University of South-Eastern Norway
Faculty of Health and Social Sciences
Institute of Optometry, Radiography and Light design
–
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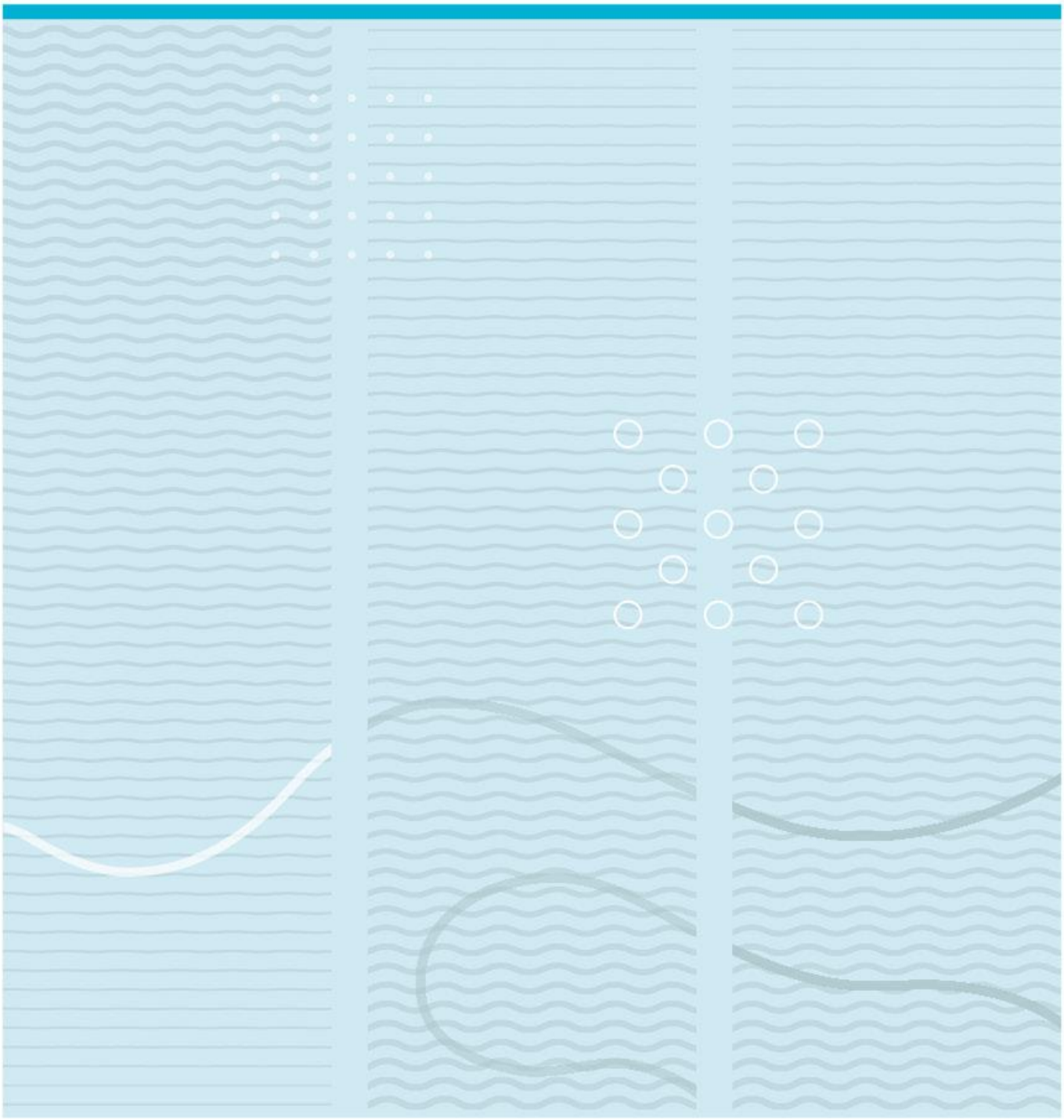
Anne Synnøve Bakken

Contrast-enhanced mammography in assessment of breast cancer

Contrast-Enhanced Mammography versus Breast Magnetic Resonance Imaging: Comparison of diagnostic performance and assessment of extent of disease.



University of South-Eastern Norway
Faculty of Health and Social Sciences
Institute of Optometry, Radiography and Light design
PO Box 235
NO-3603 Kongsberg, Norway

http://www.usn.no

This thesis is part of a 120 ETCs master program in clinical health care.

Foreword

This Master of Science-thesis consist of an article manuscript, a supplementary thesis and a number of annexes. This thesis requires some knowledge of radiography and radiology in general, and in breast diagnostics more specifically. It is recommended to read the manuscript first, and then review the supplementary thesis and annexes for more background- and additional information. The article manuscript is planned submitted to Acta Radiologica after the thesis has been censored. A publication plan according to the Vancouver conventions emerges from annex 2.

The research presented in this master-thesis is conducted at the Breast diagnostic centre (BDS) at Oslo University hospital (OUS). My work has been supervised by Professor Therese Seierstad (OUS), Professor Hilde Olerud (USN) and Associate Professor Aud-Mette Myklebust (USN). Thank you for sharing your knowledge and for all the support along the way. And Hilde, thank you so much for the pep-talks – this would not have been possible without them.

I would also like to thank the management at BDS, especially Tone Snare Berge (section manager for radiography), for giving me the opportunity to participate and complete this master-program. I have learned a lot in the recent years, and I hope it will benefit BDS in the future.

To all my colleagues at BDS, who in one way or another have contributed or encouraged me along the way - thank you! Tatjana, thank you for using so much your time to help me out.

