European Radiology (2019) 29:1194–1202
https://doi.org/10.1007/s00330-018-5711-9

BREAST

Diagnostic accuracy of cone-beam breast computed tomography: a systematic review and diagnostic meta-analysis

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Received: 9 May 2018 / Revised: 17 July 2018 / Accepted: 8 August 2018 / Published online: 25 September 2018

Abstract

Purpose To review the published evidence on cone-beam breast computed tomography (CBBCT) and summarize its diagnostic accuracy for breast lesion assessment.

Materials and Methods A systematic literature search was conducted using the EMBASE, MEDLINE and CENTRAL libraries. Studies were included if reporting sensitivity and specificity for discrimination of benign and malignant breast lesions via breast CT. Sensitivity and specificity were jointly modeled using a bivariate approach calculating summary areas under the receiver-operating characteristics curve (AUC). All analyses were separately performed for non-contrast and contrast-enhanced CBBCT (NC-CBBCT, CE-CBBCT).

Results A total of 362 studies were screened, of which 6 with 559 patients were included. All studies were conducted between 2015 and 2018 and evaluated female participants. Four of six studies included dense and very dense breasts with a high proportion of microcalcifications. For NC-CBBCT, pooled sensitivity was 0.789 (95% CI: 0.66–0.89) and pooled specificity was 0.697 (95% CI: 0.471–0.851), both showing considerable significant between-study heterogeneity (I^2 = 89.4%, I^2 = 94.7%, both $p < 0.001$). Partial AUC for NC-CBBCT was 0.817. For CE-CBBCT, pooled sensitivity was 0.899 (95% CI: 0.785–0.956) and pooled specificity was 0.788 (95% CI: 0.709–0.85), both exhibiting non-significant moderate between-study heterogeneity (I^2 = 57.3%, $p = 0.0527$; I^2 = 53.1%, $p = 0.0738$). Partial AUC for CE-CBBCT was 0.869.

Conclusion The evidence available for CBBCT tends to show superior diagnostic performance for CE-CBBCT over NC-CBBCT regarding sensitivity, specificity and partial AUC. Diagnostic accuracy of CE-CBBCT was numerically comparable to that of breast MRI with meta-analyses reporting sensitivity of 0.9 and specificity of 0.72.

Key Points

- *CE-CBBCT rather than NC-CBBCT should be used for assessment of breast lesions for its higher diagnostic accuracy.*
- *CE-CBBCT diagnostic performance was comparable to published results on breast MRI, thus qualifying CE-CBBCT as a potential imaging alternative for patients with MRI contraindications.*

Keywords Breast · Cone-beam computed tomography · Contrast media · Radiation dosage · Meta-analysis

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-018-5711-9) contains supplementary material, which is available to authorized users.

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Abbreviations

ACR	American College of Radiology
AUC	Area under the curve
CBBCT	Cone-beam breast CT
CE-CBBCT	Contrast-enhanced cone-beam breast CT
MG	Mammography
MRI	Magnetic resonance imaging
NC-CBBCT	Non-contrast cone-beam breast CT
US	Ultrasound

Introduction

Cone-beam breast computed tomography (CBBCT) is a novel 3D imaging modality for assessment of breast lesions [1, 2]. CBBCT provides a spatial resolution of up to 2.6 linepairs/mm and high contrast resolution, able to detect contrast differences of approximately 1% [3–5].

CBBCT can be performed after intravenous administration of iodinated contrast media as contrast-enhanced CBBCT (CE-CBBCT) or in non-contrast technique (NC-CBBCT) [1, 6]. Administration of intravenous contrast media facilitates visualization of breast lesion vascularization and might aid in discrimination of benign and malignant lesions as well as differentiation of histopathological and immunohistochemical breast cancer subtypes [7, 8].

CE-CBBCT is faster than contrast-enhanced breast magnetic resonance imaging (MRI) and offers improved patient comfort compared with mammography (MG) with breast compression [9, 10]. CBBCT further allows for vacuum-assisted biopsies of breast lesions and has been shown to be faster than standard stereotactic vacuum-assisted biopsy [11]. However, CBBCT yields a comparably high average glandular dose reported to range between 6–25 mGy [4, 5, 10, 12].

Currently, CE-CBBCT may be used in women with dense breast tissue (ACR types c/d) as a supplemental imaging modality for assessment of breast lesions in patients with MRI contraindications. A broader implementation of CE-CBBCT hinges on its diagnostic potential compared with MRI as the most sensitive breast imaging modality [13].

