Intrahepatic Mass-Forming Cholangiocarcinoma: Enhancement Pattern on Gd-BOPTA-MRI with Emphasis on Hepatobiliary Phase

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Aims and objectives

Intrahepatic cholangiocarcinoma, is defined as an adenocarcinoma arising from the intrahepatic biliary epithelium, and is typically a mass-forming tumor. It accounts for 5-10% of all cholangiocarcinomas [1]. Intrahepatic mass-forming cholangiocarcinoma (IMC) represents 10% of primary liver tumors, and is the second most common hepatic malignancy after hepatocellular carcinoma [2]. MRI has become a gold standard in characterization and detection of focal liver lesions, and offers the possibility of using liver-specific contrast agents [3]. However, the detection and characterization of intrahepatic cholangiocarcinoma by imaging is a constant challenge. Despite these facts, most studies have focused on MRI findings with extracellular agents, and there have been only a few papers describing the imaging findings of IMC using Gd-BOPTA MRI. To the best of our knowledge, only one large and extensive study on hepatobiliary enhancement patterns of IMC with Gd-BOPTA to differentiate cirrhotic hepatocellular carcinoma from cholangiocarcinoma has been published [4]. Other studies mention IMCs in the context of general imaging of hepatic lesions [5, 6] and in pictorial essays [7, 8]. Gd-BOPTA (gadobenate dimeglumine) combines both extracellular and hepatobiliary distribution through two main temporal acquisition phases: dynamic and delayed [9]. Through this liver-specific contrast medium, the radiologist evaluates variations in enhancement pattern in both phases for detection and characterization of lesions. Since IMCs derive from bile duct epithelia, no notable uptake is expected in the hepatobiliary phase (HBP) that would be valuable for the delineation and detection of the lesions, thus facilitating treatment planning. Because no reliable radiological features are available to distinguish IMCs from metastatic adenocarcinomas, the diagnosis of intrahepatic cholangiocarcinoma is made on the reasonable exclusion of an extrahepatic primary tumor. The purpose of our retrospective study was to describe the MRI appearance of intrahepatic mass-forming cholangiocarcinoma using Gd-BOPTA contrast medium, and to assess radiologic findings to improve diagnosis of this disease. Emphasis was on the hepatobiliary late phase features.

Methods and materials

Patients: A review of pathology and radiology records identified 29 patients with a diagnosis of IMC. Each patient had undergone MRI examination at our facility during the period from June 2004 to June 2014. There were 19 men and 10 women, with a mean age of 64 years (range 40-80 years). No patient had a history of exposure to clonorchiasis or Thorotrast (thorium oxide). Four patients had a history of liver cirrhosis (2 alcohol related; 2 cryptogenic).

No treatment for malignancy had been administered at the time of the MR imaging. The diagnosis of IMC was established by means of histologic analysis (27 patients with
surgical resection or percutaneous biopsy) or by the combination of typical MRI findings (rim enhancement on arterial phase with progressive filling on late phases) and laboratory studies (elevation of CA19.9). Four patients did not undergo the 10-15-minutes phases and were excluded in some statistical analyses.

**MR Technique:** All examinations were performed with a 1.5-T superconducting unit. All MR images were obtained in the axial plane with a field of view of 380 x 380 mm, adjusted for each patient. T1-weighted gradient-echo images (in- and out-phase) and breath-hold T2-weighted single-shot fast spin-echo images were obtained in all patients, as well as T1- and T2-weighted fat-suppressed sequences. We excluded DWI because we had it since 2010. Dynamic MRI was done in all 29 patients using fat-suppressed gradient-echo or 3D LAVA sequences, as was the hepatobiliary phase at 2 hours. After a set of unenhanced MRI images was obtained, a bolus of 0.1 mmOL/Kg of Gd-BOPTA (Gadobenate Dimeglumine) was injected at a rate of 2 ml/sec, followed by a 20 ml flush of normal saline using a power injector. The scan delays for multiphasic dynamic imaging were 30, 40, 60, 180 and/or 300 seconds after contrast medium injection. In one case (n.15), we did not obtain portal and 3-5-minute late phases because of the patient's discomfort after contrast medium injection. In all patients but 4, ulterior delayed phases of 10 and/or 15 minutes were obtained, and in all patients the HBP phase was obtained 2-3 hours after the administration of contrast medium. All MRI images were obtained in the axial plane with a phased array multicoil for the body centered over the liver. Section thickness was 4-6 mm, with a 2-3 mm intersection gap.

