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Hilar cholangiocarcinoma, also named Klatskin tumor, accounts for 58-75% of extrahepatic cholangiocarcinoma, the annual incidence of which increases gradually in recent years and the overall survival rate is poor without significant change during the past 30 years [1-4]. The primary investigation for suspected Klatskin tumor is a transabdominal ultrasound (US) examination, which is highly sensitive for confirming biliary duct dilatation, localizing the site of obstruction and excluding gallstones. However, it has limited role in determining the nature of the obstruction and defining the extent of tumor involvement since the lesion is always isoechoic to surrounding liver and the infiltrative nature of the lesion. Currently, contrast-enhanced computed tomography (CECT) is one of the mostly used imaging methods for detecting the tumor and locating the level of biliary obstruction before surgery, whereas it is not suitable for patients who are allergic to CT contrast media and who has impaired kidney function. The technique of contrast-enhanced ultrasound (CEUS) has been introduced in clinical settings for several years, which has been shown to have same ability in characterizing focal liver lesions as CECT since it allows dynamic depiction of blood perfusion within the liver lesion [4,5]. Therefore, it was hypothesized that Klatskin tumor might have similar manifestations on both CEUS and CECT and CEUS might also been a useful tool in determining its nature. To confirm the hypothesis, the enhancement pattern of the tumor during various phases, portal vein infiltration by the tumor, lesion conspicuity, and examination results prior to pathological examination, on both CEUS and CECT, were investigated in the present study.
Methods and Materials

From March 2004 to August 2012, 32 consecutive patients with hilar cholangiocarcinomas who had received both CEUS and CECT examinations in our institution were retrospectively enrolled in this study. The patients were 22 men and 10 women, with a mean age of 53±13 years old (age range, 20-82 years old). All the patients had solitary lesions, and the maximal diameter of the 32 lesions ranged from 1.3 to 6.7 cm (mean diameter, 2.9±1.2 cm) on conventional US. Among them, 20 lesions were 3.0 cm or less in diameter, and the remaining 12 lesions were greater than 3.0 cm. All the patients were pathologically confirmed with specimens from surgery and pathological examination revealed all the lesions were adenocarcinomas.

Written informed consents were obtained from all patients, and the study was approved by the ethical Committee of the institution.

US examination

Two US machines were used in this study. One was an Acuson Sequoia 512 machine (Siemens Medical Solutions, Mountain View, CA) and the other was an GE Logiq expert 5. A vector transducer with frequency range of 1.0-4.0 MHz was applied for Sequoia 512 and a 3.5 convex transducer with a frequency range of 1.9-6.0 MHz was applied for GE. The installed contrast-specific imaging modes were contrast pulse sequencing (CPS) for Sequoia 512 and contrast harmonic imaging (CHI) for GE Logiq 5 expert, respectively. Both modes work under low acoustic power, and the corresponding mechanical index (MI) ranges were 0.15-0.21 for CPS in Sequoia 512 and 0.05-0.08 for CHI in Logiq 5.

Conventional US was carried out to sweep the liver and the lesion at hepatic hilum prior to CEUS examination. Once the target lesion was determined, the lesion size, echogenicity, and boundary were recorded, and the images that show the above-mentioned features best were stored digitally. Afterward, the imaging mode was shifted to CEUS mode and the imaging settings were optimized to ensure sufficient tissue cancellation with the maintenance of adequate depth penetration, with the diaphragm remaining barely visible.

The US contrast agent used was SonoVue (Bracco, Milan, Italy), a sulfur hexafluoride-filled microbubble contrast agent. A total of 2.4 ml contrast agent was administrated via the antecubital vein in a bolus fashion, followed by 5 ml saline flush. Upon start of the SonoVue injection, the stop clock was started simultaneously.

During the CEUS procedure, the transducer was kept in a stable position to visualize the target lesion and the imaging settings were kept constant. The whole process of CEUS was continuously observed until the disappearance of contrast agent in liver parenchyma. According to the previous studies, the CEUS process was divided into arterial (i.e. 8-30 s from the
beginning of contrast agent administration), portal (31-120 s), and late (121-360 s) phases [6-10].