Several studies have evaluated the diagnostic accuracy of CBBCT and established comparisons to breast ultrasound (US), MG and breast MRI [4, 5, 10, 12, 14]. The majority of studies reported superior diagnostic accuracy and sensitivity for 3D CBBCT over US and MG [4, 5, 10, 12]. MRI and CE-CBBCT were comparable depending on the reader's experience [10].

However, certain variations in the reported diagnostic accuracy of CBBCT were evident across studies [4, 5, 12]. To date, there is no comprehensive review on the clinical utilization of CBBCT and its diagnostic performance.

The aim of our study was to review the published evidence on utilization of CBBCT and summarize diagnostic accuracy in terms of sensitivity and specificity for discrimination of benign and malignant breast lesions.

Materials and Methods

Search Strategy

This study was prospectively registered at PROSPERO (ID: CRD42018086879). In April 2018, a comprehensive electronic literature search was conducted using the MEDLINE, EMBASE and CENTRAL libraries with the broad search term clusters "breast cancer," "computed tomography" and "sensitivity or specificity." The complete search algorithm is provided in the Supplementary Material. The literature search was unrestricted concerning date, language and region. Further, reference lists of reviews and conference proceedings were manually searched to identify gray literature. International CBBCT experts were contacted to identify unpublished data, which did not result in inclusion of additional trials.

Study Inclusion and Exclusion

Studies were included if they fulfilled the following criteria: utilization of a dedicated cone beam computed tomography (CBBCT) for malignancy assessment of breast lesions as well as sufficient information to allow for computation of sensitivity and specificity. Exclusion criteria were simulation and phantom studies, evaluation of radiotherapy, utilization of body CT scanners and review studies. If multiple publications reported on the same patient cohort, the most comprehensive study was included. Studies identified by literature search were assessed by two independent blinded reviewers for potential inclusion, and inclusion was based on consensus.

Data Extraction

Using a standardized data extraction sheet, two independent blinded reviewers extracted the following information, resolving conflicts by consensus: study author, publication year, number of patients, patient age upon enrollment, menopausal status, breast density, CBBCT scanner, administration of contrast media, occurrence of contrast media related adverse events, average glandular dose for MG and CBBCT, number of breast lesions as well as sensitivity and specificity separately measured. Multi-reader studies providing diagnostic measurements for each reader were considered separately.

Study Quality assessment

Study quality was independently assessed by two blinded reviewers utilizing the Quality Assessment of Diagnostic

Accuracy Studies 2 (QUADAS2) tool, which is recommended by the Cochrane collaboration for quality assessment of diagnostic test accuracy studies [15–17]. Study quality was rated across four domains for risk of bias assessment and across three domains for concerns regarding applicability to our review question [16].

Statistical Analyses

NC-CBBCT and CE-CBBCT were considered index tests and histopathological assessment of breast lesions the reference standard. A 2 × 2 table with true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) findings was separately calculated for each study using standard contingency table methods. If applicable, study sensitivity and specificity were extracted from provided receiver-operating-characteristics (ROC) curves. Sensitivity and specificity were not modeled in separate meta-analyses, as each pair is correlated within one study [18]. Instead, a bivariate random-effects meta-analysis approach was used for joint modeling of both sensitivity and specificity that allows for across-study correlation [19]. Pooled estimates are based on restricted maximum likelihood methods. To obtain a summary ROC curve, only regions with reported study specificities were considered and standardized to the whole space, resulting in a conservative, partial area-under-the-curve (partial AUC) measure. Between-study heterogeneity was reported as I^2 statistics and rated as limited (I^2: 0–40%), moderate (I^2: 40–60%), substantial (I^2: 60–80%) or considerable (I^2: 80–100%) heterogeneity. Further, between-study heterogeneity was visually assessed via sensitivity-specificity plots. Separate meta-analyses were computed for NC-CBBCT and CE-CBBCT.

All statistical analyses were conducted using R version 3.3.2 and RStudio version 1.1.383 implementing R-packages "mada" and "meta" [20–23]. An alpha level of 0.05 was considered statistically significant. All provided *p* values are two-sided.

Results

Study characteristics

Of 362 screened studies, a total of 6 with 559 patients fulfilled the inclusion criteria: 3 studies evaluated NC-CBBCT, 1 study focused on CE-CBBCT and another 2 studies evaluated both NC-CBBCT and CE-CBBCT. Inclusion and exclusion are depicted in Fig. 1, adapted from the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Table 1 summarizes characteristics of included studies.

