Accuracy of Contrast-Enhanced Ultrasound in the Diagnosis of Bile Duct Obstruction

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Abstract

Purpose: To investigate the ability of contrast-enhanced ultrasound (CEUS) to differentiate benign from malignant lesions causing biliary duct obstruction.

Materials and Methods: Between November 2006 and December 2013, 59 patients with bile duct obstruction of undetermined cause in baseline ultrasound underwent CEUS study. The enhancement and posterior washout were analyzed in real time all along the study duration (5’). The final diagnosis suggested by CEUS was compared with histologic diagnosis (47.5%) or with radiologic follow-up with TC, RM or ERCP.

Results: Final diagnoses included 42 malignant lesions (cholangiocarcinoma n=22, metastases n=6, pancreatic carcinoma n=6, hepatocarcinoma n=4, gallbladder carcinoma n=2, ampullary carcinoma n=1 and lymphoma n=1) and 17 benign lesions (lithiasis or biliary sludge n=15, xanthogranulomatous cholecystitis n=1 and indeterminate n=1). CEUS accuracy compared with final diagnoses based on combined reference standard was 86.4%. CEUS correctly identified 36 of 42 malignant lesions (sensibility 85.7%) and 15 of 17 benign lesions (specificity 88.2%). The positive predictive value of CEUS for malignancy was 94.7%, while the negative predictive value was 71.4%.

Conclusion: CEUS is useful to differentiate between benign and malignant causes of obstructive jaundice. This technique improves the detection of bile duct invasion in hepatic neoplasms and permits better evaluation of intra- and extraductal extension of hilar hepatobiliary tumors.

Introduction

Conventional ultrasound is the first-line imaging method for investigating biliary diseases. Once bile duct obstruction is detected, it is necessary to determine both the stop level and its nature. Baseline sonography may be able to localize the intra- or extrahepatic origin of cholestasis but, in general, has a relatively low accuracy for this purpose [1,2]. As a consequence, in many cases it is necessary to combine ultrasound (US) with other noninvasive methods, including computed tomography (CT) or magnetic resonance (MR), or invasive imaging techniques, including endoscopic retrograde cholangiopancreatography (ERCP) or echo-endoscopy, to get the final diagnosis.

Development of new sonographic contrast media and improvements in detection techniques with low acoustic power have represented significant advances in ultrasound diagnosis. Second-generation ultrasound contrast agents include gas microbubble-based substances, stabilized by a biocompatible thin shell, usually of lipid composition. The resulting diameter of 3–5µm, smaller than red cells, is still much bigger than the particles used with CT and MR. For this reason, the ultrasound contrast is confined to the intravascular space, and does not cross to the extracellular milieu, facilitating a thorough study of micro- and macrocirculation in the target lesion [3]. Other advantages of contrast-enhanced ultrasound (CEUS) over CT and MR include its hypoallergenic, non-nephrotoxic conditions [4], as well as great versatility, because it can be performed in almost any setting, involves no radiation and permits real-time dynamic study of enhancement.

The utility of CEUS in the diagnosis of liver tumors is widely accepted. The European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) published the first guide of clinical practice for this technique in 2004 [5]. More recently, the use of intravascular and intracavitary CEUS in different organs has resulted in...
new EFSUMB guidelines for non-hepatic use in 2008. A more recent update (2011) has recognized the usefulness of CEUS for the diagnosis of biliary diseases [6]. There are few studies in the literature exploring the benefits of CEUS in biliary diseases [7–9]. Moreover, all of them evaluate its use in gallbladder and biliary duct disease from a general point of view, but do not investigate its diagnostic value in biliary duct obstruction. The aim of this study was to determine the usefulness of CEUS to differentiate among benign and malignant biliary duct obstruction.