**CT examination**

The Xvision single slice helical CT machine (Toshiba, Tokyo, Japan) or the Aquilion 64-slice helical CT machine (Tokyo, Japan) was used for CECT examination. The intervals between CEUS and CECT examinations were less than 14 days and no treatment was carried out before CEUS or CECT examinations. The imaging settings for single slice helical CT examination were as follows: 5-10 mm collimation, 1:1 pitch, 120 kV, 250 mAs and those for 64-slice helical CT examination were 0.5 mm × 64 mm collimation, 120 kV, 150-200 mAs. The standard dual-phase scan procedure was used for both machines. An unenhanced helical sequence scan through the liver was performed in advance, thereafter 50-100 ml (1.5 ml/kg) of nonionic iodinated contrast material (Ultravist, Schering, Berlin, Germany) was administered via antecubital vein by power injection at a rate of 3 ml/s (single slice helical CT) or 4 ml/s (64-slice helical CT). The arterial phase sequence was obtained at 25-32 s after contrast material administration, followed by a portal venous phase sequence beginning at 60 s after contrast infusion.

**Data analysis**

The US and CEUS images were reviewed retrospectively by two investigators who had more than 5 years of experience in liver US and CEUS examinations. They were not involved in US examination and were blind to clinical histories, histopathologic results, and other imaging findings of the patients. The disagreement in evaluating the images was solved by consensus. The enhancement extent, enhancement pattern, and the changes along with the dynamic phases, were evaluated. The enhancement of the lesion was referenced to the adjacent liver parenchyma and was classified into nonenhancement, hypoenhancement, isoenhancement, and hyperenhancement. The enhancement patterns of the lesions were categorized into peripheral rim-like enhancement, homogeneous enhancement and heterogeneous enhancement, according to the guideline recently released by EFSUMB study group [8].

The CT images were interpreted by the consensus of two experienced radiologists who were unaware of the clinical and other imaging information of the patients. The enhancement extent of the lesions was subdivided into nonenhancement, hypoenhancement, isoenhancement, and hyperenhancement, with reference to the adjacent liver parenchyma, alike in CEUS. And the enhancement patterns were also subdivided into peripheral rim-like enhancement, homogeneous enhancement and heterogeneous enhancement. Comparisons of the enhancement pattern during the arterial phase and the enhancement extent during the arterial and portal phases between CEUS and CECT were performed, whereas comparison in late phase was not performed.
as the routine scanning protocol of CECT did not include late phase scanning in our institution.

The presence of portal vein infiltration was also evaluated on US, CEUS and CECT. On US, portal vein was considered to be involved by tumor when there was (1) vessel occlusion detected by color Doppler imaging, (2) US findings of encasement, defined as an abrupt decrease in vessel caliber or focal mural irregularity, (3) absence of a cleavage plane between the tumor and the echogenic wall of the vessel, and (4) focal disappearance of the echogenic wall of the vessel [11-15]. Portal vein infiltration was diagnosed with CECT when there was (1) a soft tissue infiltration around the vascular structure, (2) portal vein encasement by tumor, and (3) focal luminal narrowing of the portal vein or its branches in serial images [13,14]. The surgical findings were used as the reference to determine whether or not portal vein infiltration was present. The conspicuity of the tumor on CEUS and CECT was also compared and the visualization of the tumor was subdivided into three scales: (1) definitely distinct, that was, the contour of the tumor was well delineated and the contrast between the tumor and surrounding tissue was obvious; (2) distinct, that was, the contour of the tumor was visible and the contrast between the tumor and surrounding tissue was visible; and (3) indistinct, that was, the contour of the tumor was barely visible and there was no visible contrast between the tumor and surrounding tissue.

The examination results of CEUS and CECT in advance of surgery were recorded and compared. All the diagnoses were made by experienced radiologists. The criteria for diagnosis of hilar cholangiocarcinoma for CEUS or CECT were as follows: (1) intrahepatic bile duct dilation, (2) absence of extrahepatic bile duct dilation, (3) intraluminal mass at hepatic hilum, with or without liver infiltration, and (4) various enhancement extents during arterial phase [11-15].

