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● *Original Contribution*

CAN THE CONTRAST-ENHANCED ULTRASOUND WASHOUT RATE BE USED TO PREDICT MICROVASCULAR INVASION IN HEPATOCELLULAR CARCINOMA?

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Abstract—The objective of this study was to investigate use of the washout rate of hepatocellular carcinoma on contrast-enhanced ultrasound (CEUS) for pre-operative determination of the presence of microvascular invasion. The study included 271 patients who underwent liver resection for hepatocellular carcinoma between April 2008 and December 2012, and were examined with contrast-enhanced ultrasound before surgery. Patients were followed up at 3-mo intervals for 3 y. Four washout patterns were classified according to the start time of washout: rapid, portal, delayed and slow. Rapid washout, presence of two or more tumors and tumor size ≥5 cm were identified as independent pre-operative predictors of microvascular invasion on multivariate analysis. Recurrence rates for patients with none, one, two or three predictors were 22.6%, 34.7%, 57.6% and 75.0%, respectively. In combination with tumor number and tumor size, contrast-enhanced ultrasound washout rate may have a role in identifying hepatocellular carcinoma patients with microvascular invasion. (E-mail: zhou.xiang@yeah.net) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Hepatocellular carcinoma, Microvascular invasion, Contrast-enhanced ultrasound, Washout rate.**

INTRODUCTION

Selected patients with HCC are candidates for potentially curative therapy, such as hepatic resection and liver transplantation. Nevertheless, tumor recurrence is 70% at 5 y after resection and 15–30% after liver transplantation, leading to tumor-related death (Rodriguez-Peralvarez et al. 2013).

Microvascular invasion (MVI) is an independent predictor of tumor recurrence and poor survival after hepatectomy or liver resection and transplantation (Goessling 2009; Jun et al. 2012; Ma et al. 2013; Marelli et al. 2008; Pawlik et al. 2005; Rodriguez-Peralvarez et al. 2013; Wayne et al. 2002; Xu et al. 2014; Zhao et al. 2012). Vascular invasion, whether macrovascular or microvascular, is an expression of aggressive biological behavior by the tumor and is one of the most critical factors predictive of hepatocellular carcinoma (HCC) recurrence. The presence of MVI is not simply the advanced presentation of HCC from a previously non-invasive state, but may reflect a different, more aggressive tumor biology. Thus, there is an urgent need for an accurate, objective and reproducible method for evaluation of MVI. Pre-operative assessment of the risk for MVI could help in predicting prognosis, allowing appropriate patient selection for liver resection or transplant allocation.

In most cases, information on MVI comes from surgical specimens. Such information currently can be used only rarely for clinical decision making. Ideally, information on MVI would be available before choosing a treatment approach. However, needle biopsy is not routinely recommended because of the risk of tumor seeding by the needle tract (Pawlik et al. 2007). Although tumor grade has been investigated as a surrogate marker of MVI (Pawlik et al. 2005), HCC grades based on needle biopsy may be misleading because they often do not correlate with the grade or presence of MVI on final pathology (Pawlik et al. 2007). Hence, computed

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tomography (CT), magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (CEUS) features have been used to predict tumor grade and MVI (Chandarana et al. 2011; Chou et al. 2012; Esnaola et al. 2002; Hayashi et al. 2002; Jonas et al. 2001; Kenmochi et al. 1987; Kim et al. 2012; Marelli et al. 2008; Nakashima et al. 1999; Pawlik et al. 2005; Rodriguez-Peralvarez et al. 2013; Suh et al. 2012; Witjes et al. 2012; Xu et al. 2014).

The rate or time of washout is correlated with de-differentiation of the tumor. The greater the time of washout is, the less differentiated the tumor tends to be from abnormal arterial–venous connections (Feng et al. 2015; Jang et al. 2007; Nicolau et al. 2004). As the most important feature in the diagnostic algorithm for CEUS (Bhayana et al. 2010), washout refers to the change in background enhancement of the liver as it becomes greater than the enhancement of the hypervascular mass.

