests pulmonary or esophageal origins. Second, molecular diagnosis helps determine the degree of differentiation of the tumor. For example, tumors with TP53/RB1 mutations tend to be poorly differentiated NECs and SSTR2 is strongly expressed in well-differentiated NETs while not expressed or only weakly expressed in poorly differentiated NECs. Third, molecular diagnosis can guide treatment, selection of proper targeted therapy, and has prognostic value. Patients with SSTR2+ low-grade NENs have a good prognosis, and it is an essential marker for identifying patient populations with good responsiveness to somatostatin analog and PRRT. MGMT is an efficient DNA direct-repair enzyme that protects cell damage from alkylating agents. A recent study suggests that temozolomide (TMZ), an alkylating agent, showed good clinical efficacies in MGMT0/1+ tumors whereas clinical efficacies in MGMT2+/3+ tumors are limited. In patients with neuroendocrineneoplasms, RB1/BRCA2 mutations may predict responsiveness to platinum-based antineoplastics. Immunotherapies are highly effective in MSI/TMB-H/CPS-expressing tumors. Some rare mutations, such as NTRK and RET, are important in selecting specific targeted therapies.

MGMT is a "suicide repair enzyme" that removes the alkyl adduct at the O6 position of guanine, repairs DNA damage, and maintains tissue genomic stability. Recent studies have shown that MGMT is a potential biomarker in pNENs that helps to evaluate the therapeutic efficacy and prognosis of patients on TMZ-based regimens. TMZ is a chemotherapy drug used in patients with well- or moderately differentiated, unresectable, locally or distantly metastasized pNENs. Several retrospective and prospective studies of advanced pNENs have shown that TMZ alone or in combination with capecitabine, bevacizumab, or everolimus have an overall response rate (ORR) ranging from 33-70%[25–27] and progression-free survival (PFS) up to 18 months. Kulke et al showed that patients with MGMT loss (n = 21), detected by immunohistochemistry (IHC) testing, are more responsive to TMZ-based regimens.[28] A retrospective study conducted by Cives et al suggested that, in high-grade pNENs patients (n = 143), the expressional level of MGMT protein is not correlated to the sensitivity of TME/capecitabine combination chemotherapy.[29] A prospective phase II E2211 study

presented at the ASCO meeting (2022) suggested that MGMT expression status correlates with the treatment efficacy of TMZ, and MGMT0/1+ patients showed higher PFS and ORR.[30] A Chinese prospective randomized controlled phase II STEM trial recently published in *eClinicalMedicine* explored the relationship between MGMT status and the efficacy of TMZ combined with Tegafur-Gimeracil-Oteracil Potassium capsules in pNENs and extrapancreatic NENs. MGMT0/1+ patients showed longer PFS and higher OS under this treatment regimen compared with MGMT2/3+ patients,[31] suggesting that MGMT is a sensitive marker for predicting the efficacy of TMZ-based regimens. In conclusion, MGMT expression is a sensitive biomarker for predicting the effectiveness of TMZ-based regimens in NENs.

Expert consensus

Molecular diagnosis is necessary for diagnosing and treating pNENs with liver metastases. Molecular diagnosis helps to identify the tumor's tissue of origin and differentiation status, guide treatment, and estimate prognosis. IHC testing of MGMT guides clinicians in selecting TMZ-based regimens for pNENs patients with liver metastases since the TMZ-based regimen showed remarkable clinical efficacy in MGMT 0/1+ pNENs patients.

4. What are the pathological features for the differential diagnosis of G3 NETs (G3 NETs) and neuroendocrine carcinomas (NECs)?

The fifth edition of the World Health Organization (WHO) classification of gastrointestinal NENs divides NENs into NETs and NECs. NETs are further graded as G1, G2, and G3 based on proliferative activity. Although the proliferative activities of both G3 NETs and NECs are greater than 20%, their epidemiology, clinical manifestations, treatment strategies, and prognosis differ. Therefore, the pathological differential diagnosis of G3 NETs and NECs has significant clinical values.

The cellular morphology of G3 NETs is well-differentiated, has areas of G1/G2 NETs morphology, and is without necrosis or focal necrosis.[32,33] IHC staining of G3 NETs shows strong expressions of CK, Syn, CgA, CD56, and SSTR2, with higher expression of CgA than NECs. The expression of Ki-67 is uneven, with higher Ki-67 expression in some parts of the tissue. In molecular diagnosis, G3 NETs may have ATRX/DAXX or MEN1 mutations.[34]

In clinical practice, a pathological differential diagnosis of G3 NETs and NECs may be difficult due to limited biopsy volume, large areas of necrosis, technical errors during tissue handling, etc. Thus, the clinical history, clinical manifestation, results of serological tests, IHC staining of biomarkers, and genetic tests should all be considered while making the diagnosis.

Expert consensus

G3 NETs and NECs can be pathologically differentially diagnosed based on their morphological features, IHC biomarker testing, and molecular pathology. For cases that cannot be differentially diagnosed pathologically, an multi-disciplinary treatment (MDT) meeting should be arranged, and a comprehensive evaluation of the patient's clinical manifestation, radiological findings, and pathological findings should be conducted before making the final diagnosis and deciding on subsequent treatments.