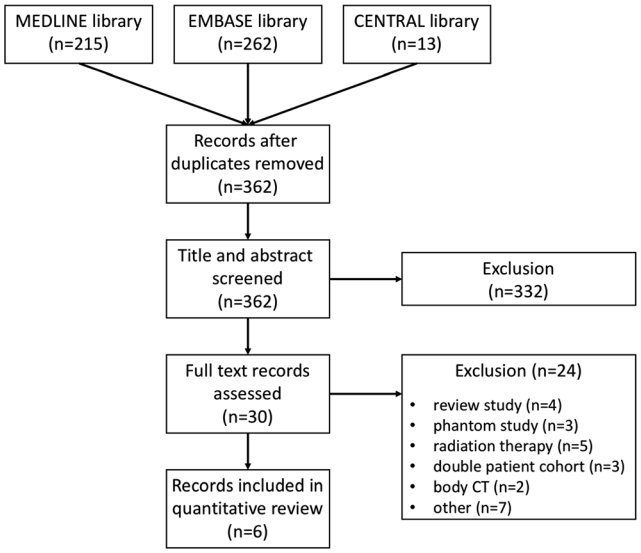

Fig. 1 Study inclusion and exclusion flow chart, adapted from the PRSIMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

All studies were conducted between 2015 and 2018 on female populations with suspicious lesions identified on MG or ultrasound. The majority of studies (83.3%, 5/6) utilized the CBBCT scanners manufactured by Koning (CBCT 1000, Koning Corp.) [4, 5, 10, 12, 14], while Aminololama-Shakeri et al used the proprietary CBBCT at the University of California at San Diego (UCSD) [24]. Average glandular dose ranged between 5.9–24.9 mGy for NC-CBBCT and 11.7–16 mGy for CE-CBBCT. ACR breast density was predominantly type c/d in three studies [5, 10, 12].

Aminololama-Shakeri et al reported on the diagnostic accuracy of CE-CBBCT for discrimination of benign and malignant microcalcifications using the proprietary UCSD CBBCT [24]. A total of 39 patients with mean age of 55 years, the majority of which had ACR type a/b breasts (72%), were included. Two independent readers evaluated CE-CBBCT images, but measures of inter-reader agreement were not presented. Diagnostic accuracy was extracted from the provided ROC curve on conspicuity scores.

The study by Cole et al examined 235 patients, aiming to compare the diagnostic accuracy of MG, CBBCT alone and CBBCT in adjunct to mammography [14]. Image assessment was performed by 18 independent radiologists and results averaged. A total of 40% of breast lesions presented as microcalcifications.

He et al reported on the diagnostic accuracy of NC-CBBCT and CE-CBBCT among 120 patients [5]. Mean patient age was 48 years. The majority of patients were premenopausal (68%) and had dense or very dense breast tissue (76% ACR type c/d). Fourteen percent of breast lesions presented as microcalcifications on imaging. Two independent readers

Table 1 Characteristics of included studies

Author	Year	Number of patients	Mean patient age (years)	Percent premenopausal status	ACR breast density	CBBCT scanner	NC-CBBCT CE-CBBCT	Average glandular dose	Contrast media-related adverse events	Breast lesions with micro-calcification
Aminololama-Shakeri	2016	39	55	-	72% Type a/b 28% Type c/d	UCSD CBBCT	CE-CBBCT	"Equivalent to MG"	-	100%
Cole	2015	235	-	-	-	Koning Breast CT	NC-CBBCT	-	-	40%
He	2016	120	48	68%	24% Type a/b 76% Type c/d	Koning Breast CT	NC-CBBCT CE-CBBCT	MG: 7 mGy NC-CBBCT: 8 mGy CE-CBBCT: 16 mGy	-	14%
Wienbeck[a]	2018	41	57.9	37%	73% Type c 27% Type d	Koning Breast CT	NC-CBBCT CE-CBBCT	MG: 3.4 mGy NC-CBBCT: 5.9 mGy CE-CBBCT: 11.7 mGy	2 Mild adverse events (nausea)	23%
Wienbeck[b]	2017	59	67.8	32%	37% Type a/b 63% Type c/d	Koning Breast CT	NC-CBBCT	MG: 2.9 mGy NC-CBBCT: 7.2 mGy	-	16%
Zhao	2015	65	55.6y	-	-	Koning Breast CT	NC-CBBCT	NC-CBBCT: 5.9–24.9 mGy	-	63%

Studies by Wienbeck et al labeled as [a,b] for identification in forest plots

ACR American College of Radiology, *CBBCT* cone beam breast CT, *NC-CBBCT* non-contrast cone beam breast CT, *CE-CBBCT* contrast-enhanced cone beam breast CT, *UCSD* University of California at San Diego, *MG* mammography

evaluated CBBCT images and resolved discrepancies by consensus; measures of inter-reader agreement were not provided.