**Statistical analysis**

Quantitative data were expressed as mean±standard deviation. The t-test was used to compare the difference between independent quantitative data and McNemar test was used to compare the difference between paired qualitative data. $P < 0.05$ was considered to indicate a statistically significant difference. The statistical analyses were performed using the SPSS 13.0 software package (SPSS Inc., Chicago, IL).
Results

On conventional US, the 32 lesions were hypoechoic in 5 (15.6%), isoechoic in 18 (56.3%), and hyperechoic in 9 (28.1%). Associated intrahepatic bile duct dilation was found in all the cases. Intrahepatic bile duct calculi were present in 3 (9.4%) of 32 patients. Infiltration to peripheral liver parenchyma was found in 10 (31.3%) patients and intrahepatic metastasis was found in 5 (15.6%) patients. Intralesional blood flow signals were detected in 7 (21.9%) of 32 lesions on color Doppler imaging and the remaining 25 (78.1%) showed no blood flow signals. On unenhanced CT, hypo attenuation was depicted in 25 (78.1%) lesions and iso-attenuation in 7 (21.9%).

The initial lesion enhancement ranged from 7 to 27 s (mean, 15±4 s) after contrast agent administration, and that for liver parenchyma ranged from 7 to 28 s (mean, 16±5 s). The enhancement of the lesion was earlier in 12 (37.5%) lesions, simultaneous in 16 (50.0%), and later in 4 (12.5%), in comparison with adjacent liver parenchyma.

During the arterial phase, hyperenhancement, isoenhancement, and hypoenhancement were visualized in 14 (43.8%), 14 (43.8%), and 4 (12.4%) of 32 lesions, respectively, on CEUS, and in 12 (37.5%), 9 (28.1%), and 11 (34.4%) lesions, respectively, on CECT (P = 0.162, Table 1). As to enhancement pattern, peripheral rim-like hyperenhancement was illustrated in 3 (9.4%) lesions on CEUS and 2 (6.3%) on CECT, homogeneous enhancement in 11 (34.4%) on CEUS and 9 (28.1%) on CECT, inhomogeneous enhancement in 18 (56.2%) on CEUS and 21 (65.6%) on CECT (P = 1.000). There was no significant correlation between enhancement pattern and tumor size on CEUS (P = 0.273, Table 2) (Fig. 1).

During the portal phase of CEUS, 30 (93.8%) lesions appeared as hypoenhancement and the tumor margins became more conspicuous, 1 (3.1%) appeared as isoenhancement, and 1 (3.1%) appeared as hyperenhancement. And on CECT, hypoenhancement was found in 23 (71.9%), isoenhancement in 8 (25.0%), and hyperenhancement in 1 (3.1%) lesion (P = 0.046, in comparison with CEUS) (Fig. 2). In late phase of CEUS, 30 (93.8%) lesions showed hypoenhancement and 2 (6.2%) showed isoenhancement. The grading scores for delineating tumor conspicuity were defined to be 1 in 6 (18.8%) of 32 lesions on conventional US, 26 (81.3%) on CEUS, and 16 (50.0%) on CECT; 2 in 19 (59.4%), 6 (18.8%), 9 (28.1%); and 3 in 7 (21.9%), 0 (0.0%), and 7 (21.9%) (conventional US versus CEUS, P = 0.000; CEUS versus CECT, P = 0.013; conventional US versus CECT, P = 0.013).

Portal vein infiltration was revealed in 19 (59.4%) patients on surgery. The accuracies in determining the portal vein infiltration for conventional US, CEUS, and CECT were 84.2% (16/19), 89.5% (17/19), and 78.9% (15/19), respectively (conventional US versus CEUS, P = 1.000; CEUS versus CECT, P = 0.500; conventional US versus CECT, P = 1.000).
CEUS correctly diagnosed 30 (93.8%) lesions as hilar cholangiocarcinomas before pathological examination, and the other 2 (6.2%) lesions were defined as indeterminate. CECT made correct diagnoses in 25 (78.1%) lesions. For the remaining lesions, 2 (6.2%) were defined as indeterminate, 4 (12.5%) were misdiagnosed as intrahepatic cholangiocarcinomas, and 1 (3.1%) was misdiagnosed as hepatocellular carcinoma. There was no significant difference in diagnostic results between CEUS and CECT before pathological examination ($P = 0.125$).
Fig. 1: Hilar cholangiocarcinoma in a 38-year-old man. (A) Conventional US shows that the lesion (arrow) is slightly hyperechoic. (B) The lesion (arrow) appears to be homogeneous hyperenhancement during the arterial phase of CEUS. (C) The lesion (arrow) becomes hypoenhancement during the portal phase of CEUS. (D) Unenhanced CT shows the lesion (arrow) is hypoattenuation. (E) In the arterial phase of CECT, the lesion (arrow) shows homogeneous isoenhancement. (F) The lesion (arrow) becomes hypoenhancement in the portal phase of CECT.

