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Delayed Phase Cone-Beam CT Improves Detectability of Intrahepatic Cholangiocarcinoma during Conventional Transarterial Chemoembolization

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Abstract

PURPOSE—To evaluate the detectability of intrahepatic cholangiocarcinoma (ICC) on dual-phase cone-beam CT (DPCBCT) during conventional transarterial chemoembolization (cTACE) compared to that of digital subtraction angiography (DSA) with respect to pre-procedure contrast-enhanced magnetic resonance imaging (CE-MRI) of the liver.

METHODS—This retrospective study included 17 consecutive patients (10 male, mean age 64) with ICC who underwent pre-procedure CE-MRI of the liver, and DSA and DPCBCT (early-arterial phase (EAP) and delayed-arterial phase (DAP)) just before cTACE. The visibility of each ICC lesion was graded by two radiologists on a three-rank scale (complete, partial and none) on DPCBCT and DSA images, and then compared to pre-procedure CE-MRI.

RESULTS—Of 61 ICC lesions, only 45.9% were depicted by DSA, whereas EAP- and DAP-CBCT yielded a significantly higher detectability rate of 73.8% and 93.4%, respectively ($p < 0.01$). Out of the 33 lesions missed on DSA, 18 (54.5%) and 30 (90.9%) were revealed on EAP- and DAP-CBCT images, respectively. DSA depicted only one lesion that was missed by DPCBCT due to streak artifacts caused by a prosthetic mitral valve. DAP-CBCT identified significantly more lesions than EAP-CBCT ($p < 0.01$). Conversely, EAP-CBCT did not detect lesions missed by DAP-CBCT. For complete lesion visibility, DAP-CBCT yielded significantly higher detectability (78.7%) compared to EAP (31.1%) and DSA (21.3%) ($p < 0.01$).

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CONCLUSION—DPCBCT, and especially the DAP-CBCT, significantly improved the detectability of ICC lesions during cTACE compared to DSA. We recommend the routine use of DAP-CBCT in patients with ICC for per-procedure detectability and treatment planning in the setting of TACE.

INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC) as it constitutes 15% of all primary liver cancers [1]. Although it is a rather rare disease, the incidence has steadily increased since the 1970s [2]. The diagnosis is often markedly delayed, because there is no effective screening strategy and the tumor is often asymptomatic for a long period. As such, most patients are not candidates for curative surgery [3]. Even after complete resection with tumor-free resection margins, recurrence occurs in about 63% of patients [4]. Transarterial chemoembolization (TACE) is an effective palliative option for inoperable ICC lesions [5]. The presence of multiple ICC lesions carries a poor prognosis, with a drop in median survival from 37 to 15 months [6]. Identification of those multi-focal lesions is therefore critical for effective TACE.

The imaging gold-standard for ICC is contrast-enhanced magnetic resonance imaging (CE-MRI), where ICC presents typically with minimal or incomplete enhancement at the periphery in the arterial phase and progressive enhancement or pseudo-washout in the delayed-phase, the latter due to progressive background liver enhancement[7, 8]. However, the transposition of MRI findings with standard intra-procedural imaging such as digital subtraction angiography (DSA) is often challenging, especially due to some lesions being occult or hypovascular on DSA images [9, 10]. This may result either in inadequately treated or even untreated lesions, or TACE being performed in a less selective manner because of the difficulty in correctly identifying the tumors and its feeding blood vessels.

Since the introduction of C-arm cone-beam computed tomography (CBCT) in Interventional Radiology [11, 12], this imaging modality has been shown to be a valuable tool in the management of liver malignancies [13–17]. In particular, CBCT was shown to provide a three-dimensional visualization of the tumor-feeding arteries and to detect lesions that are occult on DSA and thus result in changes of treatment planning and treatment delivery [9, 10]. However, all studies that were dealing with the detectability of liver tumors on CBCT [16–19] were focusing on HCC and to date no study on detectability of ICC is available. In addition, CE-MRI served for comparison in only one of these studies [19]. Therefore, the purpose of this study was to evaluate the ability of dual-phase CBCT (DPCBCT) to identify ICC lesions during TACE compared to conventional DSA, in relation to CE-MRI of the liver.

MATERIAL & METHODS

Study Cohort

This single-center, retrospective study was compliant with the Health Insurance Portability and Accountability Act and was approved by the Institutional Review Board. Informed

consent was waived. Between May 2011 and September 2013, a total of 349 DPCBCTs were performed in 242 patients with different hepatic malignancies during intra-arterial therapies (IATs).