**Image Interpretation:** The MR images were retrospectively evaluated on a PACS console by two abdominal radiologists with experience in liver imaging (>10 years). Individual reviews were done, and discrepancies were resolved by consensus. In patients showing intrahepatic metastases, the largest lesion was chosen for analysis. The radiologists focused on the following features: size, number, location (right or left lobe), shape (round-oval or irregular), capsule, T1 and T2 signal (comparable to adjacent liver parenchyma), dynamic enhancement pattern and hepatospecific delayed pattern. transient hepatic intensity difference (THID), hepatic atrophy, capsular retraction, vascular infiltration, biliary dilatation, metastatic nodes, and ascites were also evaluated. The dynamic pattern of the lesions was described on a 5-point scale [0= only peripheral enhancement, 1= peripheral enhancement with associated dishomogeneous global enhancement, 2= progressive centripetal incomplete filling, 3= progressive dishomogeneous (no centripetal) incomplete filling, and 4= complete or nearly complete enhancement]. In the 10-15-minute late phase, we also evaluated signal intensity and homogeneity of the lesions, and eventual presence of a hypointense peripheral rim. A particular emphasis was placed on the hepatobiliary late phase pattern, and the following features were evaluated: signal of lesions (cloud= persistent enhancement with a cloud-like signal intensity inside the lesion; defect= hypointensity due to wash-out of the lesion), peripheral rim (No= absent, Yes= present), signal of the rim (Iso= isointensity, Hypo= hypointensity, Hyper= hyperintensity; c= continuous, d= discontinuous).
Results

The tumors ranged from 2.7 to 15.5 cm (mean 9.1 cm) in maximum diameter. In 14 patients (48%) satellites nodules near the largest lesion and/or intrahepatic metastasis were detected. The lesions were located in the right lobe in 21 cases (72%), in the left lobe in 3 cases (10%), and in both lobes in 5 cases (17%). Contours of the lesion were lobulated or irregular in all patients but two (93%), with absence of capsule. On T1-weighted images, the IMC appeared as a homogeneous hypointense mass relative to the liver in 25 patients, and inhomogeneously hypointense in the other 4 patients. On T2-weighted images, all lesions were heterogeneous with intralesional hyperintensity. In the arterial phase, all lesions showed rim enhancement. On dynamic MRI images, cholangiocarcinoma had the following vascular patterns (Figure 1a, 1b, 1c): a) peripheral rim-like enhancement in the arterial and portal venous phases, followed by filling-in on the delayed images (n=27; 93.1%); progressive and centripetal filling was observed in 16 cases (59.2%), while 11 lesions (40.7%) showed progressive dishomogeneous filling. However, complete or near complete enhancement in the late phases was observed in only 6 cases (22.2%); b) early inhomogeneous enhancement followed by prolonged complete enhancement (n=1; 3.4%); c) early peripheral enhancement with non-filling of the central area on the delayed images (n=1; 3.4%). In late phases at 10-15 minutes, 24 of 25 lesions (96%) showed late enhancement; 21 lesions (84%) were inhomogenous because of enhancement areas (iso- or hyperintense) mixed with hypointense areas, while 3 lesions were homogeneously hyperintense; just one lesion was homogeneously hypointense. In 56% of cases with 10-15-minute late phase, a hypointense peripheral rim was identified (Figure 1a, 2b, 2c). This rim was discontinuous in 12 lesions (86%) but continuous in 2. We had only one case with a hyperintense peripheral rim on 10-15-minute late phase and HBP. On hepatobiliary images, only one IMC was hypointense, while 28 (96%) lesions showed a mainly central area of enhancement described as a "cloud" (Figure 3). Furthermore, 82% of IMC (n=24) exhibited a hypointense peripheral rim associated with cloud appearance, defining a "target pattern" (Figure 1a,1b,2a,2b,2c); this rim appeared continuous in 16 lesions (70%) and discontinuous in 7 lesions. In 14 lesions (58%) with the hypointense peripheral rim on HBP the hypointense peripheral rim on 10-15-minute late phase coexisted, but we found no significant association between them (p= 0.150). Hepatic artery encasement was detected in 8 patients (27%), invasion of portal vein branches in 10 patients (34%), and infiltration of hepatic veins in 13 patients (44%). Narrowing or obstruction of portal vein is not an uncommon finding in IMCs located centrally in the liver. Transient hepatic intensity difference (THID) on immediate gadolinium-enhanced T1-weighted images in the segment with the tumor was observed in 19 patients (65%); 11 patients (57%) with THID showed coexistence of vascular infiltration (no evident causes in the other cases). In 18 cases (62%), capsular retraction was adjacent to the tumor. Segmental or lobar atrophy of the tumors lobe was seen in 8 patients (27%), and encasement of portal vein branches or hepatic veins was observed in 5 patients (62%) with hepatic atrophy. Dilatation of the intrahepatic bile ducts, in particular adjacent to the lesions, was seen in 18 patients (62%). IMCs originate from bile ducts.
so biliary obstruction by tumor infiltration can occur. Metastatic lymphadenopathy was detected in 14 patients (48%), in the following sites: porta hepatic, portocaval space, celiac and para-aortic. Ascites was observed in 8 cases (28%), and 4 patients had cirrhosis.