In 2017, Wienbeck et al presented results on NC-CBBCT [12]. The study population with mean age of 59 years included a majority of ACR type c/d density breasts (63%) and mostly women with postmenopausal status (68%). Microcalcifications were detected in 16% of the breast lesions. Two independent blinded readers evaluated CBBCT imaging studies, with a high inter-reader agreement (ICC = 0.87).

In 2018, Wienbeck et al conducted a study to compare the diagnostic accuracy of CE-CBBCT and NC-CBBCT with breast MRI and MG, including 41 patients with dense or very dense breast tissue (73% ACR type c, 27% ACR type d) [10]. Mean age was 57.9 years. The majority of patients were postmenopausal (63%). On CBBCT, 23% of breast lesions exhibited microcalcifications. Two independent blinded readers evaluated all images, with high inter-observer agreement: intraclass correlation coefficient for both NC-CBBCT and CE-CBBCT was ICC = 0.74.

Zhao et al evaluated NC-CBBCT in a cohort of 65 patients with mean age of 55.6 years [4]. Microcalcifications were evident in 63% of cases. CBBCT image interpretation was performed by two independent readers resolving conflicts by consensus. Measures of inter-reader variability were not provided.

CE-CBBCT protocols

Protocols for administration of iodinated intravenous contrast media varied across studies evaluating CE-CBBCT [5, 10, 24]. Aminololama-Shakeri et al used a total volume of 100 ml Iodixanol 320 (mg iodine/ml) with a flow-rate of 4 ml/s and acquired CE-CBBCT images at 90 s post-intravenous administration [24]. Wienbeck et al administered 90 ml Iopromide 350 (mg iodine/ml) with a flow-rate of 3 ml/s and acquired CE-CBBCT images at 120 s post-intravenous administration, followed by a 30-ml bolus injection of saline solution [10]. He et al used 0.1 mmol/kg Iohexol with a flow rate of 2 ml/s at 50–80 s as time of image acquisition, followed by a 30-ml bolus injection of saline solution [5].

Radiation Dose and Adverse Events

A total of four studies provided measures of the average glandular radiation dose for CBBCT: for NC-CBBCT, mean doses ranged from 5.9–24.9 mGy and for CE-CBBCT from 11.7–16 mGy [4, 5, 10, 12]. Only He et al reported that the NC-CBBCT radiation dose was comparable to that of MG, whereas NC-CBBCT was significantly larger versus MG in the studies by Wienbeck et al [5, 10, 12]. In studies reporting on CE- and NC-CBBCT, CE-CBBCT mean radiation dose was two-fold higher than that of NC-CBBCT because of its acquisition as a native and contrast-enhanced scan (5.9–8 mGy versus 11.7–16 mGy) [5, 10].

Only one study by Wienbeck et al reported on adverse events: two patients presented with nausea related to administration of iodinated contrast media [10]. No severe or late adverse events were reported in any of the included studies.

Study Quality

As shown in Fig. 2, the overall study quality rated by the QUADAS2 tool was high. Only the study by Cole et al received a lower study quality rating, mainly due to the presentation as a conference abstract without full information on study design and conduct [14].

NC-CBBCT meta-analysis

A total of five studies with eight distinct observations on sensitivity and specificity contributed to the meta-analysis on NC-CBBCT [4, 5, 10, 12, 14].

Sensitivity and specificity point estimates with 95% confidence intervals across individual studies and readers are provided in Fig. 3. Point estimates for sensitivity ranged from 0.47-0.91 and demonstrated considerable statistically significant between-study heterogeneity (I^2 = 89.4%, 95% CI: 80.6–94.2%, $p < 0.001$). Specificity point estimates ranged between 0.31 and 0.88 with considerable statistically significant between-study heterogeneity (I^2 = 94.7%, 95% CI: 91.3–96.7%, $p < 0.001$). Considerable between-study heterogeneity was visually confirmed by a large dispersion of sensitivity-specificity pairs as shown in Fig. 4.

Due to the small number of available studies, further subgroup analyses to evaluate potential sources of heterogeneity were not performed.

Using a bivariate random-effects meta-analysis with simultaneous modeling of sensitivity and specificity, a pooled NC-CBBCT sensitivity of 0.789 (95% CI: 0.66–0.89) and a pooled NC-CBBCT specificity of 0.697 (95% CI: 0.471–0.851) were obtained. The partial AUC for NC-CBBCT was 0.817. Figure 4 depicts the summary ROC curve with the point estimate and associated 95% confidence region for pooled sensitivity/specificity pairs.

CE-CBBCT meta-analysis

A total of three studies with five distinct observation pairs of sensitivity/specificity contributed to the meta-analysis on CE-CBBCT [5, 10, 24].

