

Iopromide for Contrast-Enhanced Mammography: A Systemic Review and Meta-Analysis of Pertinent Literature

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Breast Cancer: Basic and Clinical Research
Volume 17: 1–13
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DOI: 10.1177/11782234231189467



ABSTRACT

BACKGROUND: Contrast-enhanced mammography (CEM) is an emerging breast imaging modality. Clinical data is scarce.

OBJECTIVES: To summarize clinical evidence on the use of iopromide in CEM for the detection or by systematically analyzing the available literature on efficacy and safety.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES AND METHODS: Iopromide-specific publications reporting its use in CEM were identified by a systematic search within Bayer's Product Literature Information (PLI) database and by leveraging a recent review publication. The literature search in PLI was performed up to January 2023. The confirmatory-supporting review publication was based on a MEDLINE/EMBASE + full text search for publications issued between September 2003 and January 2019. Relevant literature was selected based on pre-defined criteria by 2 reviewers. The comparison of CEM vs traditional mammography (XRM) was performed on published results of sensitivity and specificity. Differences in diagnostic parameters were assessed within a meta-analysis.

RESULTS: Literature search: A total of 31 studies were identified reporting data on 5194 patients. Thereof, 19 studies on efficacy and 3 studies on safety. Efficacy: in 11 studies comparing iopromide CEM vs XRM, sensitivity was up to 43% higher (range 1%-43%) for CEM. Differences in specificity were found to be in a range of -4% to 46% for CEM compared with XRM. The overall gain in sensitivity for CEM vs XRM was 7% (95% CI [4%, 11%]) with no statistically significant loss in specificity in any study assessed. In most studies, accuracy, positive predictive value, and negative predictive value were found to be in favor of CEM. In 2 studies comparing CEM with breast magnetic resonance imaging (bMRI), both imaging modalities performed either equally well or CEM tended to show better results with respect to sensitivity and specificity. Safety: eight cases of iopromide-related adverse drug reactions were reported in 1022 patients (0.8%).

CONCLUSIONS: Pertinent literature provides evidence for clinical utility of iopromide in CEM for the detection or confirmation of breast cancer. The overall gain in sensitivity for iopromide CEM vs XRM was 7% with no statistically significant loss in specificity.

KEYWORDS: Iopromide, contrast-enhanced mammography

RECEIVED: September 21, 2022. **ACCEPTED:** July 6, 2023.

TYPE: Current and future prospective of breast cancer treatment and research - Meta-Analysis

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Bayer AG.

COMPETING INTERESTS: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Five out of eight authors are employees of Bayer. ADPB and CS are consultants to Bayer AG on an honorary basis. ZJT left the company.

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Introduction

X-ray mammography (XRM) today represents the primary diagnostic tool for breast cancer (BC) screening and for the evaluation of patients with suspected lesions in the breast. XRM visualizes breast pathologies by measuring attenuation differences between tumors and lesions and the physiologic fibro-glandular breast tissue. The sensitivity of XRM is limited particularly in women with dense breasts.¹ Contrast-enhanced breast magnetic resonance imaging (bMRI) features higher sensitivity than XRM.²⁻⁴ Contrast-enhanced bMRI visualizes lesions by enhancing the tumor's neo-angiogenesis and the

leakage of contrast into the tumor tissue.⁵ Like MRI, contrast-enhanced mammography (CEM) is able to assess both imaging principles by visualizing tumor morphology as well as its vascularization.⁶ CEM is an advancement of digital XRM providing 2 images at 2 energy levels which are subsequently combined electronically to highlight the areas of enhancement. CEM requires intravenous administration of an iodine-based contrast medium prior to image acquisition.

According to the American College of Radiology (ACR) Appropriateness Criteria, CEM may be appropriate for supplemental BC screening of intermediate- and high-risk women



with non-dense breasts and average- and intermediate-risk women with dense breasts. So far ACR does not recommend CEM for other clinical settings, eg, palpable breast masses, initial workup and surveillance for local recurrence and distant metastases in asymptomatic women.⁷ However, in 2022, ACR acknowledged in a supplement to ACR BI-RADS® Mammography 2013 that CEM has been shown to be more sensitive than mammography or ultrasound for the detection of malignancy.⁸

The European Society of Breast Imaging (EUSOBI) discussed 3 studies⁹⁻¹¹ and concluded that based on preliminary results, CEM can be considered as an alternative to bMRI in the case of contraindications to MRI in general or to gadolinium-based contrast injection.⁵ Most recently, EUSOBI recommended supplemental screening in women with extremely dense breasts to be performed preferably with bMRI, because for the time being, level I evidence is available only for bMRI.¹² The recent EUSOBI recommendation, however, mentions that other imaging modalities, like CEM, may eventually offer practical advantages over bMRI.¹²

The Royal College of Radiologists' *Guidance on screening and symptomatic breast imaging* (fourth edition) stated that CEM may also be used in the symptomatic setting, where available.¹³ Along that line, also the German Guideline Program in Oncology (GGPO) stated that CEM is an option if MRI is not feasible, especially for dense breasts. The guideline quoted a number of studies showing comparable diagnostic accuracy for CEM vs bMRI.¹⁴

Jochelson et al¹⁵ excellently summarized that CEM is an emerging breast imaging modality that helps improve diagnostic accuracy when routine breast imaging produces inconclusive findings and that may serve as an alternative to bMRI.

Iopromide (Ultravist™) is a low osmolar non-ionic X-ray contrast medium (LOCM) with iodine as active ingredient.¹⁶ Initially approved in February 1985, iopromide features a clinical track record of more than 37 years. As of June 30, 2022, more than 324 million have been administered to patients in more than 118 countries.¹⁷ Numerous studies have documented the overall safety profile¹⁸⁻²⁴ in a wide range of indications (including but not limited to computed tomography, angiography, urography, cholangiopancreatography, and arthrography).

On January 20, 2023, iopromide received the European Union approval for CEM. The approved indication is “for use in adult women in CEM to evaluate and detect known or suspected lesions of the breast, as an adjunct to XRM (with or without ultrasound) or as an alternative to MRI when MRI is contraindicated or unavailable.”

