

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2019 May 15; 11(5): 348-448





REVIEW

- 348 Effect of exercise on colorectal cancer prevention and treatment
Oruç Z, Kaplan MA

MINIREVIEWS

- 367 Stereotactic body radiation therapy in patients with hepatocellular carcinoma: A mini-review
Gerum S, Jensen AD, Roeder F

ORIGINAL ARTICLE

Basic Study

- 377 Qingjie Fuzheng granules inhibit colorectal cancer cell growth by the PI3K/ AKT and ERK pathways
Yang H, Liu JX, Shang HX, Lin S, Zhao JY, Lin JM

Retrospective Study

- 393 Surgical complications after different therapeutic approaches for locally advanced rectal cancer
Zhan TC, Zhang DK, Gu J, Li M
- 404 Histopathological characteristics of needle core biopsy and surgical specimens from patients with solitary hepatocellular carcinoma or intrahepatic cholangiocarcinoma
Wu JS, Feng JL, Zhu RD, Liu SG, Zhao DW, Li N
- 416 Surgical resection of gastric stump cancer following proximal gastrectomy for adenocarcinoma of the esophagogastric junction
Ma FH, Xue LY, Chen YT, Li WK, Li Y, Kang WZ, Xie YB, Zhong YX, Xu Q, Tian YT

Observational Study

- 424 ADAMTS13 and von Willebrand factor are useful biomarkers for sorafenib treatment efficiency in patients with hepatocellular carcinoma
Takaya H, Namisaki T, Shimozato N, Kaji K, Kitade M, Moriya K, Sato S, Kawaratani H, Akahane T, Matsumoto M, Yoshiji H
- 436 Analysis of B-ultrasound and contrast-enhanced ultrasound characteristics of different hepatic neuroendocrine neoplasm
Kang XN, Zhang XY, Bai J, Wang ZY, Yin WJ, Li L

Contents

World Journal of Gastrointestinal Oncology

Volume 11 Number 5 May 15, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Hiroshi Doi, MD, PhD, Assistant Professor, Lecturer, Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka 589-8511, Japan

AIMS AND SCOPE

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJGO* covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, etc. The current columns of *WJGO* include editorial, frontier, field of vision, review, original articles, case report.

We encourage authors to submit their manuscripts to *WJGO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

The *WJGO* is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJGO* as 3.140 (5-year impact factor: 3.228), ranking *WJGO* as 39 among 80 journals in gastroenterology and hepatology (quartile in category Q2), and 114 among 222 journals in oncology (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: Yun-Xiaojuan Wu Proofing Editorial Office Director: Jin-Lei Wang

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Rosa M Jimenez Rodriguez, Pashtoon Murtaza Kasi

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

May 15, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

E-mail: bpgoffice@wjgnet.com <https://www.wjgnet.com>



Observational Study

Analysis of B-ultrasound and contrast-enhanced ultrasound characteristics of different hepatic neuroendocrine neoplasm

Xiao-Ning Kang, Xiao-Yu Zhang, Jie Bai, Zun-Yi Wang, Wen-Jie Yin, Li Li

ORCID number: Xiao-Ning Kang (0000-0002-9480-8929); Xiao-Yu Zhang (0000-0002-6363-0435); Jie Bai (0000-0002-9825-5030); Zun-Yi Wang (0000-0002-4318-0813); Wen-Jie Yin (0000-0001-3874-2289); Li Li (0000-0001-5716-0177).

Author contributions: Kang XN, Zhang XY, and Li L designed the research; Kang XN, Bai J, and Wang ZY performed the research; Li L and Yin WJ contributed new reagents/analytic tools; Kang XN, Bai J, and Zhang XY analyzed the data; and Kang XN, Zhang XY, and Li L wrote the paper.

Institutional review board

statement: The study was approved by the ethics committee of Cangzhou Central Hospital.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: The authors declare that they have no competing interests.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0)

Xiao-Ning Kang, Li Li, Department of Second Ultrasound, Cangzhou Central Hospital, Cangzhou 061001, Hebei Province, China

Xiao-Yu Zhang, Jie Bai, Zun-Yi Wang, Department of Third Oncology, Cangzhou Central Hospital, Cangzhou 061001, Hebei Province, China

Wen-Jie Yin, Department of Gastroenterology, Cangzhou Central Hospital, Cangzhou 061001, Hebei Province, China

Corresponding author: Li Li, MD, Chief Physician, Department of Second Ultrasound, Cangzhou Central Hospital, No. 16 Xinhua West Road, Yunhe District, Cangzhou 061001, Hebei Province, China. lilijobdoc@126.com

Telephone: +86-317-2075790

Abstract

BACKGROUND

Hepatic neuroendocrine neoplasm (hNEN) is a highly heterogeneous tumor. The exact identification of the source and malignant degree of hNEN is important. However, there is a lack of information regarding diagnosis of hNEN with imaging. In addition, no studies have compared the imaging between hNEN and hepatocellular carcinoma (HCC) and among different sources and malignant degrees of hNEN.

AIM

To compare the ultrasound characteristics between hNEN and HCC and among different sources and malignant degrees of hNEN.

METHODS

A total of 55 patients with hNEN were recruited and defined as the hNEN group. Among them, 35 cases of hNET were defined as the hNET group. Twenty cases of hepatic neuroendocrine carcinoma (hNEC) were defined as the hNEC group. Among the 55 lesions, 29 were transferred from the pancreas, 20 were from the gastrointestinal tract, and six were from other sites. In total, 55 patients with HCC were recruited and defined as the HCC group. The characteristic differences of B-mode ultrasound and contrast-enhanced ultrasound (CEUS) between hNEN and HCC and among different sources and malignant degrees of hNEN were compared.

RESULTS

In the hNEN group, the proportions of multiple liver lesions, unclear borders,

license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 30, 2019

Peer-review started: January 30, 2019

First decision: March 14, 2019

Revised: March 19, 2019

Accepted: March 26, 2019

Article in press: March 26, 2019

Published online: May 15, 2019

P-Reviewer: Snyder J, Tatsuya O, Yukihiko T

S-Editor: Wang JL

L-Editor: Filipodia

E-Editor: Wu YXJ



and high echo lesions were higher than those in the HCC group. The proportions of non-uniform echo and peripheral acoustic halo were lower than those in the HCC group ($P < 0.05$). The washout to iso-enhancement time and washout to hypo-enhancement time were lower than those in the HCC group ($P < 0.05$). The characteristics of B-ultrasound and CEUS among different sources of hNEN were similar, and the differences were not statistically significant ($P > 0.05$). B-mode ultrasound characteristics of hNET and hNEC were similar. The proportions of low enhancement at portal venous phase, non-uniform enhancement forms, and combined tumor vasculature in the hNEC group were larger than those in the hNEN group ($P < 0.05$).

CONCLUSION

Compared with HCC, hNEN showed multiple intrahepatic lesions, uniform high echo, uniform high enhancement at arterial phase, and rapid washout. Low enhancement at portal venous phase, overall non-uniform enhancement form, and the proportion of combined tumor vasculature in hNEC were larger than those in hNET.

Key words: Hepatic neuroendocrine neoplasm; Hepatic neuroendocrine tumor; Hepatic neuroendocrine carcinoma; B-ultrasound; Contrast-enhanced ultrasound

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Clinically, hepatic neuroendocrine neoplasm (hNEN) is rare, and few reports are currently available on the imaging diagnosis of hNENs. In this study, by comparing hNEN and hepatocellular carcinoma, hNEN from different sources, and differentiation, it was found that the ultrasound characteristics of hNEN are mostly multiple, uniform hyperechoic masses. The enhancement at the arterial phase was mostly uniform and high, and the washout was rapid compared with hepatocellular carcinoma. Compared with hepatic neuroendocrine tumor, the enhancement at the portal venous phase of hepatic neuroendocrine carcinoma was low, and the enhancement form was non-uniform.

