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Research article

Contrast-enhanced cone-beam breast-CT: Analysis of optimal acquisition time for discrimination of breast lesion malignancy

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ABSTRACT

Objective: To investigate the optimal acquisition time of contrast-enhanced cone-beam breast-CT (CBBCT) for best discrimination of breast lesion malignancy and whether contrast enhancement can aid in classification of tumor histology.

Material and methods: The study included patients with BI-RADS 4 or 5 lesions identified on mammography and/or ultrasound. All patients were examined by non-contrast (NC-CBBCT) and contrast-enhanced CBBCT (CE-CBBCT) at 2 and 3 min after contrast media (CM) injection. Lesion enhancement of suspicious breast lesions was evaluated in corresponding CBBCT slices.

Results: A total of 31 patients with 57 breast lesions, 30 malignant and 27 benign, were included. Malignant breast lesions demonstrated higher contrast enhancement than benign breast lesions at both 2 min and 3 min CE-CBBCT (2 min: 48.17 vs. 0.3 HU, $p < 0.001$; 3 min: 57.38 vs. 15.43 HU, $p < 0.001$). Enhancement differences between malignant and benign breast lesions were largest at 2 min CE-CBBCT. Ductal carcinoma in situ (DCIS) showed highest mean contrast enhancement among malignant breast lesions (100.93 HU at 3 min CE-CBBCT, $p = 0.0314$) compared to invasive carcinoma of no special type with DCIS component (55.82 HU at 3 min CE-CBBCT) and invasive ductal carcinoma (52.31 HU at 3 min CE-CBBCT).

Conclusions: The contrast enhancement on CE-CBBCT best discriminates between malignant and benign breast lesions at 2 min after CM injection. The enhancement has the potential to differentiate histopathological subtypes, with highest enhancement among malignant lesions seen for DCIS.

1. Introduction

Mammography (MG) is a widely used method for breast imaging [1]. Especially in dense breast tissue, MG shows a poor differentiation between fat free breast parenchyma and non-calcifying breast lesions [2,3].

Up to date, magnetic resonance imaging (MRI) is the most sensitive imaging modality for detection of breast cancer, but it may feature a lower specificity, higher cost and longer acquisition time than other modalities [4,5]. The dedicated cone-beam breast-CT (CBBCT) is a novel breast imaging technique providing isotropic 3D images with high spatial and contrast resolution [6]. In general, the breast CT scan can be performed native (non-contrast CBBCT; NC-CBBCT) or after intravenous administration of iodinated contrast media (contrast-enhanced CBBCT; CE-CBBCT) [6].

Several studies have shown the diagnostic superiority of NC-CBBCT over MG [7–9]. The additional administration of intravenous contrast media (CM) further amplifies these diagnostic features: CE-CBBCT diagnostic accuracy has been reported to be higher than that of NC-CBBCT or MG in both high and low density breasts [7–10]. Visualization of tumor angiogenesis and high contrast resolution were discussed as possible explanations [11–13]. However, CBBCT image acquisition protocols were inconsistent across studies: specifically, the time from CM injection to CE-CBBCT acquisition ranged between 52 s to 4 min [10,14]. To the best of our knowledge, there is no literature specifying optimal timing of CBBCT scans after CM administration.

Therefore, the aim of our study was to evaluate contrast enhancement of breast lesions on CBBCT over time to ultimately identify the

Abbreviations: BI-RADS, breast imaging reporting and data system; CBBCT, cone-beam breast computed tomography; CE-CBBCT, contrast-enhanced CBBCT; CM, contrast media; HU, hounsfield unit; MG, mammography; min, minutes; MRI, magnetic resonance imaging; NC-CBBCT, non-contrast CBBCT; US, ultrasound

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optimal acquisition time for CE-CBBCT scan for best discrimination of malignant and benign breast lesions as well as the assessment of histopathological subtypes based on the lesion enhancement in CE-CBBCT.

2. Material and methods

The study received approval by the institutional review board (including additional radiation exposure) and was conducted in accordance to the Declaration of Helsinki. All patients provided written informed consent prior to inclusion. The study protocol is available from the corresponding author.

This prospective study was conducted at a University affiliated breast imaging center in central Germany from December 2015 to March 2017.

Patients were included if Breast Imaging Reporting and Data System (BI-RADS) category 4 or 5 lesions were identified via digital two-view MG and/or ultrasound (US) in dense or very dense breast tissue (type c or d) [15,16]. Further, two separate CE-CBBCT scans at 2 min and 3 min after CM administration must have been technically achievable.

Patients were excluded if enrolled in the German breast cancer screening-program, of male gender, age under 40 years, pregnant, known history of allergic reaction to contrast agents or renal insufficiency, or presenting with bilateral breast involvement necessitating repositioning during imaging. If indicated, image-guided breast biopsies were performed immediately after imaging.

2.1. Digital mammography and ultrasound

Digital two-view MG and breast US examinations were performed in all patients (Mammomat Inspiration, Siemens, Erlangen, GER; Senographe Essential, GE Healthcare, Chicago IL, USA; Logic S8 or E9 unit, GE Healthcare, Chicago, IL, USA). Mammographies were obtained in standard cranio-caudal and mediolateral oblique views. Ultrasound was performed as four-quadrant view of each breast including the axillary region.