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Fig. 2: Hilar cholangiocarcinoma in a 49-year-old man. (A) Conventional US shows that the lesion (arrow) is isoechoic. Portal vein infiltration is seen that shows disappearance of the echogenic interface forming the wall of the portal vein. (B) The lesion (arrow) appears to be inhomogeneous isoenhancement during the arterial phase of CEUS. (C) The lesion (arrow) becomes hypoenhancement during the portal phase of CEUS. (D) Unenhanced CT shows the lesion (arrow) is hypoattenuation. (E) In the arterial phase of CECT, the lesion (arrow) shows inhomogeneous isoenhancement. (F) The lesion (arrow) becomes hypoenhancement in the portal phase of CECT.

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≤3.0 cm versus >3.0 cm, t-Test, P=0.273.

Fig. 3

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Fig. 4

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\(<3.0\) cm versus > 3.0 cm, \(t\)-test, \(p=0.273\).
Conclusion

Hilar cholangiocarcinoma is initially defined as an adenocarcinoma of the hepatic duct at the bifurcation within the porta hepatis. Now, it usually includes cancers of the common hepatic duct. It is often in an advanced stage at the time of diagnosis because the tumor is infiltrative and involvement of adjacent portal vein is frequent [1-3]. The most common presenting symptom is obstructive jaundice, and most affected patients initially undergo US examination. Conventional US is the modality of choice for screening obstructive jaundice and the accuracy for determining the obstructive level is as high as 95-100% [15]. Dilation of intrahepatic bile duct with a normal-caliber extrahepatic bile duct is suggestive of hilar cholangiocarcinoma, and these findings may be the only and first clues to the presence of this pathological condition. In some cases, isoechoic or slightly hyperechoic mass is visualized within the lumen. Truncation change or taper-like stricture of the intrahepatic duct and associated mural thickening are always seen. The tumor may infiltrate the adjacent liver tissue, spread through the intrahepatic duct and even lead to intrahepatic metastasis. Despite of these, the isoechoic nature of the Klatskin tumor and its propensity to grow in an infiltrative periductal pattern make its detection and the determination of its extent difficult, especially for the inexperienced operator [3,15,16].

CECT offers the advantage of improved resolution and depiction of intratumoral hemodynamics, and is one of the widely used modalities for diagnosis of this entity. On unenhanced CT, the typical cases show masses in the duct and generally are hypo- or iso-attenuating. Other cases may only be visualized to have dilation of intrahepatic bile duct or focally thickened ductal wall obliterating the lumen and no obvious masses were found. In the arterial phase of enhanced CT, slightly inhomogeneous enhancement was usually found and the attenuation varies from hypo-, iso- to slightly hyper-attenuation. In the portal phase, hypo- or iso-attenuation is generally found and in the late phase the enhancement becomes more obvious that it reaches to peak and showswell-defined hyperattenuation about 10 min after contrast injection [13,14,17,19].

The newly advented real-time CEUS is comparable with CECT in characterizing focal liver lesions, whereas it is seldom used for diagnosis of hilar cholangiocarcinoma [4,5,20]. Khalili et al. [21] observed the enhancement pattern of 29 hilar cholangiocarcinomas by using Levovist and high MI imaging technique. They found that all the tumors showed hypoenhancement in liver-specific late phase and the conspicuity of the tumors increased significantly compared with conventional US. Bauditz et al. [22] found that visualization of a tumor and differentiation from normal liver parenchyma was possible in 36% patients by use of baseline US, whereas in 100% by use of CEUS. They also found that 89% of neoplasms showed hypovascularisation compared to surrounding liver tissue and 11% tumors were hypervascularised. In the present study, we observed the enhancement patterns of 32 hilar cholangiocarcinomas by using second generation US contrast agent and low MI imaging technique. The results showed that nearly 88% tumors enhanced earlier than or simultaneously with the adjacent liver tissue during the arterial phase.
Hyper- or isoenhancement accounted for 88% tumors, in contrast to the results by Bauditz et al. [22]. The difference was partly due to that both high MI power Doppler and low MI CPS imaging modes, as well as Levovist and SonoVue, were used in the study of Bauditz et al. [22], whereas only low MI imaging mode and SonoVue were used in the present study. To our knowledge, this is the first report of evaluating hilar cholangiocarcinoma solely using low MI CEUS and SonoVue. Based on the results of this study, hilar cholangiocarcinoma is also mainly supplied by arterial blood flow. On CECT, the tumor showed various enhancement extents from hyper- to hypoenhancement, and there was no significant difference between CEUS and CECT in enhancement extent during the arterial phase.