Figure 5 summarizes sensitivity/specificity point estimates with associated 95% confidence intervals across individual studies and readers. Sensitivity point estimates ranged from 0.78-0.99 and demonstrated moderate non-significant between-study heterogeneity (I^2 = 57.3%, 95% CI: 0–84.1%, $p = 0.0527$). Specificity point estimates ranged between 0.71 and 0.86 showing moderate non-significant between-study heterogeneity (I^2 = 53.1%, 95% CI: 0–82.8%, $p = 0.0738$). The moderate between-study heterogeneity was visually confirmed by limited dispersion of sensitivity-specificity pairs as shown in Fig. 6.

Due to the small number of available studies, further subgroup analyses for evaluation of potential sources of heterogeneity were not performed.

Using a bivariate random-effects meta-analysis, a pooled CE-CBBCT sensitivity of 0.899 (95% CI: 0.785–0.956) and a pooled CE-CBBCT specificity of 0.788 (95% CI: 0.709–0.85) were obtained. The partial AUC for CE-CBBCT was 0.869. Figure 6 shows the summary ROC curve with point estimate and associated 95% confidence region for pooled sensitivity/specificity pairs.

Discussion

CBBCT is a novel breast imaging modality that has shown promising initial results in a variety of clinical settings [1].

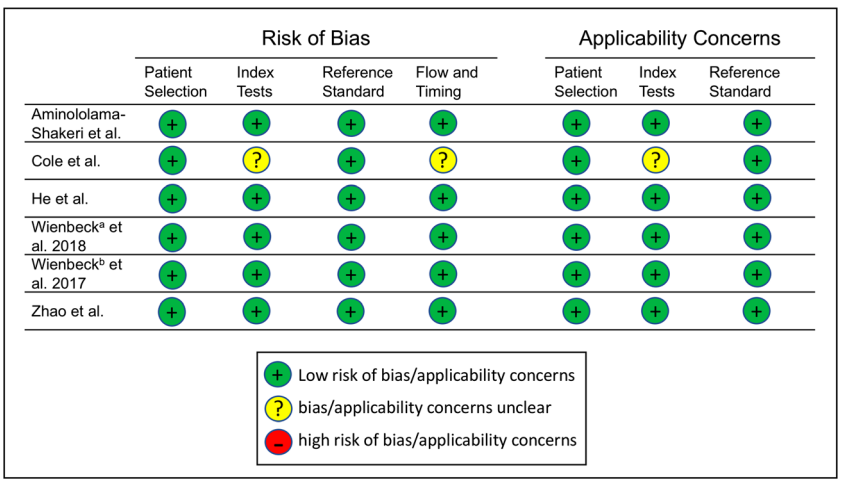

Fig. 2 Depiction of the study quality assessment using the QUADAS2 tool

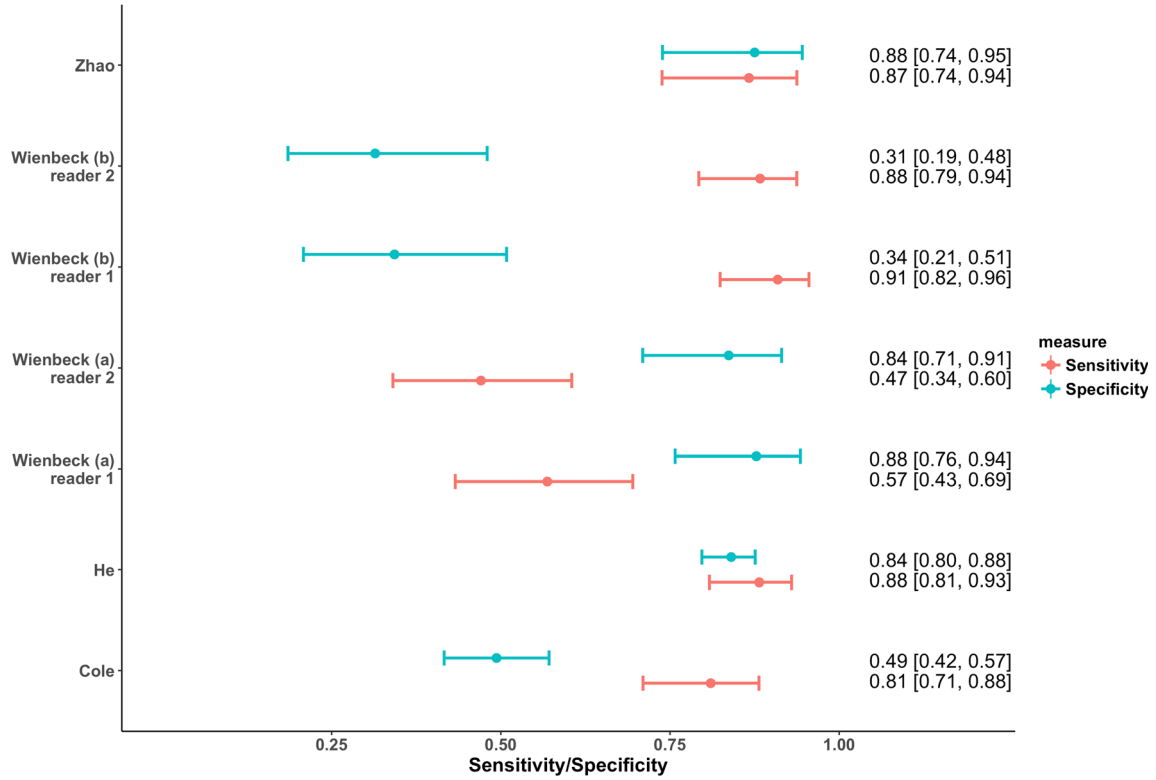

Fig. 3 Point estimates (dot) with associated 95% confidence intervals (bars) for sensitivity and specificity measures for NC-CBBCT obtained from each study and reader