5. What is the clinical applicative value of endoscopy in diagnosing and treating pNETs?

5.1. For patients of pNENs with liver metastasis, is ultrasound-guided percutaneous liver biopsy or endoscopic ultrasound-guided liver biopsy (EUS-LB) preferred to confirm the pathology of liver metastasis?

There has been an exceedingly rapid development in endoscopic ultrasonography, especially in advancing the aspiration needles, enabling more effective cytological testing (with EUS-FNA) and easier acquisition of histological specimens (with EUS-FNB). The potential advantages of EUS-LB include real-time imaging simultaneously with specimen acquisition, blood vessel circumvention, and increased accessibility to multiple liver regions (ie, left lobe, caudate lobe, and right lobe). EUS-LB exhibits improved imaging quality of small liver lesions and thus attracts increasing attention from domestic and international scholars. Meanwhile, EUS-FNA/B trans-gastric aspiration of liver cells requires a shorter route than the conventional percutaneous route and is rarely affected by the patient's body position and body habitus. At the same time, the quality of the liver tissue samples obtained through EUS-LB is comparable to conventional ultrasound-guided liver biopsy, presenting no significant difference in diagnostic efficacy.[35]

EUS-FNA/B has outstanding diagnostic sensitivity and accuracy for pNENs. Ki-67 IHC staining of EUS-FNA/B specimens can diagnose and stage pNENs. EUS-FNA/B also contributes to the differential diagnosis of other solid pancreatic lesions or diffusely enlarged pancreas, such as mass-forming pancreatitis, autoimmune pancreatitis, lymphoma, and pancreatic metastases.[36]

The disadvantages of EUS-FNA/B compared to conventional biopsy are high cost, anesthesia or sedation, need for multispecialty collaboration, and operative difficulty, which means that the procedure's outcome is highly dependent on the proficiency of the endoscopist. On the other hand, anesthesia may reduce procedure-related complications such as pain and anxiety, which can be considered an advantage. Ultrasound-guided percutaneous liver biopsy presents greater advantages in terms of low cost and operative difficulty,[37] making EUS-FNA/B less optimal in comparison. However, EUS-FNA/B only probes organs adjacent to the digestive tract, making it less invasive and especially advantageous in obtaining primary pancreatic lesions samples. It can also simultaneously accomplish the biopsy of the liver metastases and the primary pancreatic lesion, and thus is appropriate for the situation when samples from both sites are needed for diagnostic confirmation. Furthermore, EUS-FNA/B can be a complementary procedure to ultrasound-guided liver biopsy when liver metastases biopsy is too challenging to acquire in the conventional way.[38,39]

Expert consensus

Ultrasound-guided percutaneous liver biopsy should be the preferred method. Considering the prominent advantage of EUS-FNA/B in obtaining liver biopsies, it should be regarded as a crucial auxiliary procedure when conditions are met. EUS-FNA/B is favored when the ultrasound-guided liver biopsy is unsatisfactory or when the primary pancreatic lesion sample needs to be obtained concomitantly with liver metastases.

5.2. For pNENs liver metastases patients whose liver metastatic lesion has been diagnosed, is a biopsy of the primary lesion necessary?

A recent study has suggested the existence of subclonal differences between the pNENs primary lesion and metastatic lesion,[40] which may be related to the drug resistance mechanism of NENs. Thus, making treatment decisions based solely on the metastatic lesion may be inadequate, and a comprehensive evaluation of the primary and metastatic lesions may identify potential therapeutic targets for overcoming drug resistance. Another study has shown different Ki-67 expressions between the primary and metastatic lesions,[16] and growing evidence suggests that the disparities between the Ki-67 expressions of lesions may be related to prognosis.[21,41] Therefore, a comprehensive evaluation of pNENs liver metastatic and primary lesions provides valuable guidance for treatment decisions and prognosis.

Expert consensus

Biopsy evaluation of both primary and liver metastatic lesions is advised for patients unsuitable for surgical treatment.

5.3. What is the recommended diagnostic technique for acquiring pathology and cytology of the primary lesion of patients with pNENs liver metastases?

Ultrasound can noninvasively detect most liver regions, and ultrasound-guided liver biopsy has the advantages of low cost, easy-to-promote technology, adequate tissue collection, and high diagnostic sensitivity.[37] However, due to the deep anatomical location of the pancreas, the ultrasound-guided puncture is technically challenging, and the biopsy is riskier than EUS-FNA/B. Thus, the risks and technical difficulties of simultaneously performing an ultrasound-guided biopsy of the primary pancreatic lesion and metastatic lesion are high. EUS-FNA/B is currently the preferred technique for the biopsy of pancreatic lesions.[42] It operates closer to the organs adjacent to the digestive tract, is less invasive, and can simultaneously perform biopsies of the metastatic liver lesion and the primary pancreatic lesion, making it especially useful when biopsies of both primary and metastatic lesions are required.[43]

Expert consensus

Endoscopic ultrasound-guided fine needle aspiration/biopsy (EUS-FNA/B) is efficacious for both metastatic liver lesions and primary pancreatic lesions and is less invasive. EUS-FNA/B is the preferred technique for simultaneously obtaining biopsies of pNENs primary lesions and liver metastases.

5.4. Should endoscopic ultrasound-guided puncture of pNETs with liver metastases be performed with a biopsy needle (EUS-FNB) or a cytology needle (EUS-FNA)?