2.2. CBBCT

CBBCT examinations were performed at median 3 days after initial MG and/or US (Koning Breast CT, CBCT 1000, Koning Corporation, West Henrietta, NY, USA). CBBCT imaging was done in a standard manner [6,12]. CBBCT examination time for the post-contrast scan was approximately 8–10 min for one breast. Post-acquisition image processing and reconstructions were performed to achieve isotropic reconstructed volumes using a soft tissue filter and a voxel size of 0.273 mm^3 (standard mode). A dedicated 3D visualization software was utilized to evaluate CBBCT data sets (Visage CS Thin Client/Server, Visage Imaging, Richmond, USA). CBBCT images were viewed and interpreted in three orthogonal orientations (sagittal, axial and coronal) at a slice thickness of 2 mm and 3D views to aid in interpretation.

After initial NC-CBBCT, a single-shot intravenous injection of 90 mL (range 80–95 mL) non-ionic CM was administered (Iopromide, Ultravist® 300, Bayer-Schering, Berlin, GER). The contrast media was applied at a flow rate of 3 mL/ s using a power injector and followed by a 30 mL saline solution chaser with equivalent flow rate (Nemoto Kyorindo Co., Ltd., Tokyo, JPN). Two separate CE-CBBCT scans were performed at 2 min and 3 min post-CM injection.

2.3. Image analyses

Image analyses were performed by two breast radiologists with more than 7 years of breast imaging experience and 2 years of dedicated CBBCT experience.

Readers were blinded to clinical patient information and performed independent image analyses in random successive order. Readers were aware of inclusion of patients with BI-RADS 4 or 5 lesions identified on MG and/or US [15,16].

The BI-RADS 5th edition classification for both readers was separately correlated with histopathological diagnoses. As the BI-RADS lexicon is yet not adapted for CBBCT imaging, image interpretation and enhancement patterns were evaluated using modified criteria related to the MG and MRI part of the BI-RADS lexicon [15,17]. The BI-RADS assessment scale for CBBCT was applied as follows: BI-RADS 1, negative; BI-RADS 2, benign finding; BI-RADS 4 likely malignant; and BI-RADS 5 malignant.

CM kinetics on CBBCT were assessed by one reader (SW) measuring lesion intensity in Hounsfield Units (HU) of three representative rectangular regions of interest (ROIs) in coronal view with a slice thickness of 2 mm in the peripheral region of the suspicious breast lesions as well as the surrounding breast tissue and fat tissue. Lesion intensity measurements were performed before CM administration, as well as on the 2 min and 3 min post-CM CBBCT scans in the same image slices.

A priori, histopathological semi-malignant lesions (B3-lesions), all intraductal papillomas, were considered as malignant for all analyses [18,19].

2.4. Statistical analyses

Continuous variables are presented as mean with standard deviation (SD) as measure of dispersion. Categorical variables are presented as absolute number and percent.

The normality assumption of continuous variables was tested via the Shapiro Wilks test. For normally distributed independent samples the student-t test was utilized; for dependent samples the paired *t*-test. Non-parametric Wilcoxon rank-sum, Wilcoxon signed-rank and Kruskal Wallis tests were utilized for non-normally distributed samples.

To ensure stable estimates of lesion intensity on NC-CBBCT and CE-CBBCT scans, mean HU values were obtained from the three ROIs measured.

As proposed by Prionas et al., contrast enhancement of breast lesions was standardized to enhancement of fat tissue to account for any fluctuations between image acquisitions and defined as [10]:

$$enhancement\,\Delta HU = (HU_{lesion}^{postCM} - HU_{fat}^{postCM}) - (HU_{lesion}^{preCM} - HU_{fat}^{preCM})$$

Contrast enhancement of surrounding breast tissue was standardized accordingly.

For calculation of sensitivity and specificity, BI-RADS scores of each reader were dichotomized, with BI-RADS 1 or 2 indicating negative reading, and BI-RADS 4 or 5 positive reading. Sensitivity was defined as the proportion of true positive readings (TP) among true positive and false negative readings (FN). Specificity was defined as the proportion of true negative readings (TN) among true negative and false positive readings (FP). Sensitivity and specificity were compared using the McNemar test. A modified BI-RADS score was implemented for calculation of the receiver-operating curve (ROC) and corresponding area-under-the-curve (AUC) as suggested by Jiang and Metz [20]. The method proposed by De Long was used to compare dependent AUCs [21].

An alpha level of 0.05 was considered statistically significant. All provided p-values are two-sided. Statistical analyses were performed using R and RStudio (R Core Development Team, Vienna, Austria; RStudio Inc., Boston, MA, USA).

3. Results

3.1. Patient characteristics

A total of 31 patients (31 breasts) fulfilled the inclusion criteria. No patient withdrew consent or was lost to follow-up. NC-CBBCT, 2 min and 3 min post-CM as CE-CBBCT scans were performed in all patients. A mild contrast related adverse event (nausea) was reported in one