Clinical Imaging 39 (2015) 1032–1038

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: http://www.clinicalimaging.org

Predictors of intrahepatic cholangiocarcinoma in cirrhotic patients scanned by gadobenate dimeglumine-enhanced magnetic resonance imaging: diagnostic accuracy and confidence

Emilio Quaia *, Roberta Angileri, Federica Arban, Antonio Giulio Gennari, Maria Assunta Cova

Department of Radiology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, 34149, Trieste, Italy

ARTICLE INFO

Article history:
Received 30 December 2014
Received in revised form 28 May 2015
Accepted 22 June 2015

Keywords:
Cholangiocarcinoma
Magnetic resonance imaging
Fibrosis
Hepatocellular
Logistic models

ABSTRACT

Objective: To identify predictors of intrahepatic cholangiocarcinoma in cirrhotic patients scanned by gadobenate dimeglumine (Gd-BOPTA)-enhanced magnetic resonance (MR) imaging.
Methods: Fifty cirrhotic patients with 120 nodules, including 10 mass-forming intrahepatic cholangiocarcinomas and two combined hepatocellular carcinoma–cholangiocarcinomas, were scanned by Gd-BOPTA-enhanced MR imaging.
Results: T1 hypointensity [odds ratio (OR), 20.12], peripheral hyperintense rim at hepatic arterial phase (OR, 13.5), and *iso*-hyperintensity at hepatobiliary phase (OR 21.32) were found to be independent predictors of intrahepatic cholangiocarcinoma.
Conclusions: T1 hypointensity, peripheral hyperintense rim at hepatic arterial phase, and *iso*-hyperintensity at hepatobiliary phase are independent predictors of intrahepatic cholangiocarcinoma diagnosis in patients with liver cirrhosis.

1. Introduction

Intrahepatic cholangiocarcinoma (CC) is the second most common primary hepatic malignancy, after hepatocellular carcinoma (HCC), in both cirrhotic and noncirrhotic liver [1]. Intrahepatic CC can be classified as one of three types on the basis of the macroscopic appearance of the tumour: mass forming (nodular), periductal infiltrating (sclerosing), and intraductal growing (papillary-type) CC (1). The mass-forming type is defined as a definite mass located in the liver parenchyma and is the most common form of intrahepatic CC [1,2], while intraductal growing CC presents a better prognosis than the other subtypes [3]. Complete surgical resection of CC with a negative surgical margin is the most important factor in the determination of the therapeutic outcome [2–4].

On contrast-enhanced computed tomography (CT) or magnetic resonance (MR) imaging, the imaging features of intrahepatic CC are an irregularly shaped solid mass with peripheral rim enhancement and heterogeneous gradual and centripetal enhancement on dynamic contrast material-enhanced CT or MR images [5,6]. In addition, frequently noted ancillary findings of intrahepatic CC include capsular retraction, bile duct dilatation distal to the tumour, vascular encasement, satellite nodules, and central scars [5,6].

The differentiation of intrahepatic CC from HCC nodules is essential in cirrhotic patients mainly because intrahepatic CC deserves a different therapeutic management and presents a worst prognosis [7,8]. The differentiation of intrahepatic CC from HCC is crucial as the former represents a contraindication for liver transplantation due to lower disease-free and overall survival rates [7,8] while the latter gives priority on the transplant list. Consequently, a correct differentiation of intrahepatic CC from HCC is expected by the imaging techniques since liver biopsy may not be possible in cirrhotic patients with a high risk of bleeding.

MR imaging of the liver implies the use of hepatospecific MR contrast agents including gadobenate dimeglumine (Gd-BOPTA, Multihance, Bracco Imaging, Milan, Italy) and gadoxetic acid (Gd-EOB-DTPA, Primovist, Bayer-Schering Pharma, Berlin, Germany) which are characterized by an extracellular distribution followed by selective uptake by functioning hepatocytes, allowing the acquisition of delayed hepatobiliary phase (HBP) images. Even though Gd-EOB-DTPA differs from Gd-BOPTA in terms of hepatocyte uptake (50% vs. 3–5% of injected dose) [9–12], both agents provide comparable enhancement of liver parenchyma [13,14]. Anyway, the enhancement with Gd-BOPTA in the cirrhotic liver was shown to be inferior to that in the normal liver [15] even though the registered dose is 0.05 mmol/kg for Gd-BOPTA (often administered at 0.1 mmol/kg) and 0.025 mmol/kg for Gd-EOB-DTPA. The degree and patterns of contrast enhancement of intrahepatic CC at Gd-BOPTA [2] and Gd-EOB-DTPA-enhanced MR imaging have been previously analysed [4,16]. Even though both agents appeared accurate to depict a specific enhancement pattern, a prevalent HBP hypointensity and pseudo-washout