The objective of this article was to summarize clinical evidence on the use of iopromide in CEM for the detection or confirmation of BC by systematically analyzing the available literature on efficacy and safety.

Data Sources and Methods

Databases

As a first step, iopromide-specific publications were searched in Bayer's Product Literature Information (PLI) database up to January 2023.

As a second step, additional iopromide-specific publications were retrieved from Zanardo et al,²⁵ who published a systematic review on CEM based on a MEDLINE/EMBASE + full-text search from September 2003 to January 2019 (Figure 1). Full texts with the search term CEM were evaluated by 2 reviewers.

The PLI automatically (in rare cases also manually) imports data containing information from biomedical journals dealing with Bayer Pharma and Consumer Health (CH) products from 4 large, commercially and publicly available databases: MEDLINE and EMBASE (until today), Derwent Drug File and BIOSIS (until December 2019). In addition, search hits from Reactions Weekly (case reports) or Medmeme (conference abstracts) complemented PLI. The scientific areas of interest were as follows: clinical pharmacology, efficacy and pharmacokinetics, adverse effects in case reports, clinical adverse effects, pre-clinical toxicology, and pharmacokinetics. Duplicate records and reviews were deleted manually.

The search strategy is shown in Figure 1.

Statistics

Sensitivity and specificity of CEM and XRM and the respective numbers of patients with malignant/benign lesions (N) were extracted from 11 papers (Table 4). The number of patients correctly classified (m) were derived by multiplying N with the given sensitivity or specificity.

The risk difference per publication was computed using the N's and m's as basis for a generalized linear model with identity link and a binomial distribution. In case of sensitivities or specificities of 100%, a small value (.0001) was subtracted from m to make computations feasible. SAS Version 9.4 was used for this analysis step.

A meta-analysis based on the data for sensitivity and specificity was computed per method (CEM or XRM) and for the computed risk-differences using the R-package “meta.”²⁶

Results

Results of the literature search

Twenty-four publications reporting data specifically on iopromide were identified by the company's PLI database (Figure 1). In addition, 7 papers were found in the full-text literature search by Zanardo et al.²⁵ In total, 31 studies were included (Figure 1).

Nineteen studies reported efficacy results for the detection or confirmation of BC (Tables 1 and 4), 3 studies reported

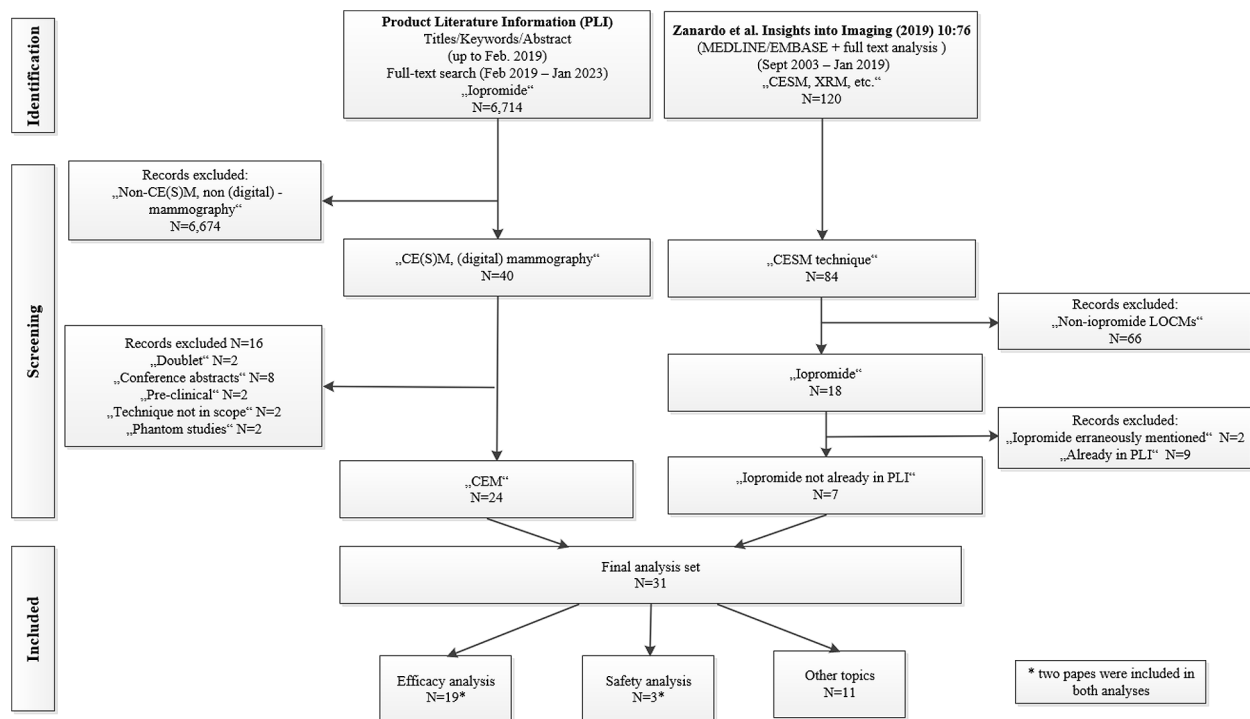


Figure 1. Literature search strategy—identification of studies in databases and literature. CEM indicates contrast-enhanced mammography; CESM, contrast-enhanced spectral mammography; LOCM, low osmolar non-ionic X-ray contrast medium; PLI, product literature information; XRM, traditional mammography.

safety results (Table 2), and 11 studies reported other findings, not relevant for efficacy or safety analysis (Table 3). 2 studies provided data for efficacy and safety analysis^{27,28} (Figure 1).

Patient population

Mean age of patients was specified in 24 of the 31 studies, covering 4348 of 5194 patients (84%). Considering the respective patient counts for the 24 studies, the mean age of the included patients was 57.2 years (the average of the specified mean ages without correction for the patient numbers was 56.1 years). Patients were referred to imaging for screening purposes and for characterization of suspicious clinical findings.

Efficacy

A total of 19 studies reported efficacy of iodopromide in contrast-enhanced mammography. Six had a prospective and 13 a retrospective design. Nine studies were read by blinded readers and 4 by unblinded readers. The other studies did not specify reading procedure (Table 1).