Materials and Methods

Study population
Between November 2006 and December 2013, 59 patients (33 men and 26 women) underwent biliary CEUS under the following requisites: 1. intrahepatic (duct diameter > 40% above that of the adjacent portal vein) or extrahepatic (> 7 mm) bile duct dilatation demonstrated by baseline ultrasound in a patient with clinical findings of obstructive jaundice, 2. Unknown cause of biliary duct obstruction. Patients were excluded if the diagnosis was straightforward after baseline ultrasound, as in cases of lithiasis with acoustic shadow or masses in the pancreatic head. We also excluded patients with known severe cardiopathy and pregnant or lactating women. The study fulfilled the ethical rules of our institution. In our unit, contrast-enhanced ultrasound is routinely used patterns. Relevant images and videos were recorded digitally.

Results
CEUS was performed in 59 patients (33 men and 26 women, with a mean age of 71.5 years (range 48–90)). The final diagnoses included 42 malignant and 17 benign lesions. A histologic analysis was possible in 28 patients (47.5%), while the diagnosis was based on data from the clinical and radiological follow-up in the remaining 31 cases (52.5%) (Table 1). Table 2 shows the final diagnoses. Among malignancies, the most frequent diagnosis was cholangiocarcinoma (22 patients). In 6 cases of hilar cholangiocarcinoma, baseline ultrasound disclosed intrahepatic bile duct dilatation with possible hilar lesions, isoechogenic to liver parenchyma. CEUS demonstrated in all cases infiltrating enhancing lesions in the biliary confluence with later washout and discrete margins (Fig. 1).

Extrabiliary cholangiocarcinoma presented as common hepatic duct lesions in 7 cases and common biliary duct lesions in 9 cases; all but one of these cases showed focal parietal thickening or intraductal lesions of variable echogenicity. CEUS demonstrated hyperenhancement and posterior washout in intraductal lesions, pointing to its tumoral nature (Fig. 2, 3). In one case CEUS showed a hypoechoic non-enhancing completely necrotic mass with portal malignant thrombosis (Fig. 4).

<table>
<thead>
<tr>
<th>Diagnostic technique</th>
<th>Number of lesions (%)</th>
</tr>
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<tbody>
<tr>
<td>Pathologic analysis</td>
<td>28 (47.5)</td>
</tr>
<tr>
<td>Contrast-enhanced CT</td>
<td>35 (59.3)</td>
</tr>
<tr>
<td>Contrast-enhanced MR</td>
<td>25 (42.4)</td>
</tr>
<tr>
<td>ERCP</td>
<td>28 (47.4)</td>
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</tbody>
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Table 2: Final diagnosis of biliary lesions (total = 59).

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>Number</th>
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<tbody>
<tr>
<td>Benign</td>
<td>17</td>
</tr>
<tr>
<td>Biliary sludge/gallstones</td>
<td>15</td>
</tr>
<tr>
<td>Xanthogranulomatous cholecystitis</td>
<td>1</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>1</td>
</tr>
<tr>
<td>Malignant</td>
<td>42</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>22</td>
</tr>
<tr>
<td>Metastases</td>
<td>6</td>
</tr>
<tr>
<td>Pancreatic carcinoma</td>
<td>6</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>2</td>
</tr>
<tr>
<td>Ampullary carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
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4 patients presented with hepatocellular carcinoma. In 2 cases, CEUS demonstrated malignant infiltration of the bile ducts, presenting with early arterial phase enhancement, followed by washout in the portal and later phases. In 2 other cases, distant metastatic, obstructive biliary lesions with similar behavior to the original tumor in the dynamic study were detected (●▶ Fig. 5).

6 cases corresponded to bile duct metastases from gastric carcinoma (n=3), colonic carcinoma (n=2) and renal carcinoma (n=1). In 4 cases CEUS demonstrated intraductal lesions in the hilar confluence and extrahepatic biliary ducts, while bile duct infiltration by contiguous liver malignancy was observed in the remaining 2 cases (●▶ Fig. 6).
CEUS identified 3 of 6 cases of pancreatic carcinoma, disclosing a hypoenhancing mass in the arterial phase not visible on baseline ultrasound.