Citation: Kang XN, Zhang XY, Bai J, Wang ZY, Yin WJ, Li L. Analysis of B-ultrasound and contrast-enhanced ultrasound characteristics of different hepatic neuroendocrine neoplasm. *World J Gastrointest Oncol* 2019; 11(5): 436-448

URL: <https://www.wjgnet.com/1948-5204/full/v11/i5/436.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v11.i5.436>

INTRODUCTION

Neuroendocrine neoplasm (NEN) is a highly heterogeneous tumor. The liver is the most important metastatic part of NEN, which is mostly transferred from other organs, such as the gastrointestinal tract. Therefore, hepatic NEN (hNEN) is more common than primary hNEN^[1-3]. The manifestations of hNEN patients are complex and mostly non-specific. Patients with hNEN often present with liver discomfort and bloating. It is necessary to identify hNEN and hepatocellular carcinoma (HCC). In addition, all NENs have malignant potential. NEN from different sources and malignant degrees differ greatly in outcome and treatment. Hence, it is important to identify accurately the source and malignant degree of hNEN.

Currently, the diagnosis of hNEN mainly depends on the results of pathological examination and immunohistochemistry^[4-6]. Although pathological examination and immunohistochemistry are the gold standard for diagnosis, they are invasive examinations. They can only be used as a means of verification and cannot be used as a screening tool for diseases. Clinically, initial screening is required through non-invasive examinations (e.g., imaging examinations, laboratory examinations, etc), and pathological diagnosis is performed on highly suspected patients. However, due to the rareness of hNEN, there is a lack of current information regarding imaging examinations, and there is little experience in identifying hNEN and HCC, hNEN from different sources, and malignant degrees.

Beard *et al*^[7] reported that hNEN and HCC had similarities in ultrasound

performance, which may cause misdiagnosis due to insufficient understanding. Some studies compared the hNEN characteristics of different sources and malignant degrees and found that the B-ultrasound and contrast-enhanced ultrasound (CEUS) performance of hNEN from different sources and malignant degrees were different^[8-10]. These findings suggest that we can identify hNEN by ultrasound and CEUS, but its clinical application value has not been confirmed. Therefore, the present study compared the ultrasound performance between hNEN and HCC. In addition, the characteristics of B-mode ultrasound and CEUS from different sources and malignant degrees of hNEN were analyzed in order to provide a reference for the diagnosis and treatment of hNEN.

MATERIALS AND METHODS

Research object

A total of 55 patients with hNEN admitted to Cangzhou Central Hospital from January 2014 to May 2018 were recruited. All patients obtained a complete B-mode ultrasound and CEUS data. They were defined as the hNEN group. Among them, 27 were males and 28 were females with an age range of 36-68 years old and an average of 55.23 ± 14.52 years old. Three patients in the hNEN group had hepatitis. The inclusion criteria of hNEN were: Surgical resection or biopsy was confirmed as hNEN, and immunohistochemistry confirmed that ChrA or Syno was positive. The exclusion criteria were: HCC, mixed liver cancer, hilar cholangiocarcinoma, and extrahepatic cholangiocarcinoma. According to the World Health Organization classification of the digestive system tumor (2010) neuroendocrine tumor (NET) grading standard^[11], 35 cases of hepatic NET (hNET) (G1 and G2) were defined as the hNET group, and 20 cases of hNEC (G3) were defined as the hNEC group. Among the 55 hNEN lesions, 29 were transferred from the pancreas, 20 were from the gastrointestinal tract, and six were from other sites (two cases from the gallbladder, two cases from the abdomen, and two cases from the lung). During the study period, 55 patients with HCC were recruited as the HCC group. There were 38 males and 17 females with an age range of 35-71 years old and an average age of 54.29 ± 17.27 years old. There were 51 HCC patients associated with hepatitis, and the hepatitis infection rate was significantly higher than that of hNEN patients. The difference was statistically significant ($\chi^2 = 86.443$, $P = 0.000$). All patients signed informed consent, and this study was reviewed by the Ethics Committee of Cangzhou Central Hospital.

Research methods

Ultrasound examination: Ultrasound examination was performed using a Philips ultrasound affinity 70 diagnostic instruments equipped with CEUS imaging software. B-mode ultrasound and CEUS examinations were performed in each patient. The patient was placed in a supine position. The depth, focus, gain, and grayscale and color Doppler (CDFI) range were adjusted before examination. B-mode ultrasound examinations, including CDFI scans, were performed first. Lesion diameter (unit: cm), number (single/multiple), lesion property (solid/cyst), echo uniformity (uniform/non-uniform), echo level (high/low/mixed/equal), boundary (clear/unclear), accompanying signs (peripheral acoustic halo, posterior echo attenuation) of the liver lesions, and CDFI images were recorded.

Subsequently, a 2.4 mL contrast agent of SonoVue (Bracco) was used for CEUS. After the bolus injection into the left median cubital vein, 5 mL of saline was injected. The timing was started when the injection began. The whole examination process was about 3-5 min, and the image data were recorded. The time phase of hepatic CEUS was: 10-30 s after the injection of the contrast agent was the arterial phase, 31-120 s was the portal venous phase, and 121-360 s was the late phase. All examinations were performed by physicians with more than 10 years of ultrasound experience in our hospital.

Data collection and image analysis: B-mode ultrasound lesion diameter, number, boundary, lesion property, echo level, echo uniformity, and the number and proportion of accompanying signs (peripheral acoustic halo, posterior echo attenuation) of the liver lesions were observed and recorded. The characteristic differences of B-mode ultrasound between hNEN and HCC groups, transferred from different hNEN sources, and between hNEC and hNET groups were compared.

CEUS: The initial enhancement time (unit:s) of liver parenchyma and lesions was recorded. The washout to iso-enhancement time (unit:s) and washout to hypo-enhancement time (unit:s) of liver lesions were recorded as well. Then, the number and proportion of different enhancement levels at arterial phase (reference to the

enhancement level of adjacent liver tissue, divided into high/equal/low enhancement), enhancement levels at portal venous phase and late phase (equal/low enhancement), enhancement forms (uniform or non-uniform enhancement), enhancement-washout modes (fast enhancement and washout/equal enhancement and fast washout/low enhancement and fast washout), and special signs (adjacent and internal tumor vasculature, tumor necrosis no-enhancement zone, capsule enhancement in the late phase) of liver lesions were recorded. The characteristic differences of CEUS between hNEN and HCC groups, transferred from different hNEN sources, and between hNEC and hNET groups were compared.

Statistical analysis

All statistical analyses were performed with SPSS version 19.0 (IBM, Armonk, NY, United States) software. The numerical data were expressed as mean \pm SD and the categorical variables as number and percentage. The *t* test was used to compare the two groups of numerical data, and the three groups of numerical data were compared using one-way analysis of variance. The comparisons between the categorical variables were performed by chi-square test. If the minimum theoretical frequency was less than one, the Fisher's exact test was used. $P < 0.05$ was considered a statistically significant difference.

RESULTS

Pathological features of hNEN

Hematoxylin-eosin staining showed that the tumors were arranged by uniform circular or oval cells, which were nested or glandularly distributed. The cells were well-differentiated. There were fewer mitotic figures, and the atypia was not obvious (Figure 1). Immunohistochemical staining showed that 42 patients with hNEN were positive for ChrA (Figure 2), and 45 patients were positive for Syno (Figure 3).

Comparison of B-mode ultrasound characteristics between the hNEN group and the HCC group

Among all the B-mode ultrasound features, lesion diameter and the proportions of different lesion property and posterior echo attenuation were similar between the hNEN and HCC groups, and the differences were not statistically significant ($P > 0.05$). The proportions of multiple liver lesions, unclear boundary, and high echo lesion in the hNEN group were higher than those in the HCC group, and the differences were statistically significant ($P < 0.05$). The proportions of non-uniform echo and peripheral acoustic halo in the hNEN group were lower than those in the HCC group, and the differences were statistically significant ($P < 0.05$; Table 1).