CEM vs XRM. Eleven studies reported efficacy results of iodopromide CEM vs XRM. Sensitivity was always higher for CEM, ranging from 62% to 100%. The advantage ranged from 1%⁴⁴ up to 44%⁴⁰ (Table 4, Figure 2). Overall, CEM provided a gain in sensitivity of 7% (95% CI [4%, 11%]) in the meta-analysis. No

hints for heterogeneity were found for the difference in sensitivities for the studies included ($P = .06$) (Figure 3).

A similar diagnostic advantage of CEM was seen for specificity in most studies. The differences were found to be in a range of -3%⁴⁰ to 46%²⁸ (Table 4, Figures 4 and 5). Overall, CEM was found to provide a gain in specificity of 16% (95% CI [6%, 26%]). However, a hint for heterogeneity was found for the difference in specificities ($P < .01$). Therefore, no clear pattern on the advantage was found. Nevertheless, at least no disadvantage of CEM vs XRM can be concluded based on the study-level differences (Figure 5).

Accuracy, and positive and negative predictive values (PPV, NPV) were not recorded by all authors. However, those who did record found more favorable results for CEM (Table 4). Three cases with intra-individual comparison of both modalities are shown on Figure 6.

Four case studies with intra-individual comparisons of XRM vs CEM images are shown on Figure 6.

CEM vs bMRI. 2 studies reported efficacy results of iodopromide CEM vs bMRI. Sensitivity was similar⁴³ or higher for CEM.³⁸ Specificity was higher⁴³ or not reported.³⁸ Accuracy, PPV, and NPV were in favor of CEM in both studies (Table 4).

CEM uncontrolled. Six efficacy studies presented uncontrolled findings. Sensitivity was in the range of 25% to 100%,²⁹ specificity from 61%⁴² to 98%³⁰ (Table 4).

Table 1. Efficacy studies on CEM using iopromide for the detection or confirmation of BC.

AUTHOR COUNTRY (N = 19)	STUDY POPULATION/ INDICATION	N (N = 2920)	STUDY DESIGN	IMAGE EVALUATION
Amato et al ²⁹ /IT	Proven ILC	31	Retrospective	Not specified
Bicchierai et al ³⁰ /IT/Zan	Biopsy B3 lesions	40	Retrospective	Not specified
Bicchierai et al ³¹ /IT	Biopsy proven BC	326	Retrospective	5 blinded readers
Chalabi et al ³² /Egypt	Various indications	123	Retrospective	Not specified
Diekman et al ³³ /DE	Known or suspicious findings	21	Prospective	Not specified
Diekmann et al ²⁷ /DE	Suspicious lesion	70	Prospective	3 unblinded readers
Houben et al ³⁴ /NL	Suspicious calcifications	147	Retrospective	1 blinded reader
Lalji et al ³⁵ /NL/Zan	Screening recalls	199	Retrospective	10 blinded readers
Lobbes et al ²⁸ /UK	Screening recall	113	Retrospective	2 blinded readers
Lobbes et al ³⁶ /NL	Suspicious/confirmed findings	368	Retrospective	3 blinded readers
Luczynska et al ³⁷ /PL/Zan	Suspected BC	152	Prospective	6 unblinded readers
Luczynska et al ³⁸ /PL/Zan	Suspicious lesions	102	Retrospective	2 blinded readers
Luczynska et al ³⁹ /PL	Suspicion of BC	116	Prospective	Not specified
Mohamed et al ⁴⁰ /Egypt	Dense breast, lump	25	Prospective	Unblinded
Richter et al ⁴¹ /DE	Confirmed/suspicious findings	118	Retrospective	2 blinded readers
Rudnicki et al ⁴² /PL/Bay	Suspicious lesions	167	Retrospective	3 unblinded readers
Rudnicki et al ⁴³ /PL	Breast abnormalities	121	Retrospective	Not specified
Tsigginou et al ⁴⁴ /GR	Known findings	216	Prospective	2 blinded readers
Travieso-Aja et al ⁴⁵ /ES	Known malignant or benign lesions	465	Retrospective	3 blinded readers

Abbreviations: BC, breast cancer; CEM, contrast-enhanced mammography.

Table 2. Safety studies on CEM using iopromide.

AUTHOR/COUNTRY	STUDY POPULATION/ INDICATION	N (N = 1022)	STUDY DESIGN	IMAGE EVALUATION
Diekmann et al ²⁷ /DE	Known BC	70	Prospective	3 unblinded readers
Houben et al ⁴⁶ /NL	Suspected or known findings	839	Retrospective	1 blinded reader
Lobbes et al ²⁸ /UK	Suspected BC	113	Retrospective	2 blinded readers

Abbreviations: BC, breast cancer; CEM, contrast-enhanced mammography.

Safety

Adverse events (AEs)/adverse drug reactions (ADRs) related to iopromide administration were reported in 3 of the 31 studies (Table 2). In total, 8 adverse drug reactions were reported from 7 patients: 1 case of severe allergic reaction that required intensive care and led to discontinuation of the procedure,²⁷ 1 moderate⁴⁶

and 5 mild cases of urticaria,^{28,46} and 1 moderate shortness of breath.⁴⁶ In relation to the total number of 1022 patients examined in these studies, this corresponds to 0.8% (Table 5).

In the remaining 28 studies, no AEs or ADRs to iopromide were reported. However, in 11 studies, patients with known risk of allergic reactions or CIN were excluded upfront, in another 15 studies exclusion criteria to known risks of allergic

Table 3. Studies on CEM using iopromide, not specifically reporting efficacy or safety (=reason for exclusion).