Inclusion criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; Child-Pugh classification A or B; focal or multifocal hepatic malignancy; no severe ascites; albumin > 2.5 g/dl; alanine aminotransferase and aspartate aminotransferase < 5 times the upper normal limit; total serum bilirubin < 3.0 mg/dl; serum creatinine < 2.0 mg/dl; platelet count $\geq 50,000/\text{mm}^3$; international normalized ratio ≤ 1.5 ; left ventricular ejection fraction $\geq 50\%$.

Of these 242 patients, 19 were found to have ICC. Two patients were excluded for the following reasons: absence of MRI pre TACE ($n = 1$) and misaligned beam shutter during CBCT acquisition ($n = 1$). On the basis of these criteria, the final study population included 17 patients. Baseline characteristics are summarized in Table 1.

MR Imaging Technique

All patients underwent baseline MRI approximately two weeks before IAT (mean 5 days, range 0–16) using a 1.5-T MRI unit (Magnetom Avanto, Siemens Medical Solutions, Forchheim, Germany)). A phased-array torso coil was used for signal reception. A standard liver protocol was performed and included: axial T2-weighted fast spin-echo images, axial single-shot breath-hold gradient-echo diffusion-weighted echo-planar images and axial breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadodiamide [Omniscan; Amersham, Princeton, NJ]) T1-weighted three-dimensional (3D) fat-suppressed spoiled gradient-echo images in the arterial, portal venous and delayed phases (20, 70 and 180 seconds after intravenous contrast administration, respectively).

Intraprocedural Imaging (DSA and C-Arm DPCBCT)

All patients considered for IATs were discussed at our multidisciplinary liver tumor board. All patients of the study cohort were treated by conventional TACE (cTACE); a total of 24 cTACE procedures were performed. cTACE procedures were performed by a single interventional radiologist (XX) with 18 years of experience in hepatic interventions, using our standard institutional protocol [20]. Briefly, access was gained in the femoral artery using the Seldinger technique. The celiac axis was then catheterized using a 5-F Simmons-1 catheter (Cordis, Miami Lakes, FL) through which a 2.8 F Renegade HI-FLO microcatheter was coaxially advanced. Several angiographic steps were performed to define the hepatic arterial anatomy, to determine portal venous patency and tumor enhancement. Injection rates were adapted to the estimated blood vessel diameter (1–3 ml/sec).

All procedures were performed using an angiographic system (Allura Xper FD20, Philips Healthcare, Best, The Netherlands) equipped with the XperCT module, enabling C-arm CBCT acquisition and volumetric image reconstruction (Feldkamp back projection) [21]. Contrast injections (Oxilan 300 mg I/ml; Guerbet, France) were performed with a power injector (Medrad, Indianola, PA, USA). All patients underwent C-arm DPCBCT with the microcatheter placed into the hepatic artery branch that lead to the tumor-feeding vessels, in the same position as the last acquired DSA. In particular, the position of the microcatheter

tip was lobar and segmental in 8 (47%) and 9 (53%) patients, respectively. The area of interest was positioned in the system isocenter prior to each CBCT scan. The DPCBCT prototype feature enhanced the XperCT module to enable acquisition of two sequential CBCT scans (in an early- and a delayed-arterial phase (EAP and DAP)) using only one contrast injection [22, 23]. Both image acquisitions were performed before administration of the chemoembolization. The acquisition parameters were set to 120 kV tube voltage and 50 mA tube current, the latter being modulated automatically during the acquisition. The two scans were triggered at 3 and 28 seconds after a single injection of 20 ml of undiluted contrast agent with a flow rate of 2 ml/sec. The patients were instructed to be at end expiration apnea during each of the CBCT scans with free breathing between the early- and the delayed-arterial phase scans. Oxygen was administered to patients during the procedure to minimize the discomfort of breath holding. With the motorized C-arm covering a 240° clockwise arc at a rotation speed of up to 55°/s, 312 projection images (60 frames/s) were acquired in 5.2 seconds. On completion of the acquisition, the two-dimensional projections were automatically transferred to the reconstruction computer, where they were reconstructed into 3D volumetric images with an isotropic resolution of 0.6 mm, a field of view (FOV) of 250 × 250 × 194 mm and a matrix size of 384 × 384 × 296.