Our review summarizes the published evidence on CBBCT diagnostic accuracy for discrimination of benign and malignant breast lesions. We demonstrated that sensitivity and specificity were higher for CE-CBBCT compared with NC-CBBCT using a bivariate meta-analysis approach to joint modeling. The pooled CE-CBBCT sensitivity was 0.899 (95% CI: 0.785–0.956) and pooled CE-CBBCT specificity 0.788 (95% CI: 0.709–0.85) compared with a pooled NC-CBBCT sensitivity of 0.789 (95% CI: 0.66–0.89) and pooled NC-CBBCT specificity of 0.697 (95% CI: 0.471–0.851). These results were supported by a numerically larger partial AUC for CE-CBBCT (0.869) versus NC-CBBCT (0.817).

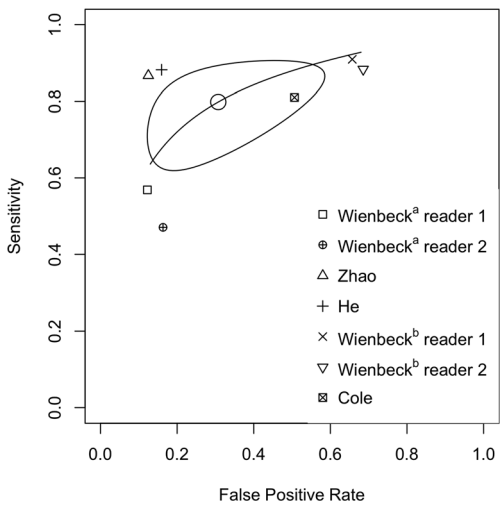

Fig. 4 Summary ROC curve for diagnostic performance of NC-CBBCT with individually labeled studies/readers. The point estimate for sensitivity and specificity is indicated by a closed circle on the ROC curve with associated 95% confidence region for sensitivity/specificity pairs

Direct statistical comparisons of CE-CBBCT and NC-CBBCT accuracy were not calculated as several studies evaluated both techniques simultaneously, resulting in correlated and thus dependent observations. To the best of our knowledge, meta-analysis approaches to account for these correlations have not been established. Still, from overlapping confidence intervals of NC- and CE-CBBCT, sensitivity and specificity differences would probably not have reached statistical significance. However, Wienbeck et al showed that CE-CBBCT AUC and sensitivity were significantly higher than NC-CBBCT in a double-reader setting evaluating ACR density type c/d breasts and accounting for correlated measures [10]. These results support the numerically superior CE-CBBCT AUC, sensitivity and specificity evident in our review, highlighting the diagnostic benefit of intravenous contrast media.