AUTHOR/COUNTRY (N = 11)	STUDY POPULATION/ INDICATION	N (N = 1435)	STUDY DESIGN	IMAGE EVALUATION
Bicchierai et al ⁴⁷ /IT	Known BC findings	348	Retrospective	Not specified
Gluch et al ⁴⁸ /AU	Known or suspected BC	6	Retrospective	Not specified
Houben et al ⁴⁹ /NL	Screening recall	351	Not specified	Unblinded
Jeukens et al ⁵⁰ /NL	Not specified	47	Not specified	Unblinded
Lobbes et al ⁵¹ /NL/Zan	Screening recall	87	Retrospective	Not specified
Lobbes et al ⁵² /NL	Suspicious/known findings	85	Retrospective	Not specified
Luczynska et al ⁵³ /PL/Zan	Known findings	174	Retrospective	1 blinded reader
Luczynska et al ⁵⁴ /PL/Zan	Suspicious lesions	82	Retrospective	3 blinded readers
Rudnicki et al ⁵⁵ /PL/Bay	Suspicious histology	94	Retrospective	2 unblinded readers
Rudnicki et al ⁵⁶ /PL/Bay	BIRADS 4, 5 or 0	151	Prospective	1 readers, unblinded
Schmitzberger et al ⁵⁷ /DE	Known malignant lesions	10	Prospective	4 blinded readers

Abbreviations: BC, breast cancer; CEM, contrast-enhanced mammography.

reactions, CIN or renal insufficiency were not explicitly mentioned. 1 study excluded patients for other reasons than known risk of allergic reactions or CIN.

Most of the AEs were reported in context of hypersensitivity reactions and are in line with the well-established safety profile of iopromide. No new safety concerns were identified during this analysis. The benefit risk profile remains favorable and unchanged.

Discussion

We systematically analyzed the usage of iopromide for CEM for detection or confirmation of BC and found strong evidence for higher diagnostic performance compared with XRM and similar performance compared with bMRI.

The PLI database is a robust source as it aggregates data from 4 leading international literature databases. The PLI retrieved more publications than MEDLINE/EMBASE alone (applied by Zanardo et al²⁵) as this system is specifically designed for the company's global pharmacovigilance department (PV). As PV is obliged to report any ADR all over the world, also country-specific journals are utilized, identifying publications in other languages apart from English. This ensures a high degree of completeness of the literature search (Figure 1).

All 31 studies on iopromide included at total of 5194 patients, 2920 and 1022 patients in the efficacy and safety analysis, respectively (2 studies reported efficacy and safety). In 11 studies (n=1435 patients) neither efficacy nor safety was reported so they were excluded from the analysis. All patients were included either for screening or for characterization of suspicious findings.

Tagliafico et al⁹ published a similar review and meta-analysis focusing on sensitivity and specificity on 8 studies including 920 patients presenting 994 lesions. Unfortunately, the type of LOCM was not specified. Zanardo et al²⁵ included 14012 patients from 84 studies looking at a large range of LOCMs. However, Zanardo et al²⁵ investigated primarily technique, protocols, and adverse reactions, while this analysis put emphasis on efficacy and safety.

In 11 studies, sensitivity and specificity of CEM vs XRM were almost always in favor of CEM with an overall gain of 7% in sensitivity and no hints for a loss in specificity. This held also true for accuracy, PPV, and NPV (Table 4). These findings support results from other groups on other LOCMs.

Tennant et al¹⁰ performed a review of 100 CEM examinations (LOCM not specified) vs low-energy images and reported CEM showing increased sensitivity (95% vs 84%, $P < .025$) and specificity (81% vs 63%, $P < .025$). They conclude that CEM provides improved efficacy in BC screening and staging as primary mammographic investigation.

Likewise, Mori et al⁵⁸ focused on 72 women with dense breasts who underwent CEM with iohexol and XRM. Sensitivity was 86.2% for CEM and 53.4% for XRM ($< .001$), and specificity 94.1% and 85.9% ($< .016$), respectively. They concluded that CEM offers superior clinical performance compared with XRM and may decrease false negatives especially for women with dense breasts.

Kim et al⁵⁹ compared both imaging modalities in BC screening on 64 cases. Median sensitivity and specificity improved with the addition of CEM (iohexol). Sensitivity: from 86% (XRM alone) to 100% (XRM + CEM), specificity, from 85% to 88%.

Table 4. Efficacy results—CEM vs XRM, bMRI and uncontrolled.

AUTHOR	INDICATION	N (N=2,920)	SENSITIVITY %	SPECIFICITY %	ACCURACY %	PPV %	NPV %
CEM vs XRM							
Chalabi et al ³²	Suspicious lesion(s)	123	92.7 82.9	82.4 76.5	89.7 81.0	92.7 89.5	82.4 65
Diekmann et al ²⁷	Suspicious lesion(s)	70	62 43	65 70			
Houben et al ³⁴	Suspicious lesion(s)	147	93.8 90.8	36.6 39.0		54.0 54.1	88.2 84.2
Lalje et al ³⁵	Screening recall	199	96.9 93.0	69.7 35.9			
Lobbes et al ²⁸	Screening recall	113	100.0 96.9	87.7 42.0		76.2 39.7	100.0 97.1
Luczynska et al ³⁷	Suspicious lesion(s)	152	100 91	41 15	80 65	77 68	100 47
Luczynska et al ³⁹	Suspicious lesion(s)	116	100 90	27 22	78 69	70 63	8 7
Mohamed et al ⁴⁰	Suspicious lesion(s)	25	100 ^a 56 ^a	63.6 ^a 66.6 ^a	84 60	77.8 75.0	100 46
Richter et al ⁴¹	Suspicious lesion(s)	118	98.8 89.2	54.6 36.4		94.3 91.4	85.7 30.8
Travieso-Aja et al ⁴⁵	Suspicious lesion(s)	465	92.3 82.5	86.0 68.6	90.2 74.4	93.0 65.5	84.8 84.4
Tsigginou et al ⁴⁴	BIRADS 3-5	216	93.9 92.9	71.3 59.4	81 73.9		
CEM vs bMRI							
Luczynska et al ³⁸	Suspicious lesion(s)	102	100 93		79 73	77 74	100 65
Rudnicki et al ⁴³	Suspicious lesion(s)	121	100 100	33 23	77 74	75 72	100 100
CEM uncontrolled							
Amato et al ²⁹	Invasive lobular carcinoma	31	25-100 ^b	0-100 ^b	40-85 ^b		
Bicchierai et al ³⁰	BIRADS 3	40	33.3-66.7	74.4-87.2		16.7- 18.2	94.4-96.7
Bicchierai et al ³¹	Staging	326	93.0	98	97	90	98
Diekmann et al ³³	Suspicious lesion(s)	21	62.5	90	73.1	90.1	60
Lobbes et al ³⁶	Suspicious lesion(s)	368	92.9	79.3			
Rudnicki et al ⁴²	Suspicious lesion(s)	167	49-59	61-88	60-61		

Abbreviations: BC, breast cancer; BIRADS, Breast Imaging Reporting & Data System; bMRI, breast magnetic resonance imaging; CEM, contrast-enhanced mammography; NPV, negative predictive value; PPV, positive predictive value; XRM, traditional mammography.