**Images for this section:**

![Fig. 1: Three different dynamic patterns of IMC on T1w dynamic and HBP sequences. (a). Typical pattern of IMC, with peripheral rim-like enhancement in arterial phase, followed by filling-in on the delayed images. Arrowhead shows a hypointense peripheral rim on 10 min phase. Arrow shows a hypointense peripheral rim on HBP. (b). Pattern with early inhomogeneous enhancement on arterial phase, followed by prolonged complete enhancement on the late phases. Arrow shows a hypointense peripheral rim on HBP. (c). Pattern with early faint peripheral enhancement on arterial phase, with non-filling of the central area on the delayed images. HBP shows a hyperintense peripheral rim.](image-url)
Fig. 2: Three different cases of IMCs (a,b,c,) with hypointense peripheral rim on HBP, delineating a "target pattern". Images obtained with T1w sequences after contrast medium administration, during arterial phase, portal phase, 3-5 minutes delayed phase, 10-15 minutes delayed phase and HBP. Hepatobiliary phase obtained 2h after Gd-BOPTA administration shows an enhancement cloud with a peripheral rim defect (arrows), corresponding well with the area of enhancement in the arterial phase. Two cases show a hypointense peripheral rim also on 10-15 minutes delayed phase (heads of arrows).
Fig. 3: One case of IMC with a cloud of enhancement on HBP. Images obtained with T1w sequences after contrast medium administration, during arterial phase, portal phase, delayed phase and HBP.
Conclusion

Intrahepatic or peripheral cholangiocarcinoma is an uncommon primary hepatic malignancy, with increasing incidence worldwide [2]. In the literature, some reports have described MRI of IMC [10, 11] but, to the best of our knowledge, there are few studies with descriptions of Gd-BOPTA MRI features relating to mass-forming cholangiocarcinoma, and in particular only one large and extensive study of the hepatobiliary pattern has been published [4]. Though some suggestive features have been reported, IMC is often difficult to differentiate from metastatic adenocarcinoma [12]. In our study we retrospectively evaluated the Gd-BOPTA MRI findings in 29 patients with IMCs, focusing on the HBP pattern. In our cases, most of the IMCs (96%) showed hyperintense signal intensity rather than a homogeneous hypointense defect on HBP images, caused by the presence of central hyperintense or isointense area that we call "cloud" of enhancement. The pattern in the HBP phase is determined by the intracellular concentration of contrast material in hepatocytes. Because there are no cells of hepatocytic origin in IMCs, we should see the lesions as hypointense. On the other hand, the hyperintensity inside the lesions can be explained because IMCs show fibrotic stroma that retains contrast material in the extracellular space [6,13]. In our study, the other interesting finding in the HBP was that most lesions (82%) showed a hypointense peripheral rim, which we call "late rim"; this finding is likely correlated with the hypervascular peripheral rim in the arterial phase, typical of IMC, so its hypointensity corresponds to the greater density of viable and vascularized tumor cells, which release the constrain medium in the HBP. In our study, because late rim appeared only in association with cloud enhancement, 82% of IMCs had a "target pattern". The target appearance of IMCs on hepatobiliary phase images has been reported in only 5 studies with Gd-BOPTA MRI [4-8]; with the exception of the study of Jeon TY [4], the other studies mention this pattern in the context of general imaging of hepatic lesions and in pictorial essays [5-8]. Though this finding on Gd-BOPTA MRI has not been explored extensively, similar results were obtained in 5 studies with Gd-EOB-DTPA [14, 15]. Nevertheless, metastases from adenocarcinoma tumors can show a target appearance because of their fibrous stromaThe target pattern is then suggestive of IMC, but is not a specific finding. On dynamic phases, we found a peripheral enhancement with progressive and concentric filling of contrast material on delayed images, described as typical of IMC. In summary, at Gd-BOPTA MRI, IMC is a large, nonencapsulated lesion, characterized by rim enhancement in the arterial phase, with centripetal and/or gradual filling in delayed phases. In delayed dynamic phases, IMC can show a peripheral hypointense rim called "peripheral wash-out". In the HBP, all IMCs but one showed a "cloud" of enhancement or a "target pattern". Although these findings are not specific and may be encountered in other lesions such as metastases from adenocarcinoma, they are suggestive of IMC and with association with other findings such as vascular encasement, focal liver atrophy, dilatation of intrahepatic bile ducts, and lymphadenopathy, may strengthen the diagnosis and help to differentiate between IMC and other lesions.
Personal information

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