The EUS-FNB biopsy needle differs from the EUS-FNA cytology needle in having a lateral beveled orifice or barb specifically designed to cut and acquire tissue strips.[36] This design allows the EUS-FNB needle to obtain tissue strips more efficiently, especially for solid lesions, facilitating pathological diagnosis. There were inconsistencies in the accuracy of puncture diagnosis using the 2 types of puncture needles based on several studies. Still, overall, the results show that the EUS-FNB needle can obtain more tissue strips in a shorter time and with fewer punctures.[44] Therefore, it is particularly suitable for cases requiring tissue specimens, such as for the differential diagnosis of NENs lymphomas, and autoimmune pancreatitis masses, and when genetic testing or molecular typing of tumors is required for precision medicine and individualized treatment. In these situations, the EUS-FNB needle may provide more tissue samples and diagnostic information.[45,46]

Expert consensus

When the endoscopic ultrasound-guided puncture is performed to obtain tissue from primary pNENs and liver metastases, the puncture biopsy needle should be selected to acquire as much tissue as possible for evaluation and diagnosis based on pathological cytology and molecular pathology.

5.5. What is the application value of endoscopic ultrasound-guided puncture ablation in patients with pNENs with liver metastases?

Endoscopic ultrasound-guided puncture ablation is a relatively new treatment technique. According to the current literature, this technique is mainly applied in treating primary pNENs. Local ablation can be performed to relieve symptoms or control the tumor locally for patients with pNENs who are not eligible for surgery. The 2 primary ablation therapies for NETs are endoscopic ultrasound-guided ethanol ablation and endoscopic ultrasound-guided radiofrequency ablation (RFA).

Ethanol ablation uses a EUS-FNA needle (22 or 25G) to puncture into the tumor and inject small, divided doses of ethanol until an enlarged hyperechoic shadow is visible in the tumor. Multiple repeated injections at different sites may be performed for larger lesions to cover the entire tumor.[47,48] The literature has reported this technique as feasible, relatively safe and effective, and suitable for treatments aiming at symptomatic relief or complete ablation of the target lesion.[47–49] However, most previous studies are case reports, case series studies, and pilot studies, whereas randomized clinical trials (RCT) studies are needed to provide more robust evidence. Multicenter, long-term follow-up, and controlled studies are still required to confirm its safety and efficacy. Hence it can only be used as an alternative treatment.

RFA, which uses a high-frequency alternating current to generate thermal energy and induce coagulative necrosis of tissue,[47] requires a dedicated radiofrequency needle and a radiofrequency generator. Guided by EUS, the needle-like electrode bypasses the great vessels, pancreatic duct, or bile duct and enters the target lesion, crossing through the least amount of normal pancreatic parenchyma. After the position of the electrode tip within the lesion margin is confirmed by the EUS, the needle delivers energy to burn the tumor tissue. Due to the characteristics of RFA and the lesion size, multiple treatments may be required to achieve complete ablation. The extent of the ablation area varies depending on power consumption, operation time, and type and length of the active electrode.[50,51] In several case reports and case series studies, EUS-RFA has been used for minimally invasive treatment of functional and nonfunctional pNENs, with no serious adverse effects in 25 successfully treated patients.[52–54] Despite some promising results from relevant studies, the available evidence needs to be expanded. Like ethanol ablation, EUS-RFA treatment can only be used as an alternative treatment to reduce tumor burden not as the recommended treatment for most patients with metastatic pNENs.

Expert consensus

Endoscopic ultrasound-guided puncture ablation can be an alternative treatment to reduce tumor load but is not recommended as a first-line treatment technique.

6. What is the surgical resectability of pNENs with liver metastases defined?

6.1. What are the criteria for surgical resectability of the primary lesion of the pancreas?

Surgical resection is the primary curative treatment for patients with pNENs liver metastases. The surgical resectability of primary and metastatic lesions should be evaluated before any treatment.

The criteria for surgical resectability of pancreatic adenocarcinoma has been established, but there still needs to be more evidence from high-quality clinical trials for defining the resectability of pNENs. Currently, whether the peripancreatic vessels, including superior mesenteric vein (SMV), superior mesenteric artery (SMA), celiac trunk (CT), and common hepatic artery (CHA), are invaded is the primary basis for defining the resectability of pNENs. Accordingly, the ENENTS guidelines classify pNENs into resectable (no contact between the tumor and the SMA and/or CT and/or CHA), borderline resectable (tumor in close association with the SMA and/or CT and/or CHA), and locally advanced (tumor invaded the SMA and/or CT and/or CHA; SMV occlusion) stages.[55]

With the evolution of treatment strategy and advancement in surgical techniques, fine tissue separation and vascular reconstruction techniques have made some previously unresectable tumors that have invasions of peripancreatic vessels (SMV, SMA, CT, and CHA) resectable. For tumors with portal vein and SMV invasion, vascular resection combined with vascular reconstruction is a mature technique that is relatively safe during the perioperative period, and can be performed in specialized medical centers. For tumors with CT invasion, pancreatectomy with celiac axis resection can be performed at specialized centers if R0 resection can be achieved. The clinical evidence is limited for patients with SMA invasion,

and whether arterial resection and reconstruction are recommended is still controversial.[55–57] However, in the ENENTS guidelines, the criteria for defining the surgical resectability of the primary lesion of pNENs did not consider the degree of peripancreatic vascular invasion. Experts have reached the consensus that the resectability of primary pNENs lesions can be determined based on the criteria of pancreatic adenocarcinoma.[58]

Expert consensus

Whether peripancreatic blood vessels (SMV, SMA, CT, and CHA) are invaded is vital for defining tumor resectability. The resectability of pNENs may be determined based on the criteria of pancreatic adenocarcinoma. For patients requiring combined portal vein or SMV resection and reconstruction, or those who can achieve R0 resection through pancreatectomy combined with celiac axis resection, operations can be performed at specialized medical centers.