Imaging Data Analysis

All DPCBCT and DSA images were evaluated retrospectively side-by-side with the portal-venous and delayed phase of the pre-interventional MRI on a free viewer software (Osirix, Pixmeo, Bernex, Switzerland) by two interventional radiologists with four years of experience (YY and ZZ), who did not participate in the TACE procedures. The observers were allowed to alter the window and zoom levels of the images to optimize perception. The presence of streak artifacts was searched. Streak artifacts, such as breathing, catheter and prosthesis artifacts, were assessed on DPCBCT images using a three-point-scale (none, localized, extensive). Extensive artifacts were considered to affect the diagnostic quality of the CBCT scan, whereas the presence of localized artifacts was deemed acceptable for diagnosis.

85 ICC lesions measuring at least 5 mm in maximum diameter were identified on baseline CE-MRI; all lesions smaller than 5 mm were excluded from evaluation. Ten lesions were outside the FOV of the CBCT acquisitions and were excluded from the analysis. In addition, since the CBCTs were not acquired from the proper hepatic artery, but rather more selectively from within the liver vasculature, only lobar or segmental contrast attenuation of the liver parenchyma was seen. Thus, lesions that were entirely situated in liver segments not opacified by the contrast medium injection during the CBCT acquisition were excluded. Whereas lesions that had supply from both the left and right hepatic arteries were not excluded if the injected contrast medium reached the tumor from one of the feeding arteries. Following this approach, 14 lesions were excluded, leaving a total of 61 ICC lesions for final analysis. The lesion diameters were measured on the portal-venous or delayed phase MR images depending on which sequence showed a better enhancement of the lesion. Conspicuity of the ICC lesions on DSA, EAP- and DAP-CBCT was classified into three grades in comparison to pre-treatment baseline CE-MRI: (1) optimal = the lesion was clearly detectable such as that in CE-MRI; (2) sub-optimal = complete extent of the lesion

was not visible compared with CE-MRI; and (3) non-diagnostic = the lesion could not be detected at all.

Statistical Analysis

Descriptive statistics were used to summarize the data. Mean and range were used for continuous variables. Frequencies and percent were used for categorical variables. To avoid statistical bias due to repeated measurements in patients who received more than one TACE procedure, only the first cTACE/CBCT of each patient was included. Using MRI as the gold standard, detectability of ICC lesions was compared to the EAP- and DAP-CBCTs, and to DSA. Statistical significance testing was performed with Friedman's Two-Way Analysis of Variance by Ranks and with Kendall's Coefficient of Concordance. In addition, the partial and complete depiction categories were combined into one group for binary testing (detected vs. not detected) using Cochran's Q test.

RESULTS

The majority of EAP- and DAP-CBCTs showed no breathing artifacts (71% and 59%, respectively), while localized breathing artifacts were present in the remaining 29% and 41% of EAP- and DAP-CBCTs, respectively. There were no extensive breathing artifacts. Localized streak artifacts due to the contrast filled catheter/arteries were observed in all acquisitions. In one patient with a history of portal vein embolization in the right liver lobe (6%), several coils caused localized streak artifacts. In another patient (6%), extensive streak artifacts were caused by a prosthetic mitral valve.

The mean size of the ICC lesions was 36 mm (range, 5 to 212 mm). Out of the 61 lesions, only 28 (45.9%) could be identified on DSA images, whereas EAP- and DAP-CBCT images depicted 45 (73.8%) and 57 (93.4%) lesions, respectively. Cochran's Q test revealed that DAP-CBCT yielded significantly superior detectability compared to EAP-CBCT ($p=0.025$) and DSA ($p<0.01$). EAP-CBCT also had a significantly higher detectability compared to DSA ($p<0.01$).

More specifically, a complete depiction was achieved by DSA, EAP- and DAP-CBCT in 13 (21.3%), 19 (31.1%) and 48 (78.7%) lesions, respectively. Partial depiction was achieved on DSA, EAP- and DAP-CBCT images for 15 (24.6%), 26 (42.6%) and 9 (14.8%) lesions, respectively. Both statistical tests - Friedman's Two-Way Analysis of Variance by Ranks and Kendall's Coefficient of Concordance - showed a significant advantage of DAP-CBCT over EAP-CBCT ($p<0.01$) and DSA ($p<0.01$), respectively, whereas the difference between EAP-CBCT and DSA was not significant ($p=0.256$).