Considerable and statistically significant between-study heterogeneity was evident for NC-CBBCT sensitivity and specificity, although the studies only utilized the CBBCT scanner manufactured by Koning. This variability might be

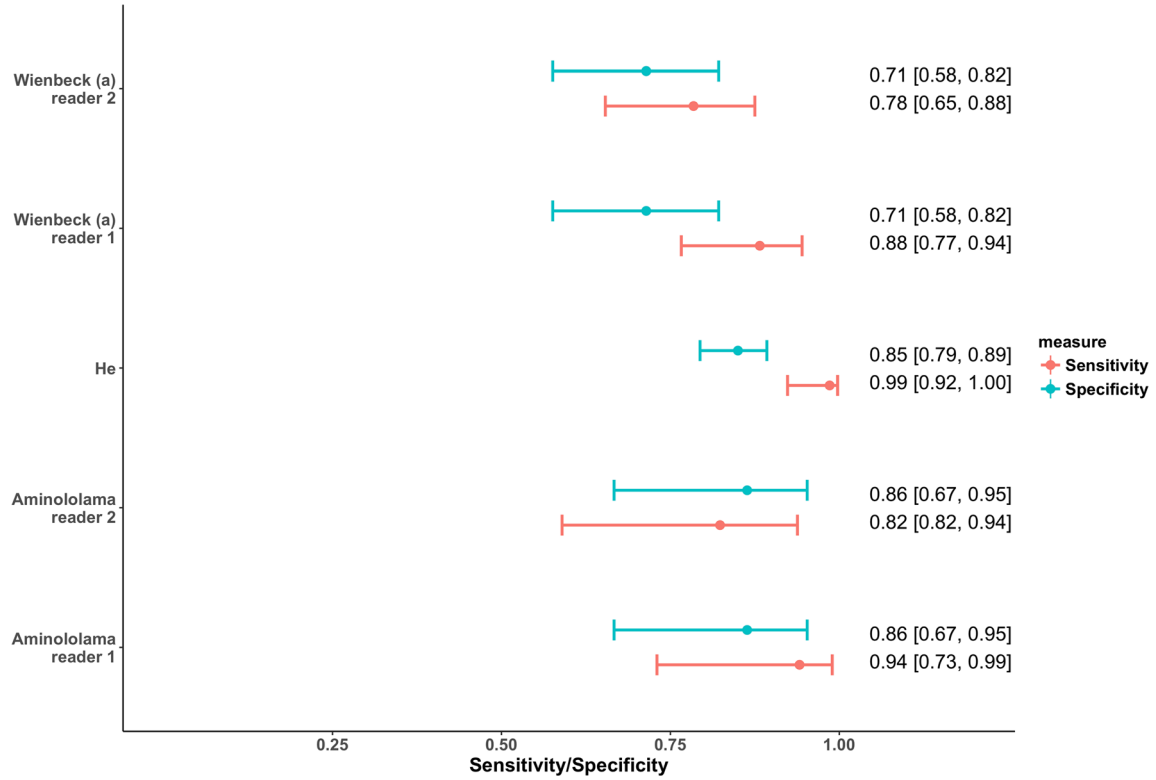

Fig. 5 Point estimates (dot) with associated 95% confidence intervals (bars) for sensitivity and specificity measures for CE-CBBCT obtained from each study and reader

attributable to diverging patient populations with a wide range of patient ages and breast densities. In contrast, studies evaluating CE-CBBCT sensitivity and specificity yielded homogeneous results, supported by a confidence region for sensitivity/specificity pairs that was more confined than for NC-CBBCT. These homogeneous CE-CBBCT results further underline the diagnostic benefit of intravenous contrast media, as comparable results were observed across several studies. First studies have been published to optimize CBBCT contrast media application, and implementation of standardized CBBCT acquisition protocols or guidelines might reduce the observed between-study heterogeneity [7].

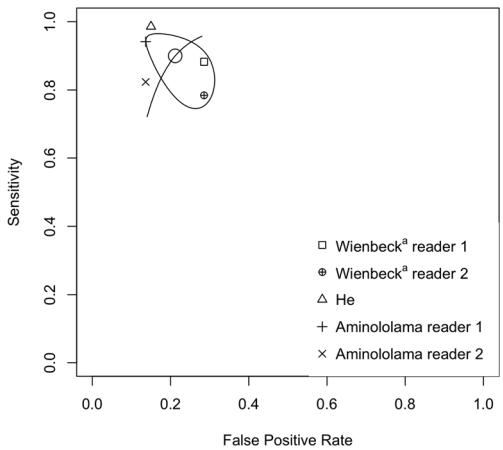

Fig. 6 Summary ROC curve for diagnostic performance of CE-CBBCT with individually labeled studies/readers. The point estimate for sensitivity and specificity is indicated by a closed circle on the ROC curve with associated 95% confidence region for sensitivity/specificity pairs

The patient cohorts included in our review demonstrated a high variability of baseline characteristics: mean patient age varied between 48–68 years, and accordingly the proportion of premenopausal women ranged from 32–48%. Further, most studies evaluated all breast density types; only Wienbeck et al focused on ACR type c/d breasts [10]. The lowest proportion of microcalcifications was 14%, while Aminololama-Shakeri et al only included breast lesions with microcalcifications [5, 24]. These diverse cohorts underline the generalizability of our findings to patient populations in routine clinical practice. Notably, CBBCT performs well even in cases with microcalcifications, where MRI might face limitations, as well as for very dense breast tissue, where the diagnostic accuracy of MG has been shown to be impaired [25–27].