Criteria for pre-operative CEUS washout assessment of MVI are not well established. Therefore, this study investigated use of the washout rate of HCC on CEUS for pre-operative MVI detection.

METHODS

Patient population

This retrospective study was approved by the research ethics board of West China Hospital, Sichuan University, China. The requirement for informed consent was waived. Included in this study were patients with hypervascular HCC based on CEUS, who had no clinical, radiographic or intra-operative evidence of extrahepatic tumor and who underwent an attempt at curative resection. The study group included only HCC cases; cholangiocarcinoma cases were excluded. Patients with hypo-enhancement of the arterial phase and clinical, radiographic or intra-operative evidence of extrahepatic tumor were excluded from the study.

Clinicopathologic variables

Clinicopathologic data, including age, sex, α-fetoprotein (AFP) level, hepatitis serology, number and size of tumors size and presence of vascular invasion (macro- or microscopic), were collected for all patients (Table 1). One experienced pathologist with no knowledge of the CEUS findings examined the pathologic data for all patients. MVI was defined as the presence of tumor emboli within the central veins or the portal or large capsular vessels under microscope. Macrovascular invasion was defined as gross invasion of segmentary branches of portal or hepatic veins. Tumor grade was assessed by analysis of both pre-operative needle core biopsy and surgical pathologic specimens. Tumor grade was scored with the nuclear grading scheme outlined by Edmondson and Steiner and categorized as low, intermediate or high. Specifically, modified Edmondson–Steiner grades of 1 and 2 were defined as well differentiated, grade 3 as moderately differentiated and grade 4 as poorly differentiated. Hepatitis activity and fibrosis stage of the surrounding parenchyma were scored as described by Ishak et al. (1995). Fibrosis was divided into six stages: stage 1–3 patients were considered non-cirrhotic, and stage 4–6 patients, cirrhotic.

CEUS and washout rate

Scans were obtained by four radiologists (L.L., X.Z., Y.L. and Y.Z.L.) with 10, 14, 18 and 25 y of experience in routine US and 4, 10, 7 and 8 y of experience in CEUS. An iU22 system (Philips Ultrasound, Bothell, WA, USA) was used with a multifrequency (5–2 MHz) convex transducer (C5-1). CEUS was performed with up to two bolus injections of 2.4 mL of SonoVue (Bracco, Milan, Italy) for viewing different sections of the tumor. Injections were separated by 10-min intervals to allow complete disappearance of the preceding bolus. The bolus was followed by a 10-mL saline flush. A low mechanical index (<0.1) was set for CEUS.

The contrast side-by-side mode was used *via* a live dual-image display. Two or three consecutive 30- to 50-s cine clips were recorded from washin to washout. On retrospective review of the clips (by X.Z. and W.Z.), still images were stored at the peak of arterial enhancement and at the first sign of washout. In large tumors with intranodular necrosis or vascular thrombosis, enhancement was evaluated within the active portion of the tumor or, when possible, in its peripheral capsule.

Washout is a visually assessed temporal reduction in enhancement of a lesion relative to surrounding liver tissue from an earlier to a later phase resulting in hypoenhancement of the portal venous or delayed phases. The arterial, portal and delayed phases were defined, respectively, as 10–30, 31–120 and 121–360 s after injection of the contrast agent, as advised by the European Federation of Societies (Claudon et al. 2013). Four washout patterns were classified according to the start time of washout: WR1, slow washout (no washout); WR2, delayed washout (washout in the delayed phase); WR3, portal washout (washout in the portal phase); and WR4, rapid washout (washout in the arterial phase). CEUS imaging and B-mode imaging were assessed for the following features: (i) maximal lesion diameter on US; (ii) tumor echogenicity on US (hyper-echoic, iso-echoic or hypoechoic, using surrounding liver as reference, in B-mode); (iii) shape and margin (regular or irregular); (iv) peripheral hypo-echoic halo on US; (v) area of tumor necrosis (central tumor area not enhanced in arterial phase); (vi) tumor border on