In one case, bile duct obstruction by lymphoma presented as a discrete hypoenhancing mass in the pancreatic head with peri-pancreatic adenopathies.

Regarding benign lesions, CEUS correctly identified 14 of 15 cases (93.3%) corresponding to biliary sludge and stones that presented as intraluminal casts with variable echogenicity on baseline ultrasound, with no enhancement after contrast administration (Fig. 7). One case of cholangitis showed diffuse hyperenhancement in the duct wall during the arterial phase and wash-out in the portal and late phase. In another case, baseline ultrasound demonstrated ductal dilatation secondary to a heterogeneous hilar mass, with calcification, extending to the gallbladder and engulfing biliary ducts and vessels. CEUS showed intense enhancement in the arterial phase, with posterior wash-out. Pathological study disclosed infiltrative xanthogranulomatous cholecystitis (Fig. 8).

We also studied 7 patients with suspected biliary prosthesis obstruction. CEUS showed no enhancement in 5 cases (Fig. 7), which came out to be sludge, and enhancement in 2 other cases corresponding to cholangiocarcinoma relapse and metastatic hypernephroma.

In 6 cases the results of CEUS were indeterminate. In 4 of these cases, lesions affected the intrapancreatic distal common biliary duct. The location of the lesions in the biliary tree is reflected in Table 3.

CEUS correctly identified 36 out of 42 malignant lesions and 15 of 17 benign lesions, resulting in an overall sensitivity of 85.7% and a specificity of 88.2%. Its positive predictive value was 94.7% while the negative predictive value was 71.4%, with an overall diagnostic accuracy of 86.4% (Table 4).

Discussion

Basal ultrasound is the first-line imaging test in patients with a suspected biliary duct obstruction, permitting a differentiation...
between intra- and extrahepatic cholestasis. However, this technique offers a low sensitivity at the time of establishing the nature of the lesion. In the present study, we have demonstrated that CEUS improves diagnosis, differentiating benign from malignant lesions in the majority of cases. We believe that CEUS represents an appropriate first-line diagnostic procedure following initial identification of a biliary obstruction by non-enhanced ultrasound allowing segregation of patients who require CT or MR for staging and surgical planning from those who can proceed directly to ERCP. Performing CEUS during the same session can save time and is financially prudent.

The comparison of CEUS and contrast-enhanced cross-sectional imaging is sometimes problematic. CEUS offers real-time dynamic study without gaps in data acquisition, while CT and MR have scan delays and, consequently, may miss the early initial enhancement in the arterial phase. Moreover, the use of a purely intravascular contrast medium can avoid some problematic effects happening with the interstitial diffusion in MR and CT contrast agents, such as masquerading of some lesions during the portal and late phase produced by the persistent enhancement [10]. Alternatively the lack of interstitial enhancement in CEUS can theoretically limit differentiation between neoplastic processes with or without an important interstitial component.
In CEUS images, intrahepatic bile duct dilation is more conspicuous, due to parenchymal enhancement, improving the detection of intraluminal lesions, whether malignant or corresponding to sludge or biliary stones. In patients with neoplastic jaundice, ascertaining exactly the cause, level and extension of the lesion is necessary, in order to select candidates for surgical resection. Similarly to CT and MR, CEUS allows a more precise determination of neoplastic parenchymatous extension in tumors of ductal origin, as also ductal extension of lesions originated in the liver parenchyma.