6.2. What is the criteria for defining surgical resectability of liver metastatic lesion?

The liver is the most common site of distant metastases for pNENs and is often associated with poor prognosis. Surgical resection can improve the survival and prognosis of pNENs patients with liver metastases. Several retrospective studies have shown that R1 resection (positive microscopic margins) has no significant negative impact on patients' overall survival and prognosis.[9] Currently, there is a lack of evidence from high-quality clinical trials for defining the resectability of liver metastases. The resectability evaluation of liver metastases is mainly based on the expected degree of tumor remission and the remnant liver volume (RLV). Liver metastases are considered resectable if R0/01 resections can be achieved with RLV ≥30%, regardless of the size and number of foci.

Expert consensus

A metastatic liver lesion is considered resectable if R0/01 resection with RLV ≥30% can be achieved.

6.3. For liver metastases, is the objective of surgical treatment to achieve R0 resection or to reach no evidence of disease?

The treatment objective for colorectal cancer patients with curatively resectable liver or lung metastases is to reach NED.[59] However, the clinical implications of NED in pNENs patients with liver metastases are still unclear. Surgical resection can significantly improve the survival and prognosis of pNEN patients with liver metastases. Recent studies have shown that the 5-year survival rate of pNENs patients with liver metastases who received surgical treatment was 61%–74%, compared with the 25%–67% 5-year survival rate for patients who received nonsurgical treatments.[60] Furthermore, there is no significant difference in survival and prognosis between patients with R0 and R1 resections. Due to the heterogeneity of NENs, routine preoperative imaging techniques often cannot detect all metastatic liver lesions. Elias et al counted the number of metastatic liver lesions in liver resection specimens in 5-mm histopathological sections.[61] They found that the number of lesions shown by pathological examination exceeded the number of lesions found in preoperative imaging and intraoperative exploration (intraoperative palpation and intraoperative ultrasound examination) in 50% of patients. Thus, achieving true R0 resection for pNENs patients with liver metastases is technically challenging. In summary, we believe that NED should be the treatment objective for pNENs patients with liver metastases.

Expert consensus

For liver metastases, the objective of surgical treatment is to reach NED.

6.4. If patients can benefit from reaching NED, is surgical resection combined with RFA the preferred approach for pNENs patients with liver metastases to achieve NED?

Local ablation by RFA is a first-line treatment for liver malignancies. For primary liver cancers, RFA can achieve a therapeutic effect similar to surgical resection for solitary tumors less than 2 cm in diameter. Moreover, for deeply and centrally located tumors, RFA can preserve more RLV and reduce the risk of postoperative complications associated with major hepatectomy, such as liver failure.[62] Several studies have confirmed the clinical value of RFA in liver metastases of NENs.[63] According to the ENETS guidelines, RFA is recommended for patients with type I liver metastases with contraindications for surgical treatments. Surgical resection ± intraoperative RFA is recommended to achieve complete remission for patients with type II liver metastases.[4]

Expert consensus

Local ablation by RFA is an effective treatment modality for secondary liver malignancies. Surgical resection combined with RFA is recommended to achieve NED.

7. Is surgery recommended for resectable G3 pNENs with liver metastases?

7.1. Is surgery recommended for resectable G3 pNETs with liver metastases?

In 2019, WHO officially classified GEP-NENs G3 into 2 types according to their differentiation: well-differentiated G3 NETs and poorly differentiated NECs. G3 NETs refer to well-differentiated NETs with a mitotic rate greater than 20 or a Ki-67 index greater than 20%.[64] G3 NETs have a better prognosis than poorly differentiated NECs but are not as favorable as G1-G2 NETs.[65] There is still controversy regarding surgical treatments of G3 pNETs with liver metastases. Current studies suggest that resection of the primary tumor and metastases is feasible for resectable G3 pNETs with liver metastases. In a study involving 15 patients with stage IV G3 NENs (7 with G3 NETs and 8 with NECs) who underwent resection of primary and metastatic tumors, the median overall survival (mOS) and the median recurrence free survival (mRFS) were 59 and 8 months, respectively. Multivariate analysis indicated no significant difference in OS between the G3 NETs and NECs groups, probably due to the small sample size and the absence of small-cell NECs.[66] Another recent study involving 455 patients with NENs liver metastases from 15 centers showed that G3 grade was the only significant predictor for poor prognosis after surgical resection of the primary lesion and liver metastases (hazard ratio [HR] 2.22, 95% confidence interval 1.04–4.77, P = .040). The mOS was only 39 months, compared with 123.98 and 118 months for G1 and G2.[67] Due to the scarcity of clinical studies on surgical resection of G3 NETs liver metastases, there is still no conclusion on whether surgical treatment should be performed. However, most studies believe that patients with resectable G3 NETs liver metastases can still benefit from surgery after a strict evaluation.