Comparison of CEUS characteristics between hNEN and HCC groups

The initial enhancement time was similar in the hNEN and HCC groups, and the difference was not statistically significant ($P > 0.05$). The washout to iso-enhancement time and washout to hypo-enhancement time in the hNEN group were lower than those in the HCC group. The differences were statistically significant ($P < 0.05$).

The proportions of different CEUS enhancement characteristics, including enhancement at arterial phase, portal venous phase, and late phase, enhancement-washout mode, enhancement form, tumor vasculature, tumor necrosis, and capsule enhancement were similar in the two groups, and the differences were not statistically significant ($P > 0.05$; Table 2).

Comparison of B-mode ultrasound characteristics transferred from different sources of hNEN

The lesion diameter in hNEN lesions transferred from the gastrointestinal tract, pancreas, and other sites was similar, and there was no statistical significance ($P > 0.05$). In addition, the proportions of hNEN B-mode ultrasound characteristics, including number of liver lesions, lesion property, boundary, echo level, echo uniformity, posterior echo attenuation, and peripheral acoustic halo, transferred from different sources were similar, and the differences were not statistically significant ($P > 0.05$; Table 3).

Comparison of CEUS characteristics transferred from different sources of hNEN

The initial enhancement time, washout to iso-enhancement time, and washout to hypo-enhancement time of hNEN transferred from the gastrointestinal tract, pancreas, and other sites were similar. The differences were not statistically significant ($P > 0.05$). The proportions of CEUS enhancement characteristics transferred from

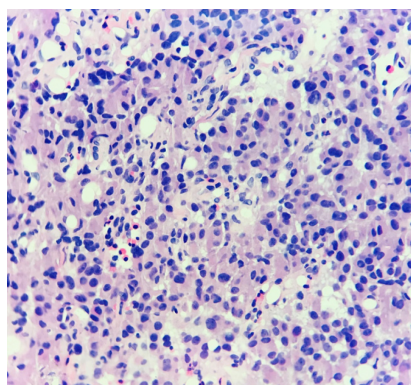


Figure 1 Hematoxylin-eosin staining results of hepatic neuroendocrine neoplasm.

different sources of hNEN, including enhancement at arterial phase, portal venous phase and late phase, enhancement-washout mode, enhancement form, tumor vasculature, tumor necrosis, and capsule enhancement, were similar, and the differences were not statistically significant ($P > 0.05$; Table 4).

Comparison of B-mode ultrasound characteristics between hNET and hNEC groups

The difference in lesion diameter between hNET and hNEC groups was not statistically significant ($P > 0.05$). The proportions of B-mode ultrasound features, including number of liver lesions, lesion property, boundary, echo level, echo uniformity, posterior echo attenuation, and peripheral acoustic halo, between hNET and hNEC groups were similar, and the differences were not statistically significant ($P > 0.05$; Table 5).

Comparison of CEUS characteristics between hNET and hNEC groups

There was no significant difference between hNEN and hNEC groups in terms of initial enhancement time, washout to iso-enhancement time, and washout to hypo-enhancement time ($P > 0.05$). Among the CEUS enhancement characteristics, the proportions of low enhancement at portal venous phase, non-uniform enhancement forms, and no tumor vasculature in the hNEC group were greater than those in the hNEN group ($P < 0.05$). The remaining CEUS enhancement characteristics, including the proportions of enhancement at arterial phase, enhancement at late phase, tumor necrosis, and capsule enhancement, were similar between the two groups. The differences were not statistically significant ($P > 0.05$; Table 6).

DISCUSSION

Imaging examination plays an important role in tumor discovery, auxiliary diagnosis, treatment, and follow-up. B-mode ultrasound and CEUS are widely used in clinical practice as non-invasive and simple imaging methods. However, due to the rareness of hNEN, there is currently little experience in imaging diagnosis of hNEN, which may result in clinicians not being able to obtain correct imaging results for hNEN, thus affecting the diagnosis and treatment of hNEN. Therefore, the present study first compared the B-mode ultrasound and CEUS performance between hNEN and HCC. Then, we compared the B-mode ultrasound and CEUS characteristics of different sources of hNEN and different malignant degrees of hNEN in order to report clinical diagnostic experience for hNEN.

Comparison of B-mode ultrasound and CEUS results between hNEN and HCC groups

Recent studies have reported that the characteristics of hNEN B-mode ultrasound are uniform hyperechoic or hypoechoic masses with clear boundaries^[12,13]. Most of hNEN CEUS characteristics are "fast forward and fast out"^[14]. Centripetal enhancement at the arterial phase appears first, and then uniform high enhancement appears^[15]. The characteristics of HCC B-mode ultrasound are hypoechoic or mixed echo masses with clear boundaries^[16]. The CEUS characteristics are "fast forward and fast out" as well. But most of the CEUS characteristics of HCC showed uniform high enhancement at the arterial phase^[17-19]. In this study, there was no significant difference in lesion size and the proportions of different lesion property and posterior echo attenuation in the comparison of B-mode ultrasound and CEUS results between hNEN and HCC

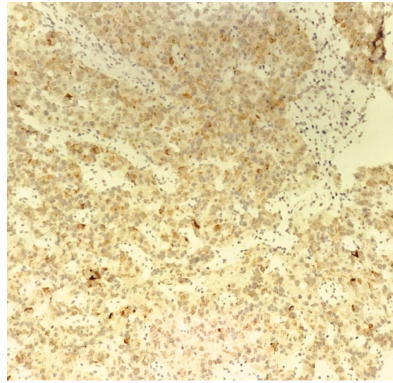


Figure 2 ChrA positive expression in hepatic neuroendocrine neoplasm.

groups. The possible reason is that both hNEN and HCC are solid and blood-rich tumors^[20]. They have similar characteristics in B-ultrasound signs and enhancement features. However, the proportions of multiple liver lesion, unclear border, and high echo lesion in the hNEN group were higher than those in the HCC group. The proportions of non-uniform echo and peripheral acoustic halo in the hNEN group were lower than those in the HCC group. It has been suggested that if the liver lesions found in the ultrasound examination are multiple, uniform high echo, and without peripheral acoustic halo, it may be hNEN. Further examination should be performed to determine if there are extrahepatic lesions.

In the comparison of CEUS results, the initial enhancement time was similar between the hNEN and HCC groups, but the washout to iso-enhancement time and washout to hypo-enhancement time in the hNEN group were lower than those in the HCC group. These findings indicated that the washout time in hNEN was earlier than that in HCC. The possible reason is that hNENs are transferred from different sources. The blood flow supply composition is different, which results in a different washout time than HCC^[21,22]. In addition, the proportions of CEUS characteristics, including enhancement of arterial phase, portal venous phase, and enhancement of late phase, enhancement forms, tumor vasculature, tumor necrosis, and capsule enhancement, were similar in the hNEN and HCC groups. Because the CEUS enhancement features of hNEN and HCC are similar, it is difficult to distinguish clinically. It is necessary to pay special attention to the difference of contrast agent washout time between hNEN and HCC.

Therefore, this study suggests two points in the ultrasound examination: (1) Intrahepatic lesions are multiple, uniform, and high echo and without peripheral acoustic halo; and (2) In the CEUS performance of intrahepatic lesions, the uniform high enhancement at arterial phase was found, and the washout is rapid. The diagnosis of hNEN needs to be considered.