Out of 33 lesions missed by DSA, 18 (54.5%) and 30 (90.9%) were identified on EAP- and DAP-CBCT, respectively (Figure 1). The DAP-CBCT depicted 12 more lesions than the EAP-CBCT, whereas the EAP-CBCT did not show any additional lesions compared to the DAP-CBCT (Figure 2).

Of the 4 lesions seen on CE-MRI and missed by DPCBCT, DSA depicted only one. On MRI, this was a centrally located, well defined lesion in segment 8 with a diameter of 49

mm. This lesion was not visible on DPCBCT images due to extensive streak artifacts caused by a prosthetic mitral valve (Figure 3). The remaining 3 lesions missed by DPCBCT had rather small diameters of 10, 14 and 15 mm, respectively, and could not be identified on DSA images either.

DISCUSSION

The main finding of this study was that DPCBCT significantly improved the detectability of ICC lesions during cTACE procedures, thereby playing a key role in improving the selectivity, targeting and precision of the treatment. With standard DSA, less than 50% of ICC lesions could be identified. In such cases, less selective TACE (e.g. lobar application) would have been the only available option had CBCT not been available. As a result, this would have potentially lead to less selective treatment, thus exposing more healthy tissue (non-targeted treatment) to the payload, while still being at risk of missing or undertreating the tumors. Although the standard EAP-CBCT showed significantly improved detectability of ICC lesions compared to DSA, the DAP-CBCT surpassed both DSA and EAP-CBCT by depicting more than 90% of the ICC lesions seen on CE-MRI.

In a previously published paper, Miyayama et al [24] reported a depiction of approximately 89% of HCC lesions using EAP-CBCT when compared to conventional computed tomography. In particular, EAP was able to detect the majority of small HCC lesions that were invisible on two-dimensional angiographies [16]. With the addition of DAP-CBCT, Loffroy et al. were able to detect 93.9% of HCC lesions seen on CE-MRI [19]. Surprisingly, we reached a similar detectability rate for ICC lesions. ICC lesions are fibrotic and display minimal peripheral enhancement on arterial-phase MR images with progressive tumor enhancement on subsequent portal- and delayed-phases [7, 8]. On DSA, many ICC lesions showed a delayed and rather limited enhancement which can potentially explain the rather low detectability rate of ICC lesions in our study. Also the projection nature of DSA compared to the cross-sectional 3D dataset of MRI and CBCT certainly plays a role as well in the lower detectability rate of the two dimensional angiographies. On CBCT, many of the ICC lesions showed minimal to no enhancement on the EAP, with the tumor periphery and the surrounding liver parenchyma enhancing on the DAP, demarcating the hypo-enhancing central portions of these lesions. Thus, as shown by our results most of the tumors could be detected on the DAP-CBCT despite the hypovascular nature of these lesions.

Regarding the lesions missed by the DAP-CBCT potential explanations include: a sub-optimal timing of contrast injection and acquisition of the second CBCT phase, resulting in a poor lesion to liver contrast. In addition, the contrast-filled catheter caused local streak artifacts in all patients, which might have masked small adjacent ICC nodules. Breathing artifacts seen in some patients might have contributed to decreased image quality and potentially missing lesions.

The present study has some limitations. First, the sample size of the current study is rather low. However, ICC is a rather rare disease. Second, most patients were diagnosed at advanced stage with multifocal disease and sometimes with large tumor nodules, which might have biased detectability. However, this represents the majority of patients with ICC

referred for IAT, as they were not considered appropriate candidates for any surgical treatment. Third, the CBCTs were not acquired from the proper hepatic artery, but rather more selectively from within the liver vasculature, thus only lobar or segmental contrast attenuation of the liver parenchyma was seen and lesions in other segments as depicted by the CE-MRI had to be excluded. However, the position of the catheter was selected based on the tumor burden as seen on the pre-interventional CE-MRI.

Despite these limitations, our results demonstrated that the addition of a second CBCT phase significantly improved identification of ICC lesions. Although the EAP-CBCT did not show any lesions missed by DAP-CBCT, the former is still required to visualize the feeding arteries in our current protocol [25]. It could be suggested that using a proximal and prolonged contrast medium injection, one could visualize both the feeding arteries and the tumor parenchyma on DAP-CBCT.

