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Comparison between acoustic radiation force impulse quantification data and perfusion-CT parameters in hepatocellular carcinoma

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ABSTRACT

Objective: To find out, if ultrasound elastography of hepatocellular carcinoma (HCC) can predict patterns of tumor perfusion in volume perfusion computed tomography (VPCT).
Material and methods: 25 consecutive patients (mean age, 68.9; range, 51–85 years) with liver cirrhosis suspected of HCC underwent VPCT and acoustic radiation force impulse (ARFI) elastography the same day. Quantitative elasticity values were registered, while blood flow (BF), blood volume (BV) and hepatic perfusion index (HPI) of the HCC lesions were calculated. Additionally, we identified histologic WHO grading, lesion size and localization. The Siemens Acuson S 3000 HELX-System with Virtual Touch™-Software and Siemens Somatom Definition Flash with Syngo® software were used.
Results: A total of 43 HCC lesions were assessed. Mean shear wave velocity was 2.6 m/s (range, 1.1–4.3 m/s). There was no significant linear correlation between the elasticity values and BF ($p = 0.751$), BV ($p = 0.426$) and HPI ($p = 0.437$). However, elasticity values were higher, the larger the tumor was ($p = 0.008$). Shear wave velocity declined with increasing distance of the HCC to the skin surface ($p = 0.028$) and depending on liver segment. In addition, elasticity values were higher in less differentiated HCCs. This trend was not statistically significant ($p = 0.842$).
Conclusion: Tissue elasticity in HCC does not correlate with the degree of tumor vascularization, but calculated values are influenced both by the tumor size and localization inside the liver.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors at all accounting for up to 90% of primary malignant neoplasms of the liver [1]. It develops primarily in cirrhotic liver parenchyma [2]. In this particular clinical setting, HCC is now allowed to be diagnosed non-invasively using typical tumor enhancement patterns [3]. Imaging features highly suggestive of HCC are the presence of rapid contrast wash-in and wash-out, which can be documented with help of different imaging modalities like contrast-enhanced ultrasound (CEUS), multiphase contrast-enhanced CT (CECT) and dynamic contrast-enhanced MRI [4–6]. In the last years, many reports have advocated the use of volume perfusion-CT (VPCT) as an alternative to 3- or 4-phase CECT [7–10]. Today, VPCT is an adequate technique to evaluate tumor vascularization and patterns of intratumoral blood flow. VPCT consists of a higher number of liver (tumor) measurements using high-temporal resolution and a comparatively short time window (mostly <60s) leading to numerous arterial, capillary and early portal-venous phases, that accurately detect any hypervascular liver lesion and additionally allow for precise quantification of tumor perfusion. The latter can be accomplished by mathematical calculation models using one (hepatic artery) or two (dual: hepatic artery and portal vein) input vessels. The former quantifies tumor perfusion in terms of blood flow (BF), blood volume (BV), k-trans, time-to-peak (TTP) and mean transit time (MTT) using a maximum slope model

Abbreviations: ALP, arterial liver perfusion; ARFI, acoustic radiation force impulse; BF, blood flow; BV, blood volume; CECT, contrast-enhanced computed tomography; CT, computed tomography; Fig., figure; HCC, hepatocellular carcinoma; HPI, hepatic perfusion index; MIP, maximum intensity projection; MRI, magnetic resonance imaging; MTT, mean transit time; PVP, portal venous perfusion; ROI, region of interest; TDC, time density curve; TTP, time-to-peak; VOI, volume of interest; WHO, World Health Organization; VPCT, volume perfusion-CT.

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(BF and TTP) and the Patlak model for calculation of BV, k-trans and MTT. Correlation between histologic grading and tumor perfusion (magnitude of perfusion parameters) has been demonstrated [11,12].

Ultrasound elastography, on the other side, represents an emerging imaging modality that provides information about tissue elasticity (e.g. in tumors or liver parenchyma). Ultrasound elastography has been extensively analyzed, mainly for quantification of liver stiffness occurring with advancing cirrhosis [13–15]. Liver stiffness measurement has already become a strong predictor of clinical HCC development [16].

Despite great similarities in terms of perfusion characteristics, HCC are quit complex in their architecture. In general, HCC tumor architecture depends on the tumor cells' ability to recruit blood vessels by forming new vessels through angiogenesis. However, experimental approaches suggested that VEGF expression – and consequently tumor vascularization – is related to the matrix stiffness of HCC [17,18]. If this experimental hypothesis could be translated into diagnostic imaging, this could be eventually used as a surrogate marker for tumor perfusion and might be of interest in patients receiving antiangiogenic treatment.

So, the aim of this study was to find out if tumor perfusion parameters (e.g. blood volume) as well as tumor size and location correlate with tumor elasticity measured by ultrasound elastography.