Comparison of B-mode ultrasound and CEUS results among hNENs from different sources

hNEN can be transferred from multiple sites, including the pancreas, gastrointestinal tract, liver, lungs, adrenal glands, *etc.* Gastroenteropancreatic NENs are the main source of hNEN^[23]. Previous studies have revealed that although the treatment of hNEN is surgery, the efficacy and 5-year survival of different sources of hNEN are different^[24-26]. The survival time of hNEN patients from the gastrointestinal tract is significantly longer than that of hNEN patients from the pancreas^[27]. Ablation, embolism, and liver transplantation have different effects on hNEN from different sources^[28,29]. In addition, some patients with hNEN need to undergo surgery again to remove the primary lesion because they have misjudged the source of hNEN before surgery^[30-33]. Therefore, predicting the possible primary site of hNEN is important in guiding the patient's examination, such as finding the extrahepatic primary tumor and the treatment plan. This study analyzed B-mode ultrasound and CEUS results of hNENs from the gastrointestinal tract, pancreas, and other sites. We found there was no significant difference in B-mode ultrasound and CEUS characteristics of hNEN from different sources. All of them were mainly multiple hyperechoic lesions, and the CEUS showed uniformly high enhancement at arterial phase and rapid washout. This indicated that it is difficult to identify hNEN from different sources only by ultrasound. Therefore, this study suggests that when hNEN is suspected to be a metastatic tumor, the pathological examination should be performed to clarify the primary lesion to prevent missed diagnosis.

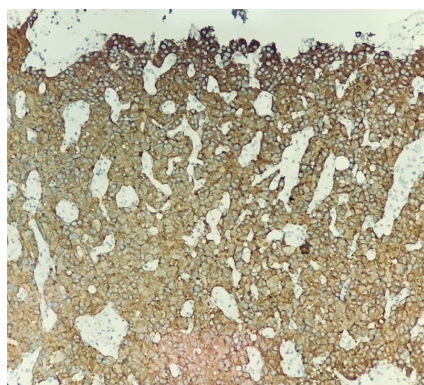


Figure 3 Synovial positive expression in hepatic neuroendocrine neoplasm.

Comparison of B-mode ultrasound and CEUS results between hNET and hNEC groups

All hNENs have malignant potential^[34-37], and hNEN can be divided into poorly differentiated hNEC (G3 grade) and highly differentiated hNET (G1 and G2 grade) according to its degree of differentiation^[38-40]. Most hNET patients require local therapy, and most hNEC patients require systemic therapy^[41-43]. Therefore, accurate identification of hNEC and hNET has great significance for clinical treatment of patients. In this study, the characteristics of B-mode ultrasound of hNEC and hNET groups were compared. It was found that both hNEC and hNET groups showed multiple solid lesions, uniform and high echo, no posterior echo attenuation, and peripheral acoustic halo. The difference was not obvious. When comparing CEUS features, it was found that the initial enhancement time, washout to iso-enhancement time, and washout to hypo-enhancement time were similar between the two groups.

The proportions of enhancement at arterial phase, enhancement at late phase, tumor necrosis, and capsule enhancement were similar as well. However, there were differences in the enhancement level at the portal vein phase. It was low enhancement in the hNEC group, while some of the hNETs showed partial equal enhancement. In addition, the proportion of combined tumor vasculature in the hNEC group was larger than that in the hNET group. The possible reason is that hNEC is mainly supplied by arteries, and washout is fast at the portal venous phase. Compared with hNEC, hNET has more portal blood supply, which leads to equal enhancement at the portal venous phase. This is consistent with the biological behavior and malignancy of the tumor^[44]. It also explains to some extent why hNEC has a low enhancement level in the portal venous phase and a large proportion of tumor blood vessels^[45,46]. In addition, compared with hNET, hNEC has more non-uniform enhancement form at the portal venous phase, probably because hNEC is more prone to cystic lesions, resulting in non-uniform enhancement in CEUS^[15,47,48]. Therefore, when the CEUS result of hNEN is equal enhancement at the portal venous phase and uniform enhancement form, hNET can be considered. If there is low enhancement at the portal venous phase, non-uniform enhancement form, and combined tumor vasculature, hNEC should be highly suspected. Further medical treatment measures should be taken.

Limitations and perspectives

Because patients with hNEN are rare, there are currently few targeted studies about hNEN. The number of patients recruited in this study was limited. Patients with primary hNEN were not included in this study. There are further research plans to conduct a multi-center study to collect detailed data from hNEN patients to make the results more comprehensive.

Conclusion

In summary, this study compared the ultrasound characteristics between hNEN and HCC and among hNENs from different sources and malignant degrees. We found that compared with HCC, hNEN showed multiple intrahepatic lesions, uniform high echo, uniform high enhancement at the arterial phase, and rapid washout. The ultrasound characteristics of hNENs from different sources were similar. The low enhancement at portal venous phase, overall non-uniform enhancement form, and the proportion of combined tumor vasculature in hNEC were larger than those of hNET, indicating that hNEC and hNET can be initially identified based on CEUS results.

Table 1 Comparison of B-mode ultrasound characteristics between hepatic neuroendocrine neoplasm and hepatocellular carcinoma groups, *n* (%)

| B-mode Ultrasound characteristics | | hNEN group, <i>n</i> = 55 | HCC group, <i>n</i> = 55 | <i>t/χ</i> ² | <i>P</i> value |
|-----------------------------------|-------------|---------------------------|--------------------------|-------------------------|--------------------|
| Diameter in cm | | 4.32 ± 1.38 | 3.91 ± 1.27 | 1.621 | 0.108 |
| Number of liver lesions | Single | 19 (34.5) | 47 (85.5) | 29.697 | 0.000 |
| | Multiple | 36 (65.5) | 8 (14.5) | | |
| Lesion property | Solid | 50 (90.9) | 47 (85.5) | 0.785 | 0.376 |
| | Cyst | 5 (9.1) | 8 (14.5) | | |
| Boundary | Clear | 29 (52.7) | 40 (72.7) | 4.705 | 0.030 |
| | Unclear | 26 (47.3) | 15 (27.3) | | |
| Echo level | High | 28 (50.9) | 13 (23.6) | 9.498 | 0.023 |
| | Low | 17 (30.9) | 24 (43.6) | | |
| | Mixed | 10 (18.2) | 17 (30.9) | | |
| | Equal | 0 (0.0) | 1 (1.8) | | |
| Echo uniformity | Uniform | 39 (70.9) | 26 (47.3) | 6.356 | 0.012 |
| | Non-uniform | 16 (29.1) | 29 (52.7) | | |
| Posterior echo attenuation | Yes | 6 (10.9) | 2 (3.6) | - | 0.271 ¹ |
| | No | 49 (89.1) | 53 (96.4) | | |
| Peripheral acoustic halo | Yes | 13 (23.6) | 27 (49.1) | 7.700 | 0.006 |
| | No | 42 (76.4) | 28 (50.9) | | |

¹Represent Fisher's exact test. hNEN: Hepatic neuroendocrine neoplasm; HCC: Hepatocellular carcinoma.**Table 2 Comparison of contrast-enhanced ultrasound characteristics between hepatic neuroendocrine neoplasm group and hepatocellular carcinoma group, *n* (%)**