^aFor Figure 3, we recalculated the number of true positives for sensitivity. This resulted in differences of 43% for sensitivity and -4% for specificity.

^bValues given for detection of index lesion, identification of adjunctive lesions and correct determination of extension for masses, non-mass enhancement and masses associated with non-mass enhancement.

While other publications point in the same direction,^{11,60} Lorek et al⁶¹ criticized that CEM overestimates the tumor size on average by 5 mm.

The 2 studies on efficacy of iopromide CEM vs bMRI showed similar⁴³ or higher sensitivity for CEM³⁸ while accuracy, PPV and NPV were in favor of CEM (Table 4).

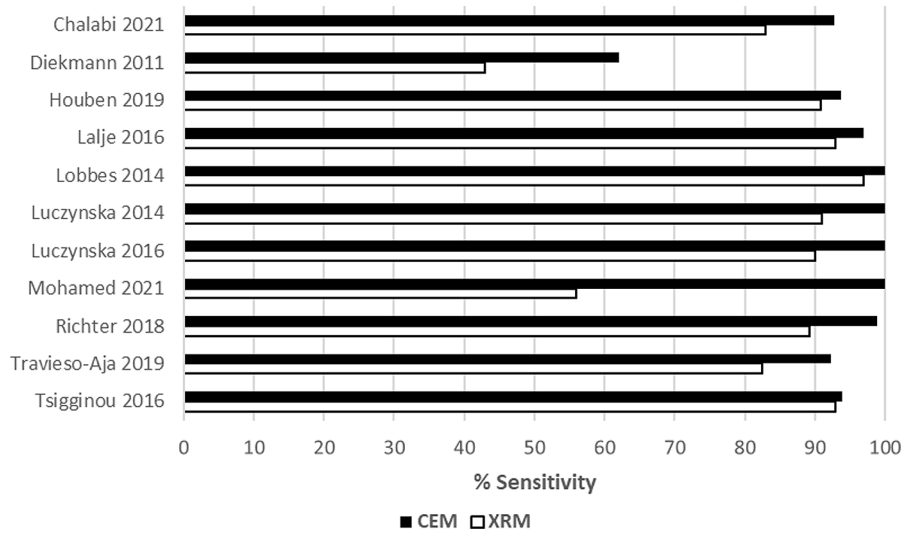


Figure 2. Sensitivities of CEM vs XRM. CEM indicates contrast-enhanced mammography; XRM, traditional mammography.

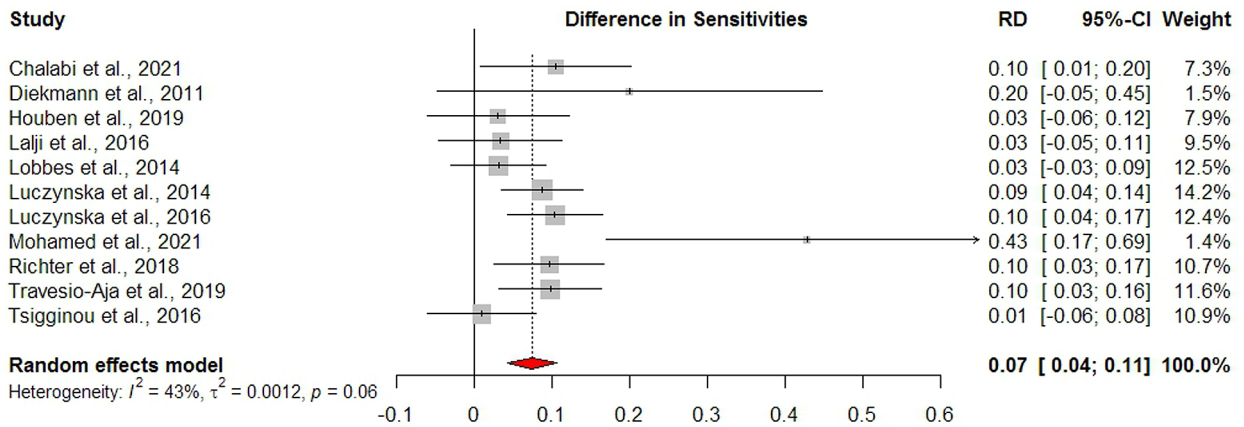


Figure 3. Differences of sensitivities of CEM vs XRM. CEM indicates contrast-enhanced mammography; CI, confidence interval; XRM, traditional mammography.

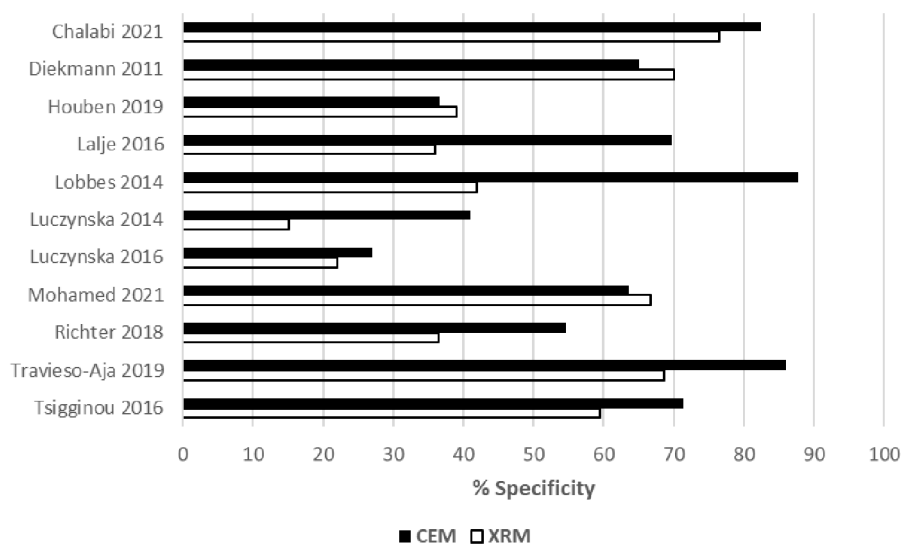


Figure 4. Specificities of CEM vs XRM. CEM indicates contrast-enhanced mammography; XRM, traditional mammography.