Cholangiocarcinoma is the most frequent biliary neoplasm, classified as intrahepatic (peripheral and hilar) or extrahepatic. Hilar cholangiocarcinoma originates in the bile duct bifurcation, and tends to infiltrate the adjacent liver parenchyma. Basal ultrasound shows intrahepatic dilatation with a normal extrahepatic duct, but has a low capacity to establish the nature of the obstruction, due to the frequent isoechogenicity of these lesions with normal liver parenchyma and its infiltrative nature [7–9]. In our experience, Klatskin tumors show a variable enhancement in early phases with a constant washout in late phases which nicely delineates the limits of the lesion. These features are consistent with those described in the literature. Xu et al. [11] studied the dynamic behavior of hilar cholangiocarcinoma in CEUS, demonstrating hyperenhancement, isoenhancement and hypoenhancement in the arterial phase in 43.8, 43.8 and 12.6% of cases, respectively, with a ring, homogeneous enhancement pattern or heterogeneous enhancement pattern in 9.4, 34.4 and 56.2% of cases, respectively. In the portal and late phases, 93.8% of the cases presented washout, which improved the delimitation of the tumor margins.

Extrahepatic cholangiocarcinoma can also show variable enhancement in the CEUS arterial phase, with washout in late phases in most cases. The essential contribution of CEUS is differentiation among tumors and non-enhancing, inert material, including lithiasis without acoustic shadow, blood clots or detritus [7, 10, 12].

Bile duct infiltration is a rare complication of hepatocellular carcinomas and can present with contiguous direct invasion or embolization of an occult parenchymatous lesion [9]. Both presentations were observed in this study, with an enhancement pattern similar to the original tumor, hyperenhancement in the arterial phase and contrast wash-out in the late phase [13].

CEUS is also useful to categorize intrabiliary metastatic lesions of a non-hepatic origin. These are infrequent lesions with a difficult differential diagnosis with malignant primary lesions. They can present as fully intraductal lesions or as secondary invasive lesions from adjacent liver metastases. Different primary tumors can cause biliary metastatic obstruction but gastrointestinal malignancies, particularly colon cancer, are most frequent [9]. In our study, gastric cancer was most common.

CEUS improves the detection of pancreatic head tumors not detected by basal ultrasound. The pancreas enhances homogeneously in the arterial phase and presents a transient venous phase, facilitating detection of carcinoma, which presents typically with hypoenhancement in all phases [6]. Fan et al. [14] reported a sensitivity, specificity and accuracy of 91.7, 97.2 and 87%, respectively, at the time of detection of pancreatic adenocarcinomas with CEUS. The results are similar to those obtained with contrast-enhanced CT. Benign lesions show no enhancement on CEUS, due to the inert nature of intraductal contents (biliary sludge, lithiasis, blood clots or detritus), allowing differentiation from tumoral casts in most cases.

Even if no enhancement is the rule in benign lesions, there are exceptions, which include inflammatory conditions such as xanthogranulomatous lesions or the faint captation of the ductal wall in cases of cholangitis. These examples emphasize that enhancement is not synonymous with malignant lesion. Alternatively, extensive necrotic malignant lesions can present without contrast enhancement in rare instances.

CEUS shares some limitations with basal ultrasound, including operator dependence. Obesity and bowel gas are important obstacles in some cases, particularly during the evaluation of the distal bile duct. This limitation was behind most indeterminate cases in this study.

Important limitations of the study are its retrospective design and the absence of a unitary reference test, due to the impossibility of obtaining a pathologic diagnosis in some cases. In the latter cases we used CT, MR and follow-up to set a reference diagnosis. Prospective studies are necessary to validate our conclusions, as are comparative investigations about agreement among CEUS, on one side, and CT or MR, on the other.

**Conclusion**

CEUS is useful to differentiate the benign or malignant nature of a biliary duct obstruction. It may offer a combined approach with CT and MR, saving the indication of these techniques in unequivocal cases of benignity and represents an alternative in those cases in which these techniques are hazardous or contraindicated, including instances of contrast allergy or kidney failure. In addition, CEUS is able to disclose tumoral invasion of biliary ducts by liver tumors and helps to define the local extension of hilar hepatobiliary neoplasms.

**References**

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