Expert consensus

The prognosis of G3 NETs patients with liver metastases is significantly poorer than that of G1 and G2 patients. There are few clinical studies on the surgical treatment of G3 pNETs liver metastases, and controversy regarding surgical treatments remains. Based on the results of small sample studies, patients with resectable G3 pNETs with liver metastases can benefit from surgery after a strict evaluation.

7.2. Is surgery recommended for resectable pancreatic NECs (pNECs) with liver metastases?

Among GEP-NENs, pNECs has a relatively poor prognosis, and previous studies have shown that its mOS is only

5.7 months.[68] Therefore, current international guidelines recommend medical therapy (including cisplatin/etoposide or carboplatin/etoposide, FOLOFOX, FOLFIRI, and TMZ ± capecitabine) as the first-line treatment. Pancreatic NECs can be further classified into small-cell NECs and large-cell NECs, with large-cell NECs having a relatively better prognosis. A small sample study involving 15 G3 NENs with liver metastases patients reported that 8 NECs patients (all large-cell type) had a prognosis similar to that of G3 NETs patients with liver metastases,[66] suggesting that large-cell NECs patients with liver metastases potentially benefit from surgical treatment. However, the evidence level is relatively low due to the small sample size. Therefore, for patients with resectable pNECs liver metastases, medical treatment is still the first-line recommendation according to the mainstream view, and whether surgical treatment is feasible still needs to be confirmed by clinical studies with larger samples.

Expert consensus

The prognosis of pNECs with liver metastases is poor, and medical therapy is recommended as the first-line treatment. Large-cell pNECs with liver metastases has a relatively better prognosis, and a small sample study suggests that resectable large-cell pNECs with liver metastasis patients may benefit from surgery. Clinical studies with a larger sample size are still needed for confirmation.

8. Is surgical management recommended for pNETs (G1/G2) patients with liver metastases when curative surgery is not feasible?

8.1. Is removal of the primary foci recommended for non-functional pNETs when curative resection can be achieved for the primary foci but not for the liver metastasis?

The recommendation for primary tumor resection (PTR) of nonfunctional pNETs with unresectable liver metastases remains controversial due to the disease's heterogeneity and the lack of high-level evidence. Retrospective studies[69,70] in which pNETs patients with unresectable liver metastases received resection of the primary tumor showed a significantly more favorable median survival than those who did not receive surgery. Yet, due to the retrospective design and relatively small scale of these studies, the results need to be interpreted cautiously.

Notably, the primary tumor location was perceived as a selection factor for surgical management by both ENETS[55] and NANETS.[71] For nonfunctional pNETs patients whose primary tumor is in the head of the pancreas, especially those who would require pancreaticoduodenectomy, the priority of PTR is relatively low because of the increased possibility of additional morbidity due to the surgical procedure and the lower likelihood of tumor-related symptoms compared with a primary intestinal focus. Instead, endoscopic or surgical bypass is recommended for co-existing complications such as jaundice or duodenal occlusion. As for those with primary tumors located in the body or tail of the pancreas, PTR is more prioritized since distal pancreatectomy (DP) has lower morbidity than pancreaticoduodenectomy and may be associated with improved life quality and survival outcomes.[72,73]

Expert consensus

The priority of PTR for nonfunctional pNETs patients with unresectable liver metastases is relatively low. Factors such as the location of the primary tumor, age, and comorbidities should be considered before individualized recommendation.

8.2. Is debulking surgery recommended for functional pNETs patients whose endocrine-related symptoms cannot be alleviated with routine treatments? If debulking surgery is recommended, should debulked tumor volume be 70% or 90%?

Although some experts questioned the reliability of the evidence from retrospective studies, debulking surgery for pNETs patients with liver metastases (pNETLM) was recommended by most surgeons since it is associated with significant improvements in symptom control and survival outcomes.[74–76] Mechanistically, the sharp decrease in hormone levels, improvement of symptoms, "resetting the clock," and delaying of liver failure due to hepatic replacement underpin the potential benefit of debulking surgery for pNETLM patients.

Conventionally, debulking over 90%[77,78] of liver metastases volume was recommended by most surgeons for palliative treatment or improving survival for patients with liver metastases. However, this requirement may restrict certain pNETLM patients who might benefit from debulking surgery. Thus, several studies reevaluated the extent of debulking surgery, and the results revealed no significant difference in PFS or OS once >70% of tumor tissue was debulked.[79,80] But due to the retrospective design and limited sample size of these studies, further prospective, large-scale comparative studies are needed to justify the threshold.

Additionally, interventional radiology started to play an essential role in managing patients with NENLM. Through occluding small arteries feeding the NENLM and inducing tumor ischemia and necrosis, transarterial embolization (TAE) has also been recommended for pNETLM patients, which could control the symptom as well as improve survival.[81,82]

Expert consensus

Cytoreduction of over 90% is still the optimal threshold for pNETLM patients to achieve both symptom control and improvements in survival. TAE for the liver metastasis combined with resection of the primary tumor may also be recommended for suitable patients.

9. What is the recommended surgical approach for pNENs with resectable liver metastases: anatomic liver resection or parenchymal-sparing hepatectomy (PSH)?