Abbreviations: CI, Confidence Interval; EP, Equilibrium phase; Gd-BOPTA, Gadobenate dimeglumine; Gd-EOB-DTPA, Gadoxetic acid; HBP, Hepatobiliary phase; HAP, Hepatic arterial phase; HCC, Hepatocellular carcinoma; CC, Cholangiocarcinoma; OR, Odds Ratio; PVP, Portal venous phase.

* Corresponding author. Department of Radiology, Cattinara Hospital, University of Trieste, Strada di Fiume 447, Trieste (Italy), 34149. Tel.: +39-040-3994372; fax: +39-040-3994500.
E-mail address: quaia@units.it (E. Quaia).

http://dx.doi.org/10.1016/j.clinimag.2015.06.013
0899-7071/

pattern has been described in intrahepatic CC on Gd-EOB-DTPA-enhanced MR imaging due to the intense contrast uptake from the liver which determines that tumors that exhibit progressive contrast enhancement on dynamic images may appear hypointense [16]. These enhancement patterns may create some difficulties in interpreting the dynamic patterns and to differentiate intrahepatic CC from HCC nodules, while Gd-BOPTA could present some advantage in the differentiation of these tumoral histotypes related to the lower contrast uptake from the adjacent cirrhotic liver parenchyma. At our knowledge, no previous paper analyzed the diagnostic capabilities of Gd-BOPTA-enhanced MR imaging in the diagnosis of intrahepatic CC found in cirrhotic patients by identifying some reliable diagnostic predictors through logistic regression analysis.

The aim of this study was to identify predictors of intrahepatic CC in cirrhotic patients scanned by Gd-BOPTA-enhanced MR imaging.

2. Materials and methods

2.1. Study population

The institutional review board of our hospital approved this single-centre retrospective case-control observational study and waived the requirement for patient-informed consent.

Through a review of the database and records of our radiology department, we retrospectively identified all patients with liver cirrhosis who were scanned by Gd-BOPTA-enhanced MR imaging between November 2009 and November 2013. Inclusion criteria for the present study were (a) nodule diameter > 1 cm; (b) pathologically confirmed diagnosis, based on US-guided percutaneous biopsy or surgical resection, of HCC, dysplastic or macroregenerative nodule, hemangioma, or intrahepatic CC or combined hepatocellular–cholangiocarcinoma (HCC-CC), or (c) HCC-established imaging diagnostic criteria, that is, contrast uptake in the arterial phase and washout in the portal venous phase (PVP)/late equilibrium phase (EP) at CT or MR imaging [17]; (d) availability of dynamic Gd-BOPTA-enhanced liver MR imaging performed no more than 3 months before the surgical resection or US-guided biopsy.

Percutaneous US-guided biopsy was performed in those lesions which did not meet the reference imaging criteria for HCC. A 16-gauge modified Menghini needle and stained with hematoxylin/eosin and the Masson trichrome method was used. A senior pathologist made the histologic diagnosis according to the diagnostic criteria established by the International Consensus Group for Hepatocellular Neoplasia [18].

Initially, 76 patients were considered eligible for the study. We excluded 26 patients due to surgery or ablation or chemoembolization before histologic analysis ($n=11$ patients), absence of adequate reference standard ($n=10$), or an inadequate MR imaging scan due to the presence of motion artifacts ($n=5$). Therefore, 50 cirrhotic patients (male/female=34/16; mean age±S.D. 71, 54±10, 97; range, 30–84) with 120 nodules were finally included. All patients had a definite diagnosis of liver cirrhosis (Child–Turcotte–Pugh Class A or B) related to viral infection [hepatitis C ($n=24$ patients), hepatitis B ($n=8$) or both ($n=1$)] or alcohol abuse ($n=17$), obtained by means of biopsy ($n=10$) or unequivocal imaging findings ($n=40$), including irregular liver margins and nodulations. There was no significant difference in age between males and females (68.84±12.91 vs. 66.62±12.14; $P>.05$).