During the portal phase, nearly 94% tumors showed hypoenhancement and 3% showed isoenhancement on CEUS. In contrast to the adjacent liver tissue, the tumor margin was clearly visualized and the tumor conspicuity was greatly enhanced. Similar results were found during the late phase. On the other hand, on CECT, hypoenhancement and isoenhancement accounted for 72% and 25% tumors. Thus in comparison with CEUS, the tumor washes out slowly on CECT. The enhancement features probably relate with the pathological changes within the tumor. Pathologically, 70% of the tumors are sclerosing adenocarcinomas, with mass of fibrous tissue hyperplasia around the gland cavity [1-3]. The CT contrast agent can rest on the fibrous tissue for a longer period and thus it washes out slowly. In contrast, US contrast agent is a blood pool agent and is confined within the blood vessels thus it cannot be dispersed in the extravascular space and is depicted as hypoenhancement in portal or late phase [7-9].

Vascular assessment is a crucial aspect of the staging of cholangiocarcinomas because vascular involvement represents the most frequent criteria of unresectability. Hilar cholangiocarcinoma has a propensity to infiltrate the peripheral liver tissue and the adjacent blood vessels, which will lead to stricture or occlusion of portal vein. Conventional US is able to evaluate the presence of portal vein infiltration from the intactness of portal vein wall and the blood flow filling status and its accuracy was reported to be 81-86% [11,12,23,24,25, 26, 27].

And the accuracy for CT was approximately 71% [17]. CEUS greatly enhances the visualization of portal vein and is able to observe the filling of contrast agent within the lumen irrespective of the blood flow velocity in portal vein and the course of portal vein, which may compensate some insufficiency of conventional US. The accuracy of CEUS in determining the portal vein infiltration slightly improved as compared with conventional US and CECT, being 90%, 84%, and 79%, respectively, whereas no significant difference was present. The tumor size of hilar cholangiocarcinoma is usually small when it is detected. The detection rate of conventional or unenhanced CT for the lesion is low, approximately 40-68% [17,19]. On the arterial and portal phases of CECT, the enhancement extent of the tumor is always similar with that of the liver, which is not suitable for lesion detection. On the late phase, however, the late enhancement will depict the tumor margin that is previously invisible. On unenhanced US, the tumor is generally isoechoic and it is difficult to define the tumor margin from the adjacent liver tissue.
After contrast agent administration, especially in portal or late phase, the tumor is appeared as hypoenhancement in comparison with adjacent liver tissue, thus the tumor margin is well delineated and the infiltration extent is well depicted. In the present study, the conspicuity of the tumor was defined as definitely distinct in 81% cases on CEUS, which was significantly higher than that on conventional US and CECT. Prior to pathological examination, the accuracy of CEUS in characterization of hilar cholangiocarcinoma is slightly higher than that of CECT, whereas the difference is not significant.

In the present study, the enhancement features of hilar cholangiocarcinoma during the late phase of CECT were not recorded due to the inadequate scanning protocol in the institution, which was the major limitation of the study, since hyper-attenuation in the late phase is an important feature of hilar cholangiocarcinoma. The diagnostic efficacy of both CEUS and CECT for hilar cholangiocarcinoma was not fully investigated although it is not the purpose of this study. Future studies with other types of lesions in the hilar bile duct should be performed. The major advantage of contrast agent administration is better conspicuity of the tumor, with possibility to better evaluate the local extent of the lesion, and to identify liver metastases. However, the detection of liver metastases on CEUS and CECT, in comparison with baseline US, was not investigated. Thus further studies are mandatory.

In general, the enhancement pattern of hilar cholangiocarcinoma during the arterial phase is similar between CEUS and CECT, however, during the portal phase, the tumor washes out more completely on CEUS than CECT.

The lesion conspicuity on CEUS improves significantly as compared with CECT. CEUS and CECT might have similar ability in characterization of hilar cholangiocarcinoma.
References