High-level evidence supporting anatomic liver resection or PSH for pNENs with resectable liver metastases is lacking due to the heterogeneity of the disease and its presentation. Anatomic liver resection has been recommended to decrease the risk of postoperative intrahepatic recurrence in HCC patients with portal vein thrombus, owing to the characteristics of intrahepatic metastasis of HCC.[83,84] For liver metastases with a high postoperative recurrence rate, the greatest significance of the PSH is to reserve more normal liver tissue to expand treatment options after recurrence, especially the chance of reoperation, to prolong survival. Some studies have demonstrated that compared with anatomic liver resection, PSH was associated with better perioperative outcomes without compromising oncological outcomes for colorectal cancer liver metastases.[85,86] Due to similarities to the biological characteristics of colorectal cancer liver metastases rather than HCC,[8,87] PSH has been accepted for pNENs with resectable liver metastases instead of relying on anatomic resections.[71] Anatomic liver resection requires liver metastases to be confined within certain anatomic boundaries. Since patients with pNENs with liver metastases ultimately die of liver replacement, preserving normal liver tissue by performing PSH should become more routine. However, when tumors invade principal arteries or veins, with consideration of liver regions' blood supply, anatomic liver resection should be performed in some specific cases.

Expert consensus

For pancreatic neuroendcrine tumor with resectable liver metastases, if complete resection can be achieved, PSH should be recommended as an appropriate surgical approach to reserve more normal liver tissue to expand treatment options in the case of recurrence.

10. Is splenectomy necessary for resectable pancreatic body/tail NENs with liver metastasis?

Splenectomy may be necessary for some pNENs patients with distal tumors, which include tumors invading the splenic vasculature, tumor thrombus, chronic pancreatitis, and peripancreatic inflammation.[88] During DP, splenic preservation may carry the risk of hemorrhage or infarction, and even limit nodal retrieval in patients with a high risk for regional metastasis, but it has the advantage of preserving patients' innate immune responses. The candidates for splenic preservation include low-risk sporadic pNENs patients with a low possibility of having occult nodal metastases, patients predicted to have favorable survival, and young patients. A previous study has shown an increased risk of septicemia, pulmonary embolism, and pancreatic cancer in a large cohort after splenectomy.[89] A recent meta-analysis revealed that compared with patients receiving DP with splenectomy, patients receiving DP without splenectomy had fewer infections, fewer clinically relevant pancreatic fistulae, shorter operative time, and less blood loss.[90] These results suggest that in carefully selected patients, the additional benefits of splenic preservation outweigh its risks. However, splenic preservation may severely hinder the dissection of splenic hilar lymph nodes. Therefore, surgeons should be cautious in performing splenic preservation in pNENs patients at significant risk for distal nodal metastasis.

Splenic preservation includes Warshaw technique and the splenic vessel preservation technique. Compared with the Warshaw technique, the splenic vessel preservation technique had a significantly lower incidence of splenic infarction and gastric varices but had a longer operative time and greater blood loss.[91–94] In addition, splenic preservation without splenic vessel preservation is not recommended. Therefore, the technical approach and decision about splenectomy should also be individualized based on patient characteristics and surgeon experience.

Expert consensus

Splenectomy is advisable for pNENs patients with significant risk for distal nodal metastasis, tumor invasion of splenic vasculature, tumor thrombus, chronic pancreatitis, and peripancreatic inflammation. However, splenic preservation should be considered, given favorable factors. In addition, the technical approach for splenectomy should be considered when making surgical decisions.

11. Is subclassification necessary for type III liver metastases of pNENs?

11.1. Should type III liver metastases be further classified into potentially resectable and unresectable types?

The liver is the most common distant metastatic site of pNENs, and approximately 60% of patients have liver metastasis at initial diagnosis. Based on the distribution of metastatic loci, the ENENTS guidelines classified liver metastases into 3 categories: single metastasis of any size (type I); isolated metastatic bulk accompanied by smaller deposits, with both liver lobes always involved (type II); disseminated metastatic spread, with both liver lobes always involved (type III). Generally, type III liver metastases are considered unresectable. The ENENTS guidelines recommend systemic therapy for grade G1 and G2 type III liver metastases, and only strictly selected patients (<1%) are considered for liver transplantation.[55]

For liver metastases of pNENs about 60%–70% of patients have type III liver metastases with poor prognosis.[95] It has been previously confirmed that surgery (R0/R1 excision) significantly improves the overall prognosis of PanNETs with liver metastases patients compared with other treatments (such as systemic therapy, radiotherapy, intervention, PRRT, etc), and NED status is also associated with a more favorable prognosis.[96] The ENETS guideline has several limitations in the classification of liver metastases. Some pNENs patients with type III liver metastases can achieve radical resection with the combination of regular hepatectomy and ablation. Therefore, categorizing all pNENs with type III liver metastases as unresectable would deny some patients the opportunity of radical surgery. TMZ-based chemotherapy has a relatively high systemic response rate (tumor shrinkage rate) in patients with advanced pNENs. Recently, 2 prospective phase II studies STEM and E2211 showed that the ORR of TMZ combined with S-1 or capecitabine in advanced PanNETs was 30%–40%.[30,31] For some pNENs liver metastases with a rich blood supply, TAE combined with long-acting octreotide significantly increased ORR compared with octreotide alone (76.5% vs 8.3%, $P < 0.01$), demonstrating the effectiveness of TAE in reducing intrahepatic tumor burden.[97] Despite a lack of high-level evidence, we have observed in clinical practice that some type III liver metastasis patients can reach NED status to prolong the OS through surgical excision and ablation after early conversion therapy. Therefore, we believe it is necessary to further classify type III liver metastases and identify patients with potentially resectable tumors from a clinical perspective. According to the expert group, for G1, G2, and some G3 grade patients with liver metastases, a functional residual liver volume ≥30% after active conversion therapy may be promising. In principle, type III liver metastases can be defined as potentially resectable if the patient can achieve NED or a tumor reduction greater than 90% through local or anatomical liver resection, portal vein embolization, associating liver partition, portal vein ligation for staged hepatectomy, ablation, or other methods. However, further clinical studies are needed to provide high-level medical evidence.