| Contrast-enhanced Ultrasound characteristics | | hNEN group, <i>n</i> = 55 | HCC group, <i>n</i> = 55 | <i>t/χ</i> ² | <i>P</i> value |
|--|---------------------------------|---------------------------|--------------------------|-------------------------|----------------|
| Initial enhancement time in s | | 16.23 ± 5.29 | 16.52 ± 5.17 | 0.291 | 0.772 |
| Washout to iso-enhancement time in s | | 26.91 ± 15.39 | 47.26 ± 16.84 | 6.615 | 0.000 |
| Washout to hypo-enhancement time in s | | 59.84 ± 37.91 | 99.63 ± 61.82 | 5.092 | 0.000 |
| Enhancement level at arterial phase | High | 53 (96.4) | 55 (100) | 2.037 | 0.154 |
| | Equal | 2 (3.6) | 0 (0) | | |
| | Low | 0 (0) | 0 (0) | | |
| Enhancement level at portal venous phase | Equal | 7 (12.7) | 11 (20.0) | 1.063 | 0.303 |
| | Low | 48 (87.3) | 44 (80.0) | | |
| Enhancement level at late phase | Equal | 2 (3.6) | 1 (1.8) | 0.343 | 0.558 |
| | Low | 53 (96.4) | 54 (98.2) | | |
| Enhancement forms | Fast forward and fast out | 53 (96.4) | 51 (92.8) | 0.705 | 0.401 |
| | Equal/slow forward and fast out | 2 (3.6) | 4 (7.2) | | |
| Enhancement forms | Uniform | 33 (60) | 39 (70.9) | 1.447 | 0.229 |
| | Non-uniform | 22 (40) | 16 (29.1) | | |
| Tumor vasculature | Yes | 34 (61.8) | 38 (69.1) | 0.643 | 0.423 |
| | No | 21 (38.2) | 17 (30.9) | | |
| Tumor necrosis | Yes | 16 (29.1) | 19 (34.5) | 0.377 | 0.539 |
| | No | 39 (70.9) | 36 (65.5) | | |
| Capsule enhancement | Yes | 7 (12.7) | 2 (3.6) | 3.025 | 0.082 |
| | No | 48 (87.3) | 53 (96.4) | | |

hNEN: Hepatic neuroendocrine neoplasm; HCC: Hepatocellular carcinoma.

Table 3 Comparison of B-mode ultrasound characteristics transferred from different sources of hepatic neuroendocrine neoplasm, *n* (%)

| B-mode Ultrasound characteristics | | gastrointestinal tract, <i>n</i> = 20 | Pancreas, <i>n</i> = 29 | Other sites, <i>n</i> = 6 | <i>F</i> / χ^2 | <i>P</i> value |
|-----------------------------------|-------------|---------------------------------------|-------------------------|---------------------------|---------------------|--------------------|
| Diameter in cm | | 3.24 ± 1.96 | 2.98 ± 1.95 | 3.41 ± 2.06 | 1.772 | 0.163 |
| Number of liver lesions | Single | 7 (35) | 10 (34.5) | 2 (33.3) | - | 1.000 ¹ |
| | Multiple | 13 (65) | 19 (65.5) | 4 (66.7) | | |
| Lesion property | Solid | 19 (95.0) | 25 (86.0) | 6 (100.0) | 1.781 | 0.410 |
| | Cyst | 1 (5.0) | 4 (13.8) | 0 (0) | | |
| Boundary | Clear | 10 (50.0) | 15 (51.7) | 4 (66.47) | - | 0.856 ¹ |
| | Unclear | 10 (50.0) | 14 (48.3) | 2 (16.7) | | |
| Echo level | High | 6 (30.0) | 17 (58.6) | 4 (66.7) | - | 0.228 ¹ |
| | Low | 10 (50.0) | 7 (24.1) | 1 (33.3) | | |
| | Mixed | 4 (20.0) | 5 (17.2) | 1 (33.3) | | |
| | Equal | 0 (0) | 0 (0) | 0 (0) | | |
| Echo uniformity | Uniform | 15 (75.0) | 20 (69.0) | 4 (66.7) | - | 0.916 ¹ |
| | Non-uniform | 5 (25.0) | 9 (31.0) | 2 (33.3) | | |
| Posterior echo attenuation | Yes | 2 (10.0) | 4 (13.8) | 0 (0) | - | 1.000 ¹ |
| | No | 18 (90.0) | 25 (86.2) | 6 (100.0) | | |
| Peripheral acoustic halo | Yes | 16 (80.0) | 21 (72.4) | 5 (83.3) | - | 0.900 ¹ |
| | No | 4 (20.0) | 8 (27.6) | 1 (16.7) | | |

¹Represent Fisher's exact test.**Table 4 Comparison of contrast-enhanced ultrasound characteristics transferred from different sources of hepatic neuroendocrine neoplasm, *n* (%)**

| Contrast-enhanced ultrasound characteristics | | Gastrointestinal tract, <i>n</i> = 20 | Pancreas, <i>n</i> = 29 | Other sites, <i>n</i> = 6 | <i>t</i> / χ^2 | <i>P</i> value |
|--|---------------------------------|---------------------------------------|-------------------------|---------------------------|---------------------|--------------------|
| Initial enhancement time in s | | 16.28 ± 5.82 | 16.83 ± 6.16 | 15.22 ± 4.92 | 1.305 | 0.372 |
| Washout to iso-enhancement time in s | | 28.82 ± 12.38 | 27.29 ± 14.92 | 21.83 ± 11.23 | 0.924 | 0.477 |
| Washout to hypo-enhancement time in s | | 64.93 ± 36.29 | 55.28 ± 31.83 | 58.21 ± 29.65 | 0.874 | 0.592 |
| Enhancement level at arterial phase | High | 19 (95.0) | 28 (96.6) | 6 (100.0) | 0.335 | 0.846 |
| | Equal | 1 (5.0) | 1 (3.4) | 0 (0) | | |
| | Low | 0 (0) | 0 (0) | 0 (0) | | |
| Enhancement level at portal venous phase | Equal | 2 (10.0) | 5 (17.2) | 0 (0) | - | 0.610 ¹ |
| | Low | 18 (90.0) | 24 (82.8) | 6 (100.0) | | |
| Enhancement level at late phase | Equal | 1 (5.0) | 1 (3.4) | 0 (0) | - | 1.000 ¹ |
| | Low | 19 (95.0) | 28 (96.6) | 6 (100.0) | | |
| Enhancement forms | Fast forward and fast out | 19 (95.0) | 28 (96.6) | 6 (100.0) | - | 1.000 ¹ |
| | Equal/slow forward and fast out | 1 (5.0) | 1 (3.4) | 0 (0) | | |
| Enhancement forms | Uniform | 13 (65.0) | 16 (55.2) | 4 (66.7) | - | 0.729 ¹ |
| | Non-uniform | 7 (35.0) | 13 (44.8) | 2 (33.3) | | |
| Tumor vasculature | Yes | 14 (70.0) | 17 (58.6) | 3 (50.0) | - | 0.667 ¹ |
| | No | 6 (30.0) | 12 (41.4) | 3 (50.0) | | |
| Tumor necrosis | Yes | 4 (20.0) | 10 (34.5) | 2 (33.3) | - | 0.569 ¹ |
| | No | 16 (80.0) | 19 (65.5) | 4 (66.7) | | |
| Capsule enhancement | Yes | 2 (10.0) | 4 (13.8) | 1 (16.7) | - | 1.000 ¹ |
| | No | 18 (90.0) | 25 (86.2) | 5 (83.3) | | |

¹Represent Fisher's exact test.

Table 5 Comparison of B-mode ultrasound characteristics between hepatic neuroendocrine tumor and hepatic neuroendocrine carcinoma groups, *n* (%)

| B-mode Ultrasound characteristics | | hNET group, <i>n</i> = 35 | hNEC group, <i>n</i> = 20 | <i>t</i> / χ^2 | <i>P</i> value |
|-----------------------------------|-------------|---------------------------|---------------------------|---------------------|--------------------|
| Diameter in cm | | 4.58 ± 2.91 | 5.08 ± 3.87 | 0.543 | 0.590 |
| Number of liver lesions | Single | 12 (34.3) | 7 (35.0) | 0.003 | 0.957 |
| | Multiple | 23 (65.7) | 13 (65.0) | | |
| Lesion property | Solid | 31 (88.6) | 19 (95.0) | 0.636 | 0.425 |
| | Cyst | 4 (11.4) | 1 (5.0) | | |
| Boundary | Clear | 18 (51.4) | 11 (55.0) | 0.065 | 0.799 |
| | Unclear | 17 (48.6) | 9 (45.0) | | |
| Echo level | High | 19 (54.3) | 9 (45.0) | 0.443 | 0.801 |
| | Low | 10 (28.6) | 7 (35.0) | | |
| | Mixed | 6 (17.1) | 4 (20.0) | | |
| | Equal | 0 (0) | 0 (0) | | |
| Echo uniformity | Uniform | 25 (71.4) | 14 (70.0) | 0.013 | 0.911 |
| | Non-uniform | 10 (28.6) | 6 (30.0) | | |
| Posterior echo attenuation | Yes | 5 (14.3) | 1 (5.0) | - | 0.399 ¹ |
| | No | 30 (85.7) | 19 (95.0) | | |
| Peripheral acoustic halo | Yes | 9 (25.7) | 4 (20.0) | - | 0.749 ¹ |
| | No | 26 (74.3) | 16 (80.0) | | |