Three intra-individual comparison studies of CEM with other LOCMs vs bMRI are of interest in this context.⁶²⁻⁶⁴ 1 retrospective study by Xing et al⁶⁴ on 235 patients administered iohexol and 2 prospective studies, 1 on 178 patients by Fallenberg (iobitridol)⁶² and 1 on 84 patients by Kim (iohexol)⁶³ reported a similar trend: Almost identical sensitivities for both modalities and a slightly higher specificity for CEM. In contrast, Pötsch et al⁶⁵ found in a meta-analysis of 7 studies

investigating 1137 lesions higher sensitivity for bMRI (97%) vs CEM (91%), however, at the cost of lower sensitivity, 69% vs 74%.

The 6 uncontrolled studies on iopromide showed a sensitivity of 25% to 100%²⁹ and a specificity of 61%⁴² to 98%⁴⁷ (Table 4).

A recent systematic review and meta-analysis comprising a total of 945 patients of 8 studies using 5 different LOCMs by

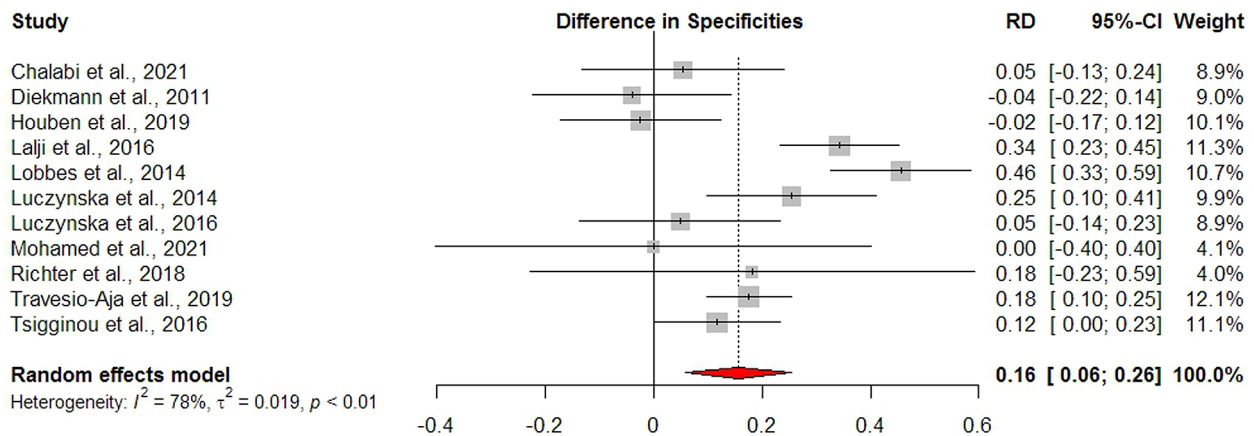
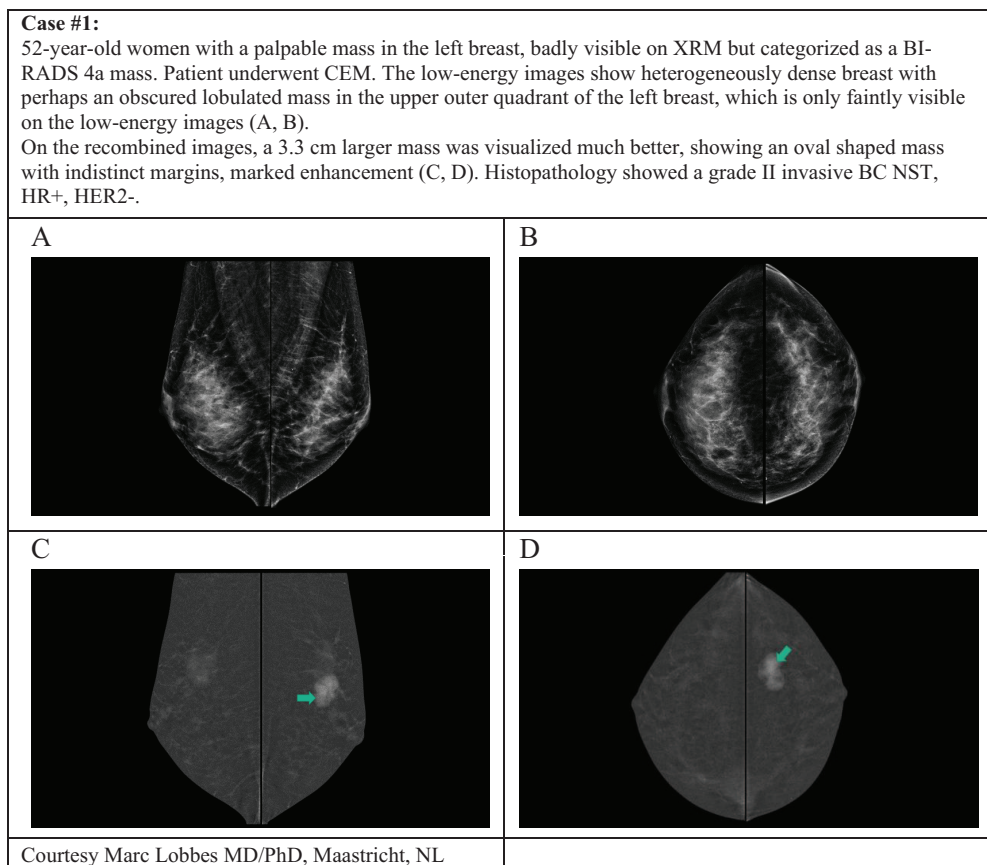
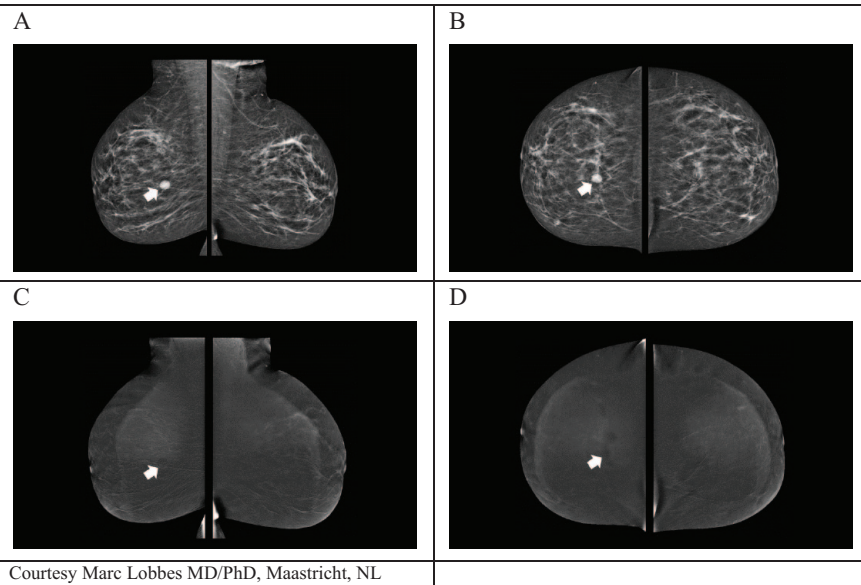