11.2. For hepatic metastatic foci, how to define potential resectability?

The panel concluded the following potential criteria of the resectable subtype for type III subclassification: (1) most metastases are located on or within 2 cm from the liver surface and can be locally resected, whereas no more than 5 deep metastatic lesions are present and can be ablated. (2) Most metastases are confined to 3 liver segments or a single lobe, whereas lesions beyond this range are oligometastases for which excision or combined ablation can be used to achieve the NED status. (3) NED can be achieved with a functional residual liver volume exceeding 30% by the key techniques of resecting metastases with hepatic parenchyma preserved and intraoperative ablation by precise preoperative planning.

Expert consensus

Given the heterogeneity of NENs and clinical experience, it is recommended to classify type III liver metastases further and select patients with potentially resectable foci for active conversion therapy. G1, G2, and some G3 grade pNENs liver metastases can be defined as potentially resectable type III liver metastases if it is deemed promising that the patient achieves NED status with a functional residual liver volume ≥30% after active conversion therapy and surgical resection + ablation.

12. What is the clinical application value of liver transplantation in treating pNENs with liver metastases?

Currently, the selection criteria and benefits of liver transplantation for liver metastases of NENs remain uncertain. In 1995, the National Cancer Institute of Milan, Italy, designed specific selection criteria for liver transplantation for patients with NET liver metastases (Milan-NET criteria), which were: (1) no extrahepatic disease; (2) histologically confirmed well-differentiated (G1-G2, Ki-67<10%) NET; (3) previous PTR; (4) liver metastatic tumor burden <50% of total liver volume; (5) stable disease or stable response to treatment for at least 6 months; (6) age < 60 years. In 2016, Mazzaferro et al[98] reported the results of a retrospective study that analyzed 88 patients with liver metastases from gastroenteropancreatic

NETs who met the Milan-NET criteria, of whom 42 received liver transplantation. There was no difference in liver metastases tumor burden between the groups. Transplant patients had significantly better 5- and 10-year survival rates (97.2% vs 88.8%, 50.9% vs 22.4%; $P < .001$) than those without transplantation. Therefore, the 2017 European Society of NETs (ENETs) expert consensus states that liver transplantation for metastatic NETs under restrictive criteria provides excellent long-term outcomes.[55] Resection of the primary tumor and dissection of locoregional lymph nodes are required before transplantation. Abdominal exploration and liver ultrasonography can be performed simultaneously to rule out peritoneal spread and evaluate the resectability of liver metastases while removing all extrahepatic tumor metastases.[99,100] Failure to detect a primary tumor before transplantation should not be considered an absolute contraindication.[101] If these stringent criteria are met, patients can benefit from liver transplantation, which may significantly improve survival compared with alternative medicines and interventional therapy.[98,101]

Expert consensus

Liver transplantation may be considered for pancreatic NETs patients with liver metastases, which brings another treatment option for patients with unresectable liver metastases. Meanwhile, the indications for liver transplantation should be strictly controlled.

13. How to choose preoperative systemic drugs for patients with pancreatic NETs with liver metastases?

More than 80% of pNETs patients have multiple intrahepatic metastases or concomitant extrahepatic metastases at the initial diagnosis. A radical resection of liver metastases that achieves NED or debulks more than 90% of visible lesions can significantly improve patient survival. Additionally, surgical resection of liver metastases can effectively reduce hormone levels and improve patients' clinical symptoms and long-term prognosis.[102]

According to the treatment strategy for patients with liver metastases, those with type I liver metastases should receive aggressive surgery to reach NED or resection of more than 90% of visible lesions.[102] Subsequently, postoperative systemic adjuvant therapy is administered according to the Ki-67 index, SSTR expression, and MGMT status. For patients with type II or some type III liver metastases who are initially not eligible for surgery, systemic drug therapy is applied to shrink the tumor in the hope of achieving a surgically resectable state.[103] There is currently a lack of data from prospective translational studies regarding pNETs liver metastases. TMZ-based chemotherapy remains the systemic therapy of choice, with high efficacy (shrinkage rate) in advanced pNETs patients. Two recent phase II prospective studies, STEM and E2211, reported that TMZ in combination with tegafur or capecitabine had an objective response rate (ORR) of 30-40% in advanced pNETs, showing better efficacy in MGMT-negative (0/1+) patients with an ORR of 36 to 57% and an ORR of 8 to 19% in MGMT-positive (2/3+) patients, indicating MGMT's role as a predictor of efficacy in TMZ combination therapy.[30,31] TMZ -based chemotherapy regimens have relatively limited efficacy on MGMT-positive (2/3+) pNETs, and there is no clear evidence on whether regimens without TMZ can be used as alternatives. A phase III multicenter, randomized, controlled SNET-p study in patients with G1/G2 pNETs showed an ORR of 19.2% for surufatinib, which was higher than the ORR for sunitinib and everolimus.[104–106] In addition, 2 retrospective studies showed that FOLFOX-based regimens had ORRs of 30%–53%[107,108] in patients with advanced pNETs, which may be considered an option of therapy without TMZ in MGMT-positive (2/3+) pNETs patients, but further prospective studies are needed to explore the efficacy of therapy without TMZ in this group.