Last, but not least… To my partner Kurt, thank you so very much for your patience and support throughout my years as a "late blooming student". Coping with all the frustration and all the relieve over these years takes a toll on a man, but I think I am done now …

Skotterud, 15th of May 2023
Anne Synnøve Bakken

Summary

Breast cancer affects a large number of people each year. The 5-year relative survival rate is high, and reasons for this is early detection and better treatment. Breast diagnostics is to assess whether relevant symptoms are related to breast cancer. Triple assessment is the primary investigation, and consist of breast imaging, clinical examination and were appropriate, needle sampling.

Breast imaging consist of several modalities and methods, which one used will vary depending on each patient case. Breast magnetic resonance imaging (BRMI) was developed in the mid-90s. It is the most sensitive technique in breast imaging, and used only on certain indications. BRMI was the only technique to provide both morphological- and functional images, until contrast-enhanced mammography (CEM) became commercially approved in 2010. Research shows that CEM has comparable diagnostic performance as BRMI, and is an emerging method in breast imaging.

A three-part project was carried out at the Breast diagnostic centre at Oslo University hospital to assess what role CEM might have in daily clinical practice. With the aim of comparing the diagnostic accuracy and correlation on measured extent of disease, 30 patients with indeterminate findings after triple assessment performed CEM in addition to BRMI – the standard patient pathway. The examinations were interpreted based on BI-RADS®-system, by experienced breast radiologists. The conclusions, given on a six-category scale, were used to calculate standard diagnostic indices. Pearson's correlation coefficient was used to assess the correlation on extent of disease.

This study showed an overall slightly higher diagnostic performance for BRMI and CEM, with a strong correlation on measured extent of disease. There were registered false negative and false positive cases on both techniques. CEM has potential to; improve efficiency in the daily workflow and for better utilization of the resources, affect to a shorter investigation phase and less psychological distress for the patients associated with a breast cancer assessment.

Sammendrag

Brystkreft rammer et stort antall personer hvert år. 5-års relativ overlevelsesraten er høy, og årsaker til dette er tidlig deteksjon og bedre behandling. Brystdiagnostikk er å vurdere om relevante symptomer er relatert til brystkreft. Tippeldiagnostikk er primærundersøkelsen, og består bildediagnostikk, klinisk undersøkelse og eventuelt vevsprøver.

Bildediagnostikken består av flere ulike modaliteter og metoder, og hvilken som benyttes vil være avhengig av hvert enkelt pasienttilfelle. MR-bryst ble utviklet på midten av 90-tallet. Den er den mest sensitive teknikken i brystdiagnostikk, og brukes kun på visse indikasjoner. MR-bryst var den eneste teknikken som kunne gi bilder med både morfologisk og funksjonell informasjon, inntil kontrast-forsterket mammografi (KM) ble kommersielt godkjent i 2010. Forskning viser at KM har sammenlignbar diagnostisk nøyaktighet som MR-bryst, og en metode som i økende grad brukes i brystdiagnostikk.

Et tre-delt prosjekt ble gjennomført ved Brystdiagnostisk senter ved Oslo universitetssykehus for å vurdere hvilken rolle KM kunne ha i den daglige kliniske driften. Med mål om å sammenligne den diagnostiske nøyaktigheten og korrelasjon i målt sykdomsutbredelse, utførte 30 pasienter med usikre funn etter trippeldiagnostikk KM i tillegg til MR-bryst, som er standard pasientforløp. Undersøkelsene ble gransket av erfarne brystradiologer, basert på BI-RADS®-systemet. Konklusjonene, gitt på en på en 6-trinns skala, ble brukt til å beregne standard diagnostiske indekser. Pearsons korrelasjonskoeffisient ble brukt til å vurdere korrelasjonen på sykdomsutbredelse.

Denne studien viste en noe høyere diagnostisk nøyaktighet på MR-bryst enn KM, med sterk korrelasjon på målt sykdomsutbredelse. Det ble registrert falsk negative og falsk positive kasus på begge teknikkene. KM har potensiale til; økt effektivitet i den daglige arbeidsflyten og bedre utnyttelse av ressursene, å påvirke til kortere utredningsfase og redusere pasientens psykiske stress relatert til en brystkreftutredning.

List of abbreviations

BDS	Breast Diagnostic centre
BRMI[1]	Breast Magnetic Resonance Imaging
CC	Cranio-caudal
CE	European conformity
CEM[2]	Contrast Enhanced Mammography
DBT	Digital Breast Tomosynthesis (3D)
DM	Digital Mammography (2D)
FDA	U.S Food & Drug Administration
FFDM[3]	Full field digital mammography
HE	High-energy
LE	Low-energy
OUS	Oslo University hospital
MLO	Mediolateral oblique
MRI	Magnetic Resonance Imaging
NPV	Negative predictive value
PACS	Patient Archive & Communication System
R	Recombined
SD	Standard deviation
US	Ultrasound
USN	University of South-Eastern Norway

[1] In this context – contrast-enhanced breast magnetic resonance imaging.
[2] CEM is in literature also referred to as CEDM (contrast-enhanced digital mammography) and CESM (contrast-enhanced spectral mammography) depending on the author, publisher and/or system vendor.
[3] In this context – as the modality

Contents

1 Introduction

1.1 Breast cancer

There were registered 4247 new breast cancer incidences in Norway in 2021 – 4224 females and 23 males (Cancer Registry of Norway, 2023a, p. 21). This make breast cancer the most frequent cancer type among women (fig. 1). The 5-year relative survival rate for the period 2018-2022 was 92% (Cancer Registry of Norway, 2023b, p. 105). Early detection, e.g. through participation in the national mammography screening program, and better treatment have contributed to this (Sebuødegård et al., 2019).