CBCT did not identify all lesions detected in the pre-TACE MRI, however, it has the benefit of being performed during the TACE procedure with minimal additional effort compared to DSA. In this way, CBCT directly contributes to the final positioning of the delivery catheter [26] through better targeting of the tumor and provides intra-procedural feedback on the technical success of the TACE procedure [27].

In conclusion, DPCBCT significantly improved the identification of ICC lesions during TACE. DAP-CBCT yielded the highest detectability rate for the complete delineation of ICC lesions and should be used as standard imaging technique during TACE in ICC patients.

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Figure 1. 66-year-old man with a history of stage IIIA ICC. The patient's initial symptoms were abdominal pain and weight loss
 Contrast-enhanced T1-weighted gradient-echo sequence in the portal-venous phase shows a large lesion in segment 4 of the liver ((a), arrowheads) and a smaller lesion in segment 8 ((b), arrow). (c) On the celiac arteriogram, only the large lesion (arrowheads) is visible. In early-arterial phase CBCT ((d), arrowheads and (e), arrow) and delayed-arterial phase CBCT ((f), arrowhead and (g), arrow) both lesions are depicted. (f) The asterisk (*) indicates a hepatic vein.

Figure 2. 62-year-old woman with a history of stage IV ICC. The patient's initial symptoms were abdominal pain and malaise

(a) Contrast-enhanced T1-weighted gradient-echo sequence in the portal-venous phase shows multiple lesions in all liver lobes, on the shown axial slice, two lesions in segment 2 (asterisks, *) and one lesion in segment 4a/8 (arrowheads) are visible. (b) On DSA acquired with the catheter tip in the left hepatic artery, these lesions were not clearly visible and only other already known lesions in segments 3 & 4b were vaguely depicted (arrowheads). (c) On early-phase CBCT, the fibrotic core of the lesions in segment 2 (asterisk) is poorly demarcated, the enhancing rims are depicted only partially (arrowheads). The lesion in segment 4a/8 is not visible. (d) On delayed-phase CBCT, the lesions in segment 2 are completely depicted (asterisks) as enhancing rims surrounding a hypo-intense center compared to the healthy liver parenchyma, whereas the lesion in segment 4a/8 is only partially depicted due to the dual blood supply from the right and left hepatic artery (arrowheads).

Figure 3.

64-year-old asymptomatic woman with a history of stage IIIA ICC incidentally discovered during an ultrasound examination. (a) Contrast-enhanced T1-weighted gradient-echo sequence in the portal-venous phase shows a large, enhancing lesion centrally located in segment 8 of the liver (arrow). (b) DSA clearly identifies the lesion (arrow). However, this lesion was not visible on both early- (c) and delayed-phase (d) CBCT due to severe streak artifacts caused by an artificial mitral valve (white arrowheads) and only perfusion inhomogeneity of the healthy liver parenchyma in close proximity to the lesion was visualized (black arrowheads).

Table 1

Baseline characteristics of the study cohort (n=17)

Characteristic	Value (%)
No. of Patients	17 (100)
Sex	
• Female	7 (41.2)
• Male	10 (58.8)
Age*	
• All patients	64 ± 6 years
• Female	64 ± 6 years
• Male	64 ± 5 years
Risk factors	
Hepatitis C	3 (17.6)
Cholelithiasis	2 (11.8)
Alcoholic liver disease	1 (5.9)
Nonalcoholic steatohepatitis	1 (5.9)
Presenting symptoms	
Abdominal pain	8 (47.1)
Weight loss	6 (35.3)
Malaise	4 (23.5)
Eastern Cooperative Oncology Group Performance Status	
• Grade 0	7 (41.2)
• Grade 1	10 (58.8)
Child-Pugh Class	
• A	16 (94.1)
• B	1 (5.9)
Biopsy proven ICC Tumor type	17 (100)
• Central ICC	3 (17.6)
• Peripheral ICC	14 (82.4)
Number of lesions	
• 1	7 (41.2)
• 2–3	5 (29.4)
• 4 or more	5 (29.4)
Tumor location	
Right lobe	6 (35.3)
Left lobe	3 (17.6)
Bilobar	8 (47.1)

Characteristic	Value (%)
Extrahepatic disease	2 (11.8)

Note: Except where indicated, data represents numbers of patients and numbers in parentheses are percentages.

* Data represented as mean $\pm$ standard deviation.

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