All studies implemented a multi-reader CBBCT assessment with at least two readers. A consensus double-reader approach was chosen by He et al and Zhao et al [4, 5], while 18 different radiologist assessed CBBCT scans in the study by Cole et al without providing further procedural details [14]. Only the studies by Wienbeck et al provided effect measures of inter-reader variability, showing a high

agreement of breast lesion assessment on both NC-CBBCT and CE-CBBCT [10, 12].

The diagnostic accuracy of CBBCT has to be interpreted in light of the associated radiation dose. Consistently, studies showed a high absolute CE-CBBCT radiation dose of up to 16 mGy, which was primarily attributable to acquisition of an additional native scan. No study reported on radiation doses for the CE-CBBCT scan alone. CBBCT advancements envision the implementation of dual-energy techniques for simultaneous acquisition of NC- and CE-CBBCT to reduce the radiation dose [10].

Further, the accuracy of CBBCT has to be compared with MRI as the breast imaging modality with the currently highest sensitivity [13]. Only one study by Wienbeck et al directly compared CBBCT and MRI in the same patient population and concluded that CE-CBBCT's diagnostic accuracy was comparable to breast MRI depending on the reader experience [10]. These results are supported by a meta-analysis on breast MRI by Peters et al [13]. The authors reported pooled MRI sensitivity of 0.9 and specificity of 0.72, which is comparable to the pooled estimates obtained for CE-CBBCT in our meta-analysis. Furthermore, the high proportion of patients with microcalcifications in our meta-analysis has to be highlighted: in breast lesions with microcalcifications, MRI specificities as low as 0.33 have been described [28]. Considering these findings, further prospective studies directly comparing CBBCT and breast MRI are warranted.

The mean average glandular dose ranged between 5.9–24.9 mGy for NC-CBBCT and between 11.7–16 mGy for CE-CBBCT. The large dosage range for NC-CBBCT is probably due to discrepant patient populations compared with other studies and varied with breast size and density according to the authors [4]. The radiation dose of CE-CBBCT was two-fold higher than NC-CBBCT because of dual acquisition imaging in all studies reporting on both techniques. These findings call for further technical advancements to reduce CBBCT radiation exposure, including implementation of the dual-energy technique and iterative reconstruction algorithms [29].

Our review is not devoid of limitations. Above all, the small number of studies reporting on utilization of CBBCT limits subgroup analyses and the overall power to detect differences in diagnostic performance. Further, one of the included studies was available only as a conference abstract, providing insufficient information on conduct and assessment of CBBCT scans, resulting in a low study quality. Especially sensitivity measures for NC-CBBCT showed large variability across included studies, and the overall small number of patients per study resulted in wide confidence intervals. Three studies only reported on multiple readers without consensus decisions, a situation where currently no statistical analysis method is without shortcomings [30]. We decided to treat multiple readers on the same data set separately to highlight inter-reader variabilities, as described in the Materials and Methods section. Still, this approach might over-represent multi-reader studies in our analyses and could thereby introduce bias [30]. Finally, CBBCT as a novel imaging modality does not have standardized acquisition protocols, resulting in discrepancies in administration of intravenous contrast media and timing of CE-CBBCT acquisition.

Still, our study is the first to summarize the published evidence on clinical application of CBBCT and its diagnostic accuracy. Included studies evaluated a diverse patient population, thus ensuring the generalizability of our results. Further, study quality was high for most studies, thereby limiting the risk of bias.

Conclusions

Our study demonstrates that CE-CBBCT tended to show superior diagnostic performance over NC-CBBCT regarding sensitivity, specificity and partial AUC. CE-CBBCT diagnostic accuracy was numerically comparable to published meta-analysis results on breast MRI. This may support utilization of CE-CBBCT as an alternative imaging modality in patients with MRI contraindications. Further prospective studies are warranted directly comparing contrast-enhanced MRI and CE-CBBCT.

Funding The authors did not receive funding for work related to this manuscript.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Susanne Wienbeck.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Two authors have significant statistical expertise.

Informed consent Written informed consent was not required for this study because it is a meta-analysis.

Ethical approval This study was performed in accordance with the Declaration of Helsinki. Ethical committee approval was not necessary because of the meta-analysis design.

Study subjects or cohorts overlap Parts of the study population have been previously reported as detailed in the Materials and Methods section as well as the references.

Methodology
• observational

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