2. Material and methods

2.1. Patient population

This prospective study was approved by the institutional review board. 25 patients (all male; mean age, 68.9 years; range, 51–85 years) with liver cirrhosis and suspected HCC were enrolled consecutively between February and August 2016. Perfusion-CT and ultrasound elastography were performed on the same day. Image data analyzed in this study were acquired prospectively as part of routine examinational work-up at our institution. For final data evaluation and comparison of the two imaging modalities a retrospective approval was requested from our institutional review board with a waiver of informed consent. Diagnosis of HCC was made by histology (n = 18) or according on current diagnostic guidelines in patients with HCC based on typical contrast-enhancement patterns (n = 7) [3].

The largest axial diameter of each lesion was measured in CT including the lesion borders. In addition, we registered the localization of each lesion relating to both the liver segment and possible subcapsular position, as well as in terms of distance to skin surface. Therefore a measurement depth of <5 cm was defined as a subcapsular location.

2.2. Ultrasound elastography technique

All examinations were performed on an Acuson S3000 system (Siemens) by two of the authors (M.E and M.H.) with 3 and 23 years of ultrasound experience. First, B-mode ultrasound was performed for planning tumor elastography using the curved-array probe. Subsequently, ultrasound elastography was performed using the curved-array probe (6C1-HD, Siemens) with a bandwidth of 1.5–6 MHz in all cases. Supplementary, the application of a linear probe (9L4, Siemens) with a bandwidth of 4–9 MHz was added, when lesions were found in a subcapsular location

2.3. Ultrasound elastography analysis

Acoustic radiation force impulse (ARFI) imaging was performed to quantify lesion stiffness. All the regions of interest (ROI) were entirely included into the lesion, in biggest ones changing the ROI location to cover the entire mass as much as possible (Fig. 1A). As Virtual Touch^{TM} tissue quantification expresses the shear wave speed in solid materials as numerical values, only numerical results were taken into consideration for this study. A minimum of three measurements was done in particular at the periphery of the tumors. Non-valid measurements due to an erroneous ROI positioning (i.e. necrotic or cystic portion of a lesion, vessels or biliary structures within the ROI or patient motion) were excluded. The maximum penetration depth for tissue quantification was 8.0 cm, and the fixed size of ROI was 10 × 6 mm. Shear wave velocity values were displayed in meters per second (m/s).

2.4. Perfusion-CT technique

CT-examinations were performed for detection of HCC in patients with liver cirrhosis as indicated by the treating physicians, independent of the current study. Informed consent was obtained for the VPCT examination. A 256-slice MDCT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) was used for all examinations. The scan range for VPCT utilizing adaptive spiral scanning technique was 11–17 cm z-axis coverage. Perfusion-CT-protocol consisted of 80 kVp, 100 mAs, 64 × 0.6 mm collimation, scan time of 40 s and time resolution of 1.5 s per acquired spiral data set [7,8,19]. 50 ml Ultravist 370 (Bayer Vital, Leverkusen, Germany) at a flow rate of 5 ml/s were injected intravenously followed by a saline flush of 50 ml NaCl. Scanning was always started with a delay of 7 s. A dual-head pump injector (Medtron, Saarbruecken, Germany) was used for the administration of the contrast agent. One set of axial images with a slice thickness of 3 mm for perfusion analysis was reconstructed with a medium smooth tissue convolution kernel (B10f). All images were transferred to an external workstation (Multi-Modality Workplace, Siemens Healthcare) for analysis.

2.5. Perfusion-CT analysis

Motion correction, noise reduction and threshold-based exclusion of bone, fat and air were performed for all image sets using Syngo® Volume Perfusion CT Body (Siemens Healthcare, Forchheim, Germany). The algorithms are based on non-rigid deformable registration for anatomic alignment and a dedicated noise reduction technique for dynamic data [20].

Perfusion parameter maps of blood flow (BF; ml/100 ml/min), blood volume (BV; ml/100 ml), arterial liver perfusion (ALP; ml/100 ml/min), portal venous perfusion (PVP; ml/100 ml/min) and hepatic perfusion index (HPI; %) were determined for all HCCs. With regards to the predominance of arterial supply in HCCs, calculation of BF and BV was done by drawing a ROI in the abdominal aorta and using an arterial only input function with the Patlak estimation model [8,21].

Determination of ALP and PVP – according to the dual blood supply of the liver by hepatic artery and portal vein – was done by using the time of peak splenic enhancement by drawing a ROI in the portal vein and spleen respectively. Arterial time density curve (TDC) for ALP was calculated dividing maximum arterial slope by maximum aortic enhancement. Portal-venous TDC for PVP was calculated dividing maximum portal-venous slope by maximum portal-vein enhancement. HPI in % represents ALP divided by the sum of ALP and PVP [8].

For the HCC lesions quantitative perfusion parameters BF, BV, ALP, PVP HPI were obtained (Fig. 1B). For this purpose, a manually drawn volume of interest (VOI) was defined in the transverse 2D image; an automatic pixel based recognition algorithm allowed for encompassing the whole tumor volume along the z-axis [22].