Figure 5. Differences of specificities of CEM vs XRM. CEM indicates contrast-enhanced mammography; CI, confidence interval; XRM, traditional mammography.

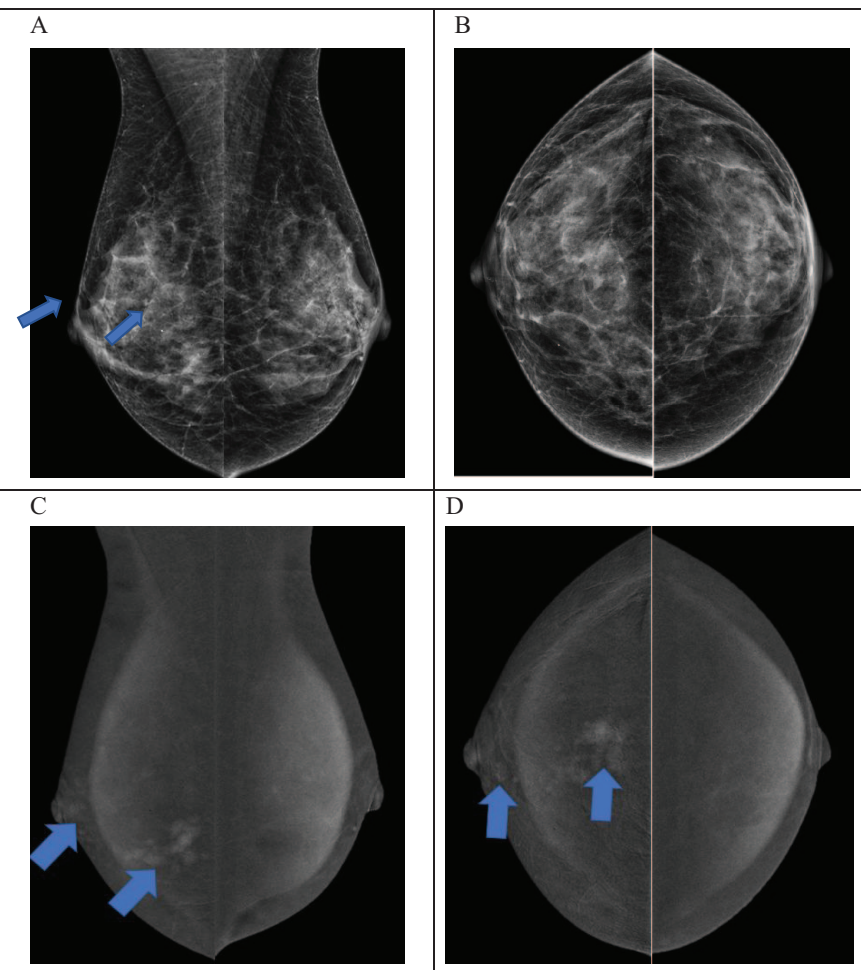


Case #2
62-year-old woman with a new, well-defined round mass developed during screening in the right breast (arrow). The mass was not palpable (A, B). On recombined images the mass does not show enhancement, 'negative enhancement' or 'eclipse sign'. Typical appearance of a simple cyst on CEM (C, D).



Courtesy Marc Lobbes MD/PhD, Maastricht, NL

Case #3
62-year-old women, recalled for the appearance of new, linear calcifications in the right breast (arrows) (A). Recombined images show segmental nodular non-mass enhancement from the nipple complete to the posterior part of the breast. Histopathology: large grade III DCIS with underlying micro invasive foci of carcinoma NST (D, E).



