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Iodine quantification to distinguish hepatic neuroendocrine tumor metastasis from hepatocellular carcinoma at dual-source dual-energy liver CT

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ABSTRACT

Purpose: To investigate the value of third-generation dual-source dual-energy computed tomography (DECT) iodine quantification to distinguish hepatic neuroendocrine tumor (NET) metastasis from hepatocellular carcinoma (HCC) in non-cirrhotic liver parenchyma.

Material and methods: Forty-six patients (mean age, 64.9 ± 10.1 years; 28 male and 18 female) with either hepatic NET metastasis or HCC, who had undergone liver DECT, were included in this retrospective study. For each lesion, arterial-phase attenuation values and DECT quantitative parameters, including iodine uptake, fat fraction, normalized iodine uptake (NIU), and lesion-to-liver-parenchyma ratio (LPR) were evaluated. Available cumulative data from histopathology, MRI, PET/CT, or interval imaging follow-up served as the reference standard for all liver lesions. In addition, the diagnostic accuracy of contrast-enhanced and material decomposition analysis for the differentiation of hepatic NET metastasis and HCC was assessed using receiver operating characteristics (ROC) curve analysis.

Results: Hepatic NET metastasis and HCC showed significant differences in arterial attenuation ($P = 0.003$), iodine uptake ($P < 0.001$), NIU ($P < 0.001$), and LPR ($P = 0.003$). No significant differences were found for unenhanced attenuation and fat fraction values ($P = 0.686$ and $P = 0.892$, respectively). NIU showed superior sensitivity (100%; iodine uptake, 71%), while both iodine uptake and NIU revealed superior specificity (100% and 90%, respectively) compared to LPR (sensitivity, 96%; specificity, 80%) and arterial attenuation analysis (sensitivity, 79%; specificity, 80%) ($P \leq 0.016$).

Conclusion: Third-generation DECT with assessment of iodine uptake improves the differentiation of hepatic NET metastasis and HCC in non-cirrhotic liver, with NIU showing the strongest diagnostic performance.

1. Introduction

Neuroendocrine tumors (NET) originate from the neural crest and commonly affect the gastrointestinal system or parenchymal organs with a wide range of clinical symptoms due to an uncontrolled release of hormones from the primary tumor or its metastases [1]. Hepatic NET metastases are present in about 30–80% of patients and represent the most important prognostic factor [2]. As metastases are frequently characterized by a hypervascular arterial enhancement pattern at contrast-enhanced computed tomography (CT), the discrimination from other hypervascular liver lesions, such as hepatocellular carcinoma (HCC), is challenging [3–5]. Further uncertainty regarding the differentiation of hepatic NET metastasis from HCC may be caused by a quite similar appearance at magnetic resonance imaging (MRI) and an overlapping histopathological immunoprofile in some cases [6–10].

Dual-energy computed tomography (DECT) enables material decomposition analysis in addition to providing morphological information [11]. Based on the differences in absorption characteristics for different atomic numbers between the two X-ray beam energies, DECT allows for precise iodine quantification in contrast-enhanced images [12]. Furthermore, this material decomposition technique has the potential to depict even small variances in tumor iodine densities, because it is not affected by confounding factors that influence CT attenuation values [13]. Thus, differences in blood supply for tumor entities with even similar morphological appearance can be quantified, providing further information for lesion characterization and therapy [14,15]. Several studies have shown that quantitative DECT imaging can contribute to the diagnosis of suspect hepatic lesions [16,17]. However, the

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potential for discrimination between hepatic NET metastasis and HCC has not been evaluated so far.

Therefore, the purpose of the present study was to assess the value of DECT-derived iodine quantification for the differentiation of hepatic NET metastasis and HCC in non-cirrhotic liver.

2. Material and methods

2.1. Patient selection and study population

This single-center retrospective study was approved by the institutional review board with a waiver for written informed consent. Fifty-five patients with hypervascular hepatic metastases due to gastro-enteropancreatic NET and 67 patients with hypervascular HCC were initially included in the present study. All patients had undergone clinically-indicated DECT examinations on the same third-generation dual-source DECT scanner (SOMATOM Force, Siemens Healthcare, Forchheim, Germany) between March 2015 and September 2017. Exclusion criteria for the present study were hepatic lesions with a craniocaudal diameter < 6 mm (n = 6) to avoid partial volume effects in the reconstructed axial images with 3 mm collimation [18] as well as the lack of an adequate reference standard (see "Reference standard" section for details) (n = 23). Further exclusion criteria in the group of patients with HCC were subjects with liver cirrhosis (n = 20) and HCC lesions with a maximum diameter > 35 mm (n = 27) as these conditions largely influence the arterial blood supply according to previous studies [19,20]. Especially advanced HCCs (> 35 mm) are frequently characterized by a vascular infiltration, the presence of arteriovenous shunts, and consequently heterogenous hemodynamics [21,22]. The diagnosis of liver cirrhosis was based on both typical imaging features and histopathological confirmation in all cases. Both patients with single and multiple liver lesions were included in the present study. None of the patients included in the present study received any NET or HCC specific therapy before.