2.2. MR imaging examination

The MR imaging examination was performed using a superconducting magnet operating at 1.5 T (Achieva, 1,5T release 2.1.3.4, Philips Healthcare, Best, The Netherlands) with a peak gradient amplitude of 30 mT/m and a peak slew rate of 150 T/m/s. Images were acquired in the transverse plane with a combined four-channel anteroposterior phased-array surface coil. Parallel imaging with a sensitivity-encoding (SENSE) technique with a factor of 1.5–1.7 was employed. A three-quarter field of view was used in the phase-encoding direction. Presaturation pulses were applied above and below the imaging volume to diminish flow artifacts.

MR imaging parameters are detailed in Table 1. The baseline MR imaging examination included a breath-hold T2-weighted fast spin-echo MR imaging sequence, a fat-suppressed T2-weighted sequence, a T1-weighted in-phase and out-of-phase sequence, and a T2-weighted fast-field echo sequence. Dynamic MR imaging was performed after Gd-BOPTA injection (0.1 mmol/kg; 2 ml/s) via a forearm or antecubital vein at 2 ml/s through an 18-gauge intravenous catheter employing an automated injector (Spectris MR Injector; Medrad, Indianola, PA, USA), followed by 20 ml of saline at 2 ml/s. Between the precontrast and dynamic image acquisitions, an MR fluoroscopic sequence for contrast bolus chase (TR/TE, 4/0.87 msecs, flip angle 40°, slice thickness 80 mm, field-of-view 530×530 mm with a matrix of 256×128, acquisition time 0.512 s) was performed, and yielded a subtracted coronal two-dimensional projection of the abdominal aorta every second. Dynamic hepatic arterial phase (HAP) MR images with a 5-s delay from the contrast visualization in the abdominal aorta, PVP, and EP MR images with 70 s and 3 min delay from the beginning of contrast injection and HBP MR images acquired 2 h from contrast injection were acquired.

2.3. Consensual visual image analysis

Two radiologists (blinded), respectively with 8 and 10 years of experience with MR imaging of the abdomen, analysed the MR images in consensus.

All readings were performed on a PACS—integrated workstation (21.3-inch TFT display, resolution 2048×1536 pixels, Ebit Sanità AET, Genoa, Italy) at a central location. The two readers were aware of each patient's clinical history and were free to use processing tools such as windowing, gradation adjustment or magnification and scrolling of the MR images. The readers localized each nodule on a liver segment [19,20] and focused on the following features: (a) the relative signal intensity of the lesion center and periphery compared with that of the adjacent liver parenchyma; (b) the enhancement pattern of the lesion on the HAP, PVP, EP, and HBP.

The morphologic features of the tumours were assessed at MR imaging and included the maximum diameter of the lesion, the contour (nodular, lobular, or irregular or geographic), and the presence of a capsule defined as a continuous peripheral rim of smooth hyperenhancement in the PVP or EP that unequivocally is thicker or more conspicuous than the rims surrounding background nodules.

Uniform criteria were adopted to define nodule intensity on MR image analysis. The periphery of the lesion was defined as an area confined to less than 25% of the lesions' outer portion. Nodules displaying higher, similar (comparable), or lower relative signal intensities of the lesion center and periphery compared with the adjacent liver parenchyma (within 3 cm from the outer border of the nodule) were defined as homogeneously or inhomogeneously hyper-, *iso*-, or hypointense, respectively. A peripheral hyperintense rim on HAP, visualized as a continuous circular rim surrounding the nodule, was recorded. The nodule intensity on HAP was assessed on subtracted images in nodule-appearing hyperintense on T1-weighted sequences and whether contrast enhancement was detected after image subtraction nodules were recorded as hyperintense.

Temporal changes in the degree of enhancement during dynamic phase imaging were analysed with the following terms: (a) persistent enhancement: contrast enhancement that remains invariable through the HAP, PVP, and EP; (b) gradual enhancement: contrast enhancement that increases over time, homogeneously or heterogeneously, in the whole tumour; (c) centripetal enhancement: enhancement starting from the periphery and filling progressively the tumour. The following findings were also documented: (d) capsular retraction in tumours with a peripheral location; (e) adjacent bile duct dilatation; (f) evidence of satellite nodules.