¹Represent Fisher's exact test. hNET: Hepatic neuroendocrine tumor; hNEC: Hepatic neuroendocrine carcinoma.**Table 6 Comparison of contrast-enhanced ultrasound characteristics between hepatic neuroendocrine tumor and hepatic neuroendocrine carcinoma groups, *n* (%)**

| Contrast-enhanced Ultrasound characteristics | | hNET group, <i>n</i> = 35 | hNEC group, <i>n</i> = 20 | <i>t</i> / χ^2 | <i>P</i> value |
|--|---------------------------------|---------------------------|---------------------------|---------------------|--------------------|
| Initial enhancement time in s | | 16.83 ± 5.08 | 16.28 ± 4.93 | 0.834 | 0.854 |
| Washout to iso-enhancement time in s | | 30.84 ± 10.38 | 27.68 ± 9.74 | 1.856 | 0.804 |
| Washout to hypo-enhancement time in s | | 65.28 ± 37.84 | 51.72 ± 31.85 | 1.152 | 0.833 |
| Enhancement level at arterial phase | High | 33 (94.3) | 20 (100.0) | 1.186 | 0.276 |
| | Equal | 2 (5.7) | 0 (0) | | |
| | Low | 0 (0) | 0 (0) | | |
| Enhancement level at portal venous phase | Equal | 7 (20.0) | 0 (0) | 4.583 | 0.032 |
| | Low | 28 (80.0) | 20 (100.0) | | |
| Enhancement level at late phase | Equal | 1 (2.9) | 1 (5.0) | - | 1.000 ¹ |
| | Low | 34 (97.1) | 19 (95.0) | | |
| Enhancement forms | Fast forward and fast out | 34 (97.1) | 19 (95.0) | - | 1.000 ¹ |
| | Equal/slow forward and fast out | 1 (2.9) | 1 (5.0) | | |
| Enhancement forms | Uniform | 28 (80.0) | 5 (25.0) | 16.042 | 0.000 |
| | Non-uniform | 7 (20.0) | 15 (75.0) | | |
| Tumor vasculature | Yes | 15 (42.9) | 19 (95.0) | 14.661 | 0.000 |
| | No | 20 (57.1) | 1 (5.0) | | |
| Tumor necrosis | Yes | 10 (28.6) | 6 (30.0) | 0.013 | 0.911 |
| | No | 25 (71.4) | 14 (70.0) | | |
| Capsule enhancement | Yes | 6 (17.1) | 1 (5.0) | - | 0.402 ¹ |
| | No | 29 (82.9) | 19 (95.0) | | |

¹Represent Fisher's exact test. hNET: Hepatic neuroendocrine tumor; hNEC: Hepatic neuroendocrine carcinoma.**ARTICLE HIGHLIGHTS****Research background**

Hepatic neuroendocrine neoplasm (hNEN) is a rare tumor clinically. It is important to identify

the source and malignant degree of hNEN and distinguish it from hepatocellular carcinoma (HCC). Imaging examination is required for the initial screening of hNEN. However, there is a lack of data regarding imaging diagnosis of hNEN.

Research motivation

Because of the lack of imaging examination experience, the screening and identification of hNEN is difficult. Research has revealed that there are some differences among hNEN with different sources and malignant degrees screened by ultrasound and contrast-enhanced ultrasound (CEUS). By analyzing the characteristics of ultrasound and CEUS, our study hopes to provide more helpful information in the diagnosis of hNEN.

Research objectives

In this study, the ultrasound performance between hNEN and HCC and data of hNEN with different sources and malignant degrees were compared. The purpose of this study was to improve the accuracy of the identification of hNEN and provide useful information for its clinical diagnosis.

Research methods

A total of 55 patients with hNEN were recruited, the hNEN group. There were 35 cases in the hepatic neuroendocrine tumor (hNET) group, and 20 cases in the neuroendocrine carcinoma (hNEC) group. About 55 patients with HCC were recruited as the HCC group. The characteristic differences of B-mode ultrasound and CEUS between hNEN and HCC, hNEN from different sources, and between hNEC and hNET were compared and analyzed.

Research results

Compared with the HCC group, the proportions of multiple liver lesions, unclear borders, and high echo lesions were higher and the proportions of non-uniform echo and peripheral acoustic halo were lower in the hNEN group. In the hNEN group, the washout to iso-enhancement time and washout to hypo-enhancement time were lower than those of the HCC group. The proportion of low enhancement of portal venous phase, non-uniform enhancement forms, and combined tumor vasculature in the hNEC group was greater than that in the hNEN group.

Research conclusions

Compared with HCC, the ultrasound performance of hNEN showed more intrahepatic lesions, uniform high echo, uniform high enhancement at arterial phase, and rapid washout. Compared with hNET, the CEUS characteristics of hNEC are low enhancement of portal venous phase, non-uniform enhancement forms, and combined tumor vasculature.

Research perspectives

To expand this research, future studies should include more hospitals in order to collect detailed data from more hNEN patients. The ultrasound results of primary hNEN also need to be analyzed further to provide stronger evidence for clinical diagnosis.

REFERENCES

- 1 Yang K, Cheng YS, Yang JJ, Jiang X, Guo JX. Primary hepatic neuroendocrine tumor with multiple liver metastases: A case report with review of the literature. *World J Gastroenterol* 2015; **21**: 3132-3138 [PMID: 25780316 DOI: 10.3748/wjg.v21.i10.3132]
- 2 Tamburrino D, Spoletni G, Partelli S, Muffatti F, Adamenko O, Crippa S, Falconi M. Surgical management of neuroendocrine tumors. *Best Pract Res Clin Endocrinol Metab* 2016; **30**: 93-102 [PMID: 26971846 DOI: 10.1016/j.beem.2015.10.003]
- 3 Ortiz J, Balasubramanian M, Brown T, Cetrulo L. Liver transplant for neuroendocrine tumor metastatic to the liver: literature review and report of extirpation at 16-year recurrence. *Exp Clin Transplant* 2015; **13**: 86-91 [PMID: 25343464 DOI: 10.6002/ect.2013.0215]
- 4 Haug AR, Cindea-Drinus R, Auernhammer CJ, Reincke M, Beuschlein F, Wängler B, Uebleis C, Schmidt GP, Spitzweg C, Bartenstein P, Hacker M. Neuroendocrine tumor recurrence: diagnosis with 68Ga-DOTATATE PET/CT. *Radiology* 2014; **270**: 517-525 [PMID: 24056402 DOI: 10.1148/radiol.13122501]
- 5 Wang LM, An SL, Wu JX. Diagnosis and therapy of primary hepatic neuroendocrine carcinoma: clinical analysis of 10 cases. *Asian Pac J Cancer Prev* 2014; **15**: 2541-2546 [PMID: 24761861 DOI: 10.7314/APJCP.2014.15.6.2541]
- 6 Zhao ZM, Wang J, Ugwuowo UC, Wang L, Townsend JP. Primary hepatic neuroendocrine carcinoma: report of two cases and literature review. *BMC Clin Pathol* 2018; **18**: 3 [PMID: 29507528]
- 7 Beard RE, Finkelstein SD, Borhani AA, Minervini MI, Marsh JW. A massive hepatic tumor demonstrating hepatocellular, cholangiocarcinoma and neuroendocrine lineages: A case report and review of the literature. *Int J Surg Case Rep* 2017; **37**: 26-32 [PMID: 28623758 DOI: 10.1016/j.ijscr.2017.05.039]
- 8 Manta R, Nardi E, Pagano N, Ricci C, Sica M, Castellani D, Bertani H, Piccoli M, Mullineris B, Tringali A, Marini F, Germani U, Villanacci V, Casadei R, Mutignani M, Conigliaro R, Bassotti G, Zullo A. Pre-operative Diagnosis of Pancreatic Neuroendocrine Tumors with Endoscopic Ultrasonography and Computed Tomography in a Large Series. *J Gastrointest Liver Dis* 2016; **25**: 317-321 [PMID: 27689195 DOI: 10.15403/jgld.2014.1121.253.ned]
- 9 Hoeffel C, Job L, Ladam-Marcus V, Vitry F, Cadiot G, Marcus C. Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography. *Dig Dis Sci* 2009; **54**: 2040-2046 [PMID: 19034651 DOI: 10.1007/s10620-008-0570-x]
- 10 Kim TK, Jang HJ. Contrast-enhanced ultrasound in the diagnosis of nodules in liver cirrhosis. *World J*