Expert consensus

More than 80% of pNETs patients have multiple intrahepatic metastases or concomitant extrahepatic metastases at initial diagnosis. A radical resection of liver metastases that achieves NED or debulks more than 90% of visible lesions can significantly improve patient survival. For patients with type II and some type III pNETs liver metastases who cannot achieve NED or more than 90% resection initially, preoperative recommendations include: 1. MGMT-negative (0/1+) patients should be treated with systemic chemotherapy regimens that have relatively high ORR such as STEM or CAPTEM to shrink the tumors, and surgery can be performed after MDT multidisciplinary review and discussion to improve patients' overall survival. 2. MGMT-positive (2/3+) patients can be treated with therapies without TMZ, such as regimens based on surufatinib alone or oxaliplatin combined with fluoropyrimidines, to shrink the tumors, and surgery should be performed after MDT multidisciplinary rounds and discussion.

14. Is systemic treatment required after the surgery for pancreatic NETs liver metastases or when NED has been achieved by local treatment (RFA, intervention, etc)?

In patients with pNETs liver metastases, the average 5-year overall survival rate is about 60%–80% after surgical resection of liver metastases, whereas 20%–40% of patients still face the risk of postoperative recurrence. In addition, due to the peculiarities of imaging features of pNETs liver metastases, there are certain limitations in the accurate preoperative assessment of the number of metastases, leading to uncertainty in the NED status after liver metastasis surgery and local treatment. The analysis of a study by the Japanese NET Society (JNETS) found that, after R0/1 resection of pNETs liver metastases, the recurrence rate of intrahepatic metastases was 63.4%.[109] Despite the high postoperative recurrence rate, a few studies have reported on its postoperative treatment.

Combining local treatment such as RFA and TAE/transarterial chemoembolisation (TACE) with systemic drug therapy is also a common treatment option for patients with pNETs liver metastases. Some studies have reported that, for pNETs liver metastases, local treatment combined with systemic drug therapy has better efficacy and prognosis than local treatment alone. The combination of local treatment such as RFA and TAE/TACE with systemic drug therapy is suitable for patients with postoperative recurrence of liver metastases who cannot receive repeated local treatments due limited liver reserve, those with contraindications to surgery, some type III liver metastases patients, and elderly patients.[110]

Professor Jin Gang, in association with 3 hospitals in Shanghai, reported a retrospective study at ENETS 2020, which showed that adjuvant SSA therapy significantly improved patients' disease-free survival at 60 months compared to the observation group (90.0 vs 76.0%, $P = .0253$) after R0 surgery for G2 pancreatic NETs.[111]

Patients with pNETs liver metastases who have reached the NED status after metastatic tumor resection or local treatment such as RFA or TAE/TACE remain at high risk for recurrence. Despite limited data on postoperative treatments, postoperative adjuvant therapy and systemic therapy before and after local treatments are recommended.

Expert consensus

Patients with pNETs liver metastases who have reached the NED status after metastatic tumor resection or local treatment such as RFA and TAE/TACE remain at high risk for postoperative recurrence. The medical treatment regimen should be as follow: (1) After surgical resection of type I liver metastases, if Ki-67 ≤10% and SSTR positive/SRI expression, adjuvant SSA therapy can be chosen, especially for G2 patients; clinical observation is also an option for a small number of patients.

(2) For patients with type II or type III liver metastases who have reached the NED status after surgery or local treatments such as RFA and TAE/TACE, there is a lack of support from evidence-based medicine regarding their postoperative adjuvant therapy or systemic therapy after local treatment, it is recommended that they adhere to the effective preoperative treatment regimen or participate in clinical studies for further exploration.

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Author contributions

HZ and DZ led and organized the whole guideline update project. YC, LJ, SS, SH, HZ, and DZ were responsible for organizing experts from the internal medicine group, the imaging group, the pathology group, the endoscopy group, and the surgery group to discuss and revise the guidelines respectively. Other authors were involved in updating the guideline and writing the manuscript. All participants jointly defined and approved a protocol establishing the design of guideline. YC, LJ, SS, and SH participated into revising and logical consequence of the final manuscript. All authors approved the final manuscript, authorship, and copyright transfer agreement.

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Conflicts of interest

CY, HX, WW, WL are Editorial Board members of Journal of Pancreatology. They were blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare that they have no conflicts of interest.

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Not applicable.

Data availability statement

The data involved in our consensus is openly available in a public repository.

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