Courtesy Marc Lobbes MD/PhD, Maastricht, NL

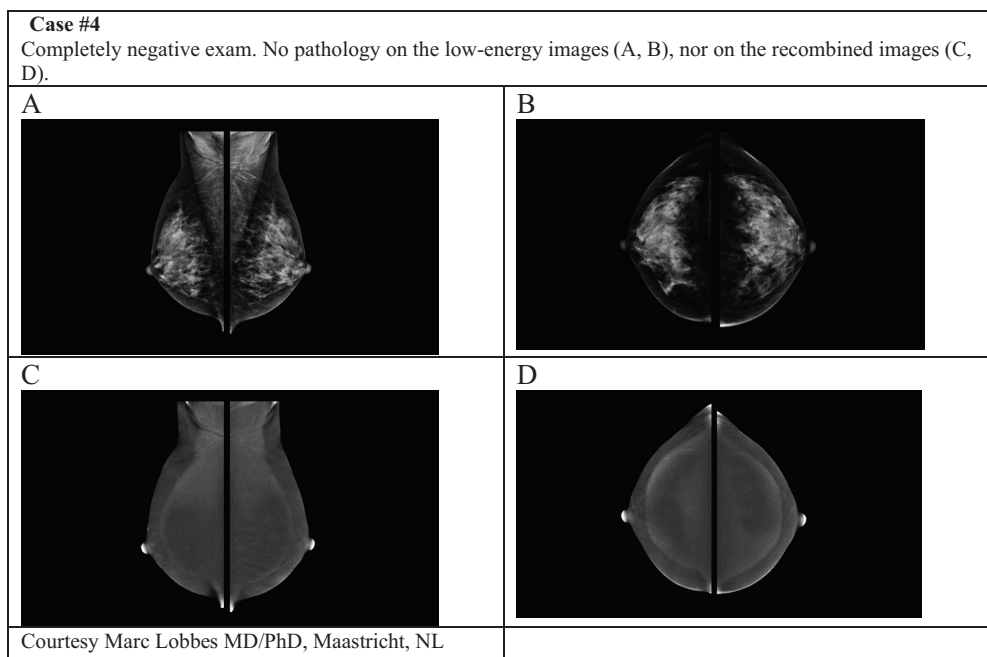


Figure 6. Cases showing intra-individual comparison of iopromide CEM and XRM. CEM indicates contrast-enhanced mammography; DCIS, Ductal carcinoma in situ; XRM, traditional mammography.

Table 5. Safety results of studies on contrast-enhanced mammography using iopromide.

AUTHOR (YEAR)	N	RELATED ADVERSE DRUG REACTIONS	%
Diekmann et al ²⁷	70	1 severe allergic reaction	1.4
Houben et al ⁴⁶	839	4 mild urticaria 1 moderate urticaria ^a 1 shortness of breath ^a	0.7
Lobbes et al ²⁸	113	1 mild urticaria	0.9
	1022	8 (in 7 patients)	0.8

^aSame patient.

Suter et al⁶⁶ calculated a sensitivity of 85% and a specificity of 77%. Tagliafico et al⁹ found a sensitivity of 98% and a sensitivity of 58% in a meta-analysis of 8 studies with 920 patients. Although the range is quite broad, our results seem to corroborate these findings.

A total of 8 AEs of iopromide-related AEs/ADRs were reported in 7 patients from three studies comprising 1022 patients. This corresponds to a reporting rate of 0.8%. Skin reactions like urticaria, erythema, rash, and pruritus are usually the most frequent events. The most severe AEs are hypersensitivity reactions.⁶⁷ The safety findings reported here in patients receiving iopromide-enhanced CEM are well in line with other studies focusing on AEs/ADRs after intravenous iopromide administration for other indications, ie, 1.5%,¹⁸ 0.7%,¹⁹ and 2.8%.²⁰ These are also comparable with results of studies on a

broad spectrum of different LOCMs, 0.37%,²² 0.34%,⁶⁸ and 0.97%.⁶⁹ The reported AEs/ADRs related to contrast media administration are expected to be independent of the imaged region of the body.

A frequently raised concern about CEM is the increased radiation dose compared with XRM. James et al⁷⁰ retrospectively compared the radiation dose of CEM using high- and low-energy projections with the radiation dose received during XRM in 173 patients with varying breast thickness and density. At a mean breast thickness of 63 mm, the average glandular dose was 3.0 and 2.1 mGy for CEM and XRM, respectively. They conclude that this increase of 0.9 mGy falls below the dose limit of 3 mGy set by Mammography Quality Standards Act regulations (MQSA). Similarly, Gennaro et al⁷¹ reported that the dose for CEM is about 30% higher compared with standard XRM, an increase close to that of digital tomosynthesis, but it is the upper limit according to MQSA.

CEM is assumed to become an emerging new imaging modality providing higher diagnostic efficacy compared with XRM and similar efficacy compared with bMRI in BC screening and diagnostic work up. In addition, CEM also offers the opportunity for CEM-guided biopsy, a new technique that can be successfully used as an alternative to MRI-guided breast biopsy.⁷² As CEM requires only limited technical upgrades of the broadly available XRM equipment and can be implemented easily into the current XRM workflow, it might be a cost-effective alternative to bMRI, in particular as there is some evidence that patients prefer CEM over bMRI.^{73,74} CEM might also be a good option when MRI technique is not available.

Limitations

Some limitations need to be addressed:

1. This review was not based on the patient individual data of the original studies but published results.
2. As for any literature review, the retrospective nature of the data and the variability of information collected and reported is a major limitation.
3. As this review focused on studies on iopromide, the full picture regarding use of LOCMs in CEM is not reflected.
4. Each study only provided 1 pair of sensitivity/specificity results, so that the meta-analyses for the diagnostic parameters might be biased due to, eg, reader experience and selection of readers. In addition, the data sources with regard to prospective and retrospective data and blinding of readers did vary across studies, which increases uncertainty and heterogeneity in the results (Table 1).
5. Except for 3 studies, all other were performed in Europe.
6. Studies included mostly women with a high-risk predisposition for BC. It is not clear if this might impact the rate of AEs related to iopromide administration.
7. No long-term safety data after repetitive administrations were reported.
8. Studies using iopromide for other imaging modalities (eg, breast CT) were not included.
9. No dose-finding studies were found.
10. Potentially varying diagnostic performances between different commercially available mammography systems were not assessed. An impact of the mammography system on diagnostic performance cannot be excluded.

Conclusions

Pertinent literature supports iopromide to be an effective and safe agent for CEM for the detection or confirmation of BC. The overall gain in sensitivity for iopromide CEM vs XRM was 7% without compromising specificity.

Declarations

Ethics Approval and Consent to Participate

Not applicable as review & meta-analysis

Consent for Publication

Not applicable as review and meta-analysis

Author Contributions

Jan Endrikat: Conceptualization; Formal analysis; Methodology; Writing—original draft.

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Acknowledgements

Not applicable.

Availability of Data and Materials

All data were retrieved from publicly available publications. See reference list.

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