- Gastroenterol* 2014; **20**: 3590-3596 [PMID: 24707142 DOI: 10.3748/wjg.v20.i13.3590]
- 11 **Bosman FT.** *WHO Classification of Tumours of the Digestive System*. Lyon: International Agency for Research on Cancer 2010;
 - 12 **Nomura Y**, Nakashima O, Akiba J, Ogasawara S, Fukutomi S, Yamaguchi R, Kusano H, Kage M, Okuda K, Yano H. Clinicopathological features of neoplasms with neuroendocrine differentiation occurring in the liver. *J Clin Pathol* 2017; **70**: 563-570 [PMID: 27881473 DOI: 10.1136/jclinpath-2016-203941]
 - 13 **Sahu S**, Scherthaner R, Ardon R, Chapiro J, Zhao Y, Sohn JH, Fleckenstein F, Lin M, Geschwind JF, Duran R. Imaging Biomarkers of Tumor Response in Neuroendocrine Liver Metastases Treated with Transarterial Chemoembolization: Can Enhancing Tumor Burden of the Whole Liver Help Predict Patient Survival? *Radiology* 2017; **283**: 883-894 [PMID: 27831830 DOI: 10.1148/radiol.2016160838]
 - 14 **Li R**, Tang CL, Yang D, Zhang XH, Cai P, Ma KS, Guo DY, Ding SY. Primary hepatic neuroendocrine tumors: clinical characteristics and imaging features on contrast-enhanced ultrasound and computed tomography. *Abdom Radiol (NY)* 2016; **41**: 1767-1775 [PMID: 27156080 DOI: 10.1007/s00261-016-0770-3]
 - 15 **Li W**, Zhuang BW, Wang Z, Liao B, Hong LY, Xu M, Lin XN, Xie XY, Lu MD, Chen LD, Wang W. Case Report of Contrast-Enhanced Ultrasound Features of Primary Hepatic Neuroendocrine Tumor: A CARE-Compliant Article. *Medicine (Baltimore)* 2016; **95**: e3450 [PMID: 27227910 DOI: 10.1097/MD.0000000000003450]
 - 16 **Lekht I**, Nayyar M, Luu B, Guichet PL, Ho J, Ter-Oganesyan R, Katz M, Gulati M. Intra-arterial contrast-enhanced ultrasound (IA CEUS) for localization of hepatocellular carcinoma (HCC) supply during transarterial chemoembolization (TACE): a case series. *Abdom Radiol (NY)* 2017; **42**: 1400-1407 [PMID: 28008454 DOI: 10.1007/s00261-016-1016-0]
 - 17 **Kim TK**, Noh SY, Wilson SR, Kono Y, Piscaglia F, Jang HJ, Lyschchik A, Dietrich CF, Willmann JK, Vezeridis A, Sirlin CB. Contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LI-RADS) 2017 - a review of important differences compared to the CT/MRI system. *Clin Mol Hepatol* 2017; **23**: 280-289 [PMID: 28911220 DOI: 10.3350/cmh.2017.0037]
 - 18 **Kim DW**, Talati C, Kim R. Hepatocellular carcinoma (HCC): beyond sorafenib-chemotherapy. *J Gastrointest Oncol* 2017; **8**: 256-265 [PMID: 28480065 DOI: 10.21037/jgo.2016.09.07]
 - 19 **Zhang X**, Ma L, Bao H, Zhang J, Wang Z, Gong P. Clinical, pathological and prognostic characteristics of gastroenteropancreatic neuroendocrine neoplasms in China: a retrospective study. *BMC Endocr Disord* 2014; **14**: 54 [PMID: 25001493 DOI: 10.1186/1472-6823-14-54]
 - 20 **Mayo SC**, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinski SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferrero A, Schulick RD, Choti MA, Mentha G, Strub J, Bauer TW, Adams RB, Aldrighetti L, Capussotti L, Pawlik TM. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol* 2010; **17**: 3129-3136 [PMID: 20585879 DOI: 10.1245/s10434-010-1154-5]
 - 21 **Coriat R**, Walter T, Terris B, Couvelard A, Ruszniewski P. Gastroenteropancreatic Well-Differentiated Grade 3 Neuroendocrine Tumors: Review and Position Statement. *Oncologist* 2016; **21**: 1191-1199 [PMID: 27401895 DOI: 10.1634/theoncologist.2015-0476]
 - 22 **Valadares LJ**, Costa Junior W, Ribeiro HS, Diniz AL, Coimbra FJ, Herman P. Resection of liver metastasis from neuroendocrine tumors: evaluation of results and prognostic factors. *Rev Col Bras Cir* 2015; **42**: 25-31 [PMID: 25992697 DOI: 10.1590/0100-69912015001006]
 - 23 **Watson GA**, Ahmed Y, Picardo S, Chew S, Cobbe S, Mahony C, Crotty J, Wallis F, Shelly MJ, Kiely P, Ipadeola OB, Healy V, Osman N, Gupta RK. Unusual Sites of High-Grade Neuroendocrine Carcinomas: A Case Series and Review of the Literature. *Am J Case Rep* 2018; **19**: 710-723 [PMID: 29915166 DOI: 10.12659/AJCR.908953]
 - 24 **Fiore F**, Del Prete M, Franco R, Marotta V, Ramundo V, Marciello F, Di Sarno A, Carratù AC, de Luca di Roseto C, Colao A, Faggiano A. Transarterial embolization (TAE) is equally effective and slightly safer than transarterial chemoembolization (TACE) to manage liver metastases in neuroendocrine tumors. *Endocrine* 2014; **47**: 177-182 [PMID: 24385266 DOI: 10.1007/s12020-013-0130-9]
 - 25 **Memon K**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Sato KT, Gupta R, Nikolaidis P, Miller FH, Yaghamai V, Gates VL, Atassi B, Newman S, Omary RA, Benson AB, Salem R. Radioembolization for neuroendocrine liver metastases: safety, imaging, and long-term outcomes. *Int J Radiat Oncol Biol Phys* 2012; **83**: 887-894 [PMID: 22137020 DOI: 10.1016/j.ijrobp.2011.07.041]
 - 26 **de Herder WW**, Mazzaferro V, Tavecchio L, Wiedenmann B. Multidisciplinary approach for the treatment of neuroendocrine tumors. *Tumori* 2010; **96**: 833-846 [PMID: 21302641 DOI: 10.1177/030089161009600537]
 - 27 **Shin Y**, Ha SY, Hyeon J, Lee B, Lee J, Jang KT, Kim KM, Park YS, Park CK. Gastroenteropancreatic Neuroendocrine Tumors with Liver Metastases in Korea: A Clinicopathological Analysis of 72 Cases in a Single Institute. *Cancer Res Treat* 2015; **47**: 738-746 [PMID: 25687852 DOI: 10.4143/crt.2014.224]
 - 28 **Iwasaki M**, Tsuchida K, Jinnai H, Komatsubara T, Arisaka T, Tsunemi M, Nakano M, Iijima M, Hiraishi H. Multimodal Treatment of Vasoactive Intestinal Polypeptide-producing Pancreatic Neuroendocrine Tumors with Liver Metastases. *Intern Med* 2017; **56**: 517-522 [PMID: 28250297 DOI: 10.2169/intermalmedicine.56.7512]
 - 29 **Pusceddu S**, Femia D, Lo Russo G, Ortolani S, Milione M, Maccauro M, Vernieri C, Prinzi N, Concas L, Leuzzi L, De Braud F, Buzzoni R. Update on medical treatment of small intestinal neuroendocrine tumors. *Expert Rev Anticancer Ther* 2016; **16**: 969-976 [PMID: 27353232 DOI: 10.1080/14737140.2016.1207534]
 - 30 **de Baere T**, Deschamps F, Tselikas L, Ducreux M, Planchard D, Pearson E, Berdelou A, Lebouilleux S, Elias D, Baudin E. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETS. *Eur J Endocrinol* 2015; **172**: R151-R166 [PMID: 25385817 DOI: 10.1530/EJE-14-0630]
 - 31 **Geramizadeh B**, Kashkoe A, Malekhosseini SA. Liver Metastasis of Gastrointestinal Neuroendocrine Tumors: A Single Center Experience. *Hepat Mon* 2016; **16**: e37293 [PMID: 27330538 DOI: 10.5812/hepatmon.37293]
 - 32 **Konukiewitz B**, Jesinghaus M, Steiger K, Schlitter AM, Kasajima A, Sipos B, Zamboni G, Weichert W, Pfarr N, Klöppel G. Pancreatic neuroendocrine carcinomas reveal a closer relationship to ductal adenocarcinomas than to neuroendocrine tumors G3. *Hum Pathol* 2018; **77**: 70-79 [PMID: 29596894 DOI: 10.1016/j.humpath.2018.03.018]
 - 33 **Cavalcoli F**, Rausa E, Conte D, Nicolini AF, Massironi S. Is there still a role for the hepatic locoregional treatment of metastatic neuroendocrine tumors in the era of systemic targeted therapies? *World J Gastroenterol* 2017; **23**: 2640-2650 [PMID: 28487601 DOI: 10.3748/wjg.v23.i15.2640]