The final study population consisted of 46 patients (mean age, 64.9 ± 10.1 years; 28 male and 18 female), including 22 patients with hepatic NET metastasis (total number of lesions: n = 34) and 24 patients with HCC (total number of lesions: n = 32) (Table 1). A flowchart of the study population enrollment following Standards for Reporting Diagnostic Accuracy Studies (STARD) is outlined in Fig. 1.

2.2. Imaging protocol

All examinations were performed on the same dual-source DECT scanner (SOMATOM Force, Siemens) with standardized settings for the DECT mode: tube A: 90 kV; current-time product per rotation: 95 mAS; tube B: Sn150 kV with tin filter; current-time product per rotation: 59 mAs; rotation time: 0.5 s; pitch: 0.7; collimation: 2 × 192 x 0.6 mm. The study protocol consisted of arterial-phase acquisition in the DECT mode and portal-venous phase acquisition in the single-energy CT (SECT) mode. For SECT portal-venous scanning, the tube voltage was 120 kV, and the tube current-time product was 150 mAs. Venous-phase SECT images were not used for quantitative evaluation. Attenuation-based tube current modulation (CARE Dose 4D, Siemens) was applied for all acquisitions. Furthermore, third-generation advanced modeled iterative reconstruction (ADMIRE, Siemens; strength level, 3) with a medium smooth reconstruction kernel (Br40) was used. The volume CT dose index ($CTDI_{vol}$) and the dose length product (DLP) were recorded for each examination.

The arterial-phase scan was automatically started 15 s after a threshold of 120 Hounsfield units (HU) was measured in the descending aorta at the level of the celiac artery by using a dedicated 120-kV bolus tracking scan software (CARE Bolus, Siemens). The portal-venous-phase acquisition was started with a delay of 70 s after the start of the contrast agent administration. A nonionic contrast agent (Imeron 350, Bracco, Milan, Italy) at a dose of 1.2 mL per kilogram body weight was injected with a flow rate of 3 mL/s through a peripheral vein of the forearm in all examinations [23]. All series were reconstructed as axial and coronal reformat images, with a slice thickness of 3 mm and an increment of 2 mm, respectively.

Table 1
Patient and lesion characteristics.

	NET	HCC	P-value
Number of patients	**22**	**24**	
Number of lesions (n)	34	32	
Site of primary NET (n)			
Gastroduodenal	6		
Small bowel	7		
Colon	2		
Pancreas	7		
Characteristics			
Age (years)	63.6 ± 7.4[a]	65.4 ± 9.1[a]	0.102
Male (n)	12	16	0.547
Female (n)	10	8	
Body mass index (kg/m^2)	24.8 ± 3.8[a]	25.1 ± 4.2[a]	0.433

NET = neuroendocrine tumor. HCC = hepatocellular carcinoma.
[a] Data are mean values ± standard deviation.

2.3. Reference standard

The cumulative clinical diagnosis of all hepatic lesions was confirmed by histopathological analysis, additional imaging modalities, interval imaging follow-up, and/or tumor marker assessment. Histopathologic findings were used in 24 cases with HCC after CT-guided biopsy (n = 14) or surgery (n = 5). In five cases, the initial suspected diagnosis was proven by a subsequent magnetic resonance imaging (MRI) using hepatobiliary-specific contrast four weeks after the initial DECT scan. In addition, the diagnosis of HCC was confirmed by high levels of serum α-fetoprotein (> 11 ng/ml) in 21 patients, whereas three patients did not present with tumor marker increase (diagnosis proven in these cases by CT-guided biopsy).

Metachronous NET liver metastases (n = 10) were histopathologically proven in eight patients using CT-guided biopsy and in two cases after surgical resection. In cases of synchronous metastasis (n = 12), a ^{68}Gallium-DOTA-TOC positron emission tomography (PET)/CT was performed which showed a typical tracer uptake in the liver in eleven patients. In one case, liver metastases did not express a significant number of representative receptors in the PET examination and therefore the staging was completed with additional CT-guided liver biopsy.

2.4. Image evaluation

All measurements were performed by a radiologist with four years of experience in liver imaging who was blinded to the clinical diagnosis and CT reports. Dedicated software (syngo.via, version VB10B, Siemens) with an iodine subtraction algorithm (Liver VNC, Siemens) was used to calculate quantitative CT data from arterial-phase images, including virtual unenhanced, iodine uptake, and fat fraction measurements. Contrast-enhanced attenuation values and material densities were collected using circular regions of interest (ROI) with a diameter of 1 cm placed into the strongly-enhancing part of the lesion, in the normal hepatic parenchyma, and in the aorta at the level of the celiac artery. Focal necrosis or cystic tumor areas, as well as vessels and tumor calcifications were avoided. All ROI measurements were repeated three times and mean values were taken into account. In case of multiple liver lesions, mean value of the largest three lesions was used for the evaluation.

The following two parameters were subsequently derived from the iodine uptake measurements: (1) normalized iodine uptake (NIU); $NIU = IU_{lesion} / IU_{aorta}$, where IU_{lesion} is the iodine concentration in the lesion and IU_{aorta} represents the iodine uptake in the aorta; (2) lesion-