- 34 **Tanaka H**, Matsusaki S, Baba Y, Isono Y, Kumazawa H, Sase T, Okano H, Saito T, Mukai K, Kaneko H. Neuroendocrine tumor G3: a pancreatic well-differentiated neuroendocrine tumor with a high proliferative rate. *Clin J Gastroenterol* 2015; **8**: 414-420 [PMID: [26439620](#) DOI: [10.1007/s12328-015-0609-4](#)]
- 35 **Rinke A**, Gress TM. Neuroendocrine Cancer, Therapeutic Strategies in G3 Cancers. *Digestion* 2017; **95**: 109-114 [PMID: [28161703](#) DOI: [10.1159/000454761](#)]
- 36 **Klimstra DS**, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010; **39**: 707-712 [PMID: [20664470](#) DOI: [10.1097/MPA.0b013e3181ec124e](#)]
- 37 **Engelman ES**, Leon-Ferre R, Naraev BG, Sharma N, Sun S, O'Dorisio TM, Howe J, Button A, Zamba G, Halfdanarson TR. Comparison of transarterial liver-directed therapies for low-grade metastatic neuroendocrine tumors in a single institution. *Pancreas* 2014; **43**: 219-225 [PMID: [24518499](#) DOI: [10.1097/MPA.0000000000000030](#)]
- 38 **Wang LX**, Liu K, Lin GW, Jiang T. Primary hepatic neuroendocrine tumors: comparing CT and MRI features with pathology. *Cancer Imaging* 2015; **15**: 13 [PMID: [26272674](#) DOI: [10.1186/s40644-015-0046-0](#)]
- 39 **Chen JX**, Rose S, White SB, El-Haddad G, Fidelman N, Yarmohammadi H, Hwang W, Sze DY, Kothary N, Stashek K, Wileyto EP, Salem R, Metz DC, Soulen MC. Embolotherapy for Neuroendocrine Tumor Liver Metastases: Prognostic Factors for Hepatic Progression-Free Survival and Overall Survival. *Cardiovasc Intervent Radiol* 2017; **40**: 69-80 [PMID: [27738818](#) DOI: [10.1007/s00270-016-1478-z](#)]
- 40 **Pavel M**, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95**: 157-176 [PMID: [22262022](#) DOI: [10.1159/000335597](#)]
- 41 **Hijioka S**, Hosoda W, Mizuno N, Hara K, Imaoka H, Bhatia V, Mekky MA, Tajika M, Tanaka T, Ishihara M, Yogi T, Tsutsumi H, Fujiyoshi T, Sato T, Hieda N, Yoshida T, Okuno N, Shimizu Y, Yatabe Y, Niwa Y, Yamao K. Does the WHO 2010 classification of pancreatic neuroendocrine neoplasms accurately characterize pancreatic neuroendocrine carcinomas? *J Gastroenterol* 2015; **50**: 564-572 [PMID: [25142799](#) DOI: [10.1007/s00535-014-0987-2](#)]
- 42 **Heetfeld M**, Chougnat CN, Olsen IH, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T; other Knowledge Network members. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2015; **22**: 657-664 [PMID: [26113608](#) DOI: [10.1530/ERC-15-0119](#)]
- 43 **Chung H**, Chapman WC. Liver transplantation for metastatic neuroendocrine tumors. *Adv Surg* 2014; **48**: 235-252 [PMID: [25293619](#) DOI: [10.1016/j.yasu.2014.05.003](#)]
- 44 **Schaefer B**, Zoller H, Schneeberger S. Con: Liver transplantation for expanded criteria malignant diseases. *Liver Transpl* 2018; **24**: 104-111 [PMID: [29125687](#) DOI: [10.1002/lt.24975](#)]
- 45 **Rossi RE**, Burroughs AK, Caplin ME. Liver transplantation for unresectable neuroendocrine tumor liver metastases. *Ann Surg Oncol* 2014; **21**: 2398-2405 [PMID: [24562931](#) DOI: [10.1245/s10434-014-3523-y](#)]
- 46 **Shen YH**, Chen S, Zhang WT, Ji Y, Yu L, Sun HC, Qiu SJ, Ren N, Zhou J. Clinical analysis of gastroenteropancreatic neuroendocrine tumor with liver metastasis, compared with primary hepatic neuroendocrine tumor. *J Cancer Res Ther* 2014; **10** Suppl: 276-280 [PMID: [25693935](#) DOI: [10.4103/0973-1482.151532](#)]
- 47 **Mazzaferro V**, Sposito C, Coppa J, Miceli R, Bhoori S, Bongini M, Camerini T, Milione M, Regalia E, Spreafico C, Gangeri L, Buzzoni R, de Braud FG, De Feo T, Mariani L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors. *Am J Transplant* 2016; **16**: 2892-2902 [PMID: [27134017](#) DOI: [10.1111/ajt.13831](#)]
- 48 **Giesel FL**, Wulfert S, Zechmann CM, Haberkorn U, Kratochwil C, Flechsig P, Kuder T, Schwartz LH, Bruchertseifer F. Contrast-enhanced ultrasound monitoring of perfusion changes in hepatic neuroendocrine metastases after systemic versus selective arterial ¹⁷⁷Lu/90Y-DOTATOC and ²¹³Bi-DOTATOC radioreptide therapy. *Exp Oncol* 2013; **35**: 122-126 [PMID: [23828389](#) DOI: [10.1016/j.canrad.2009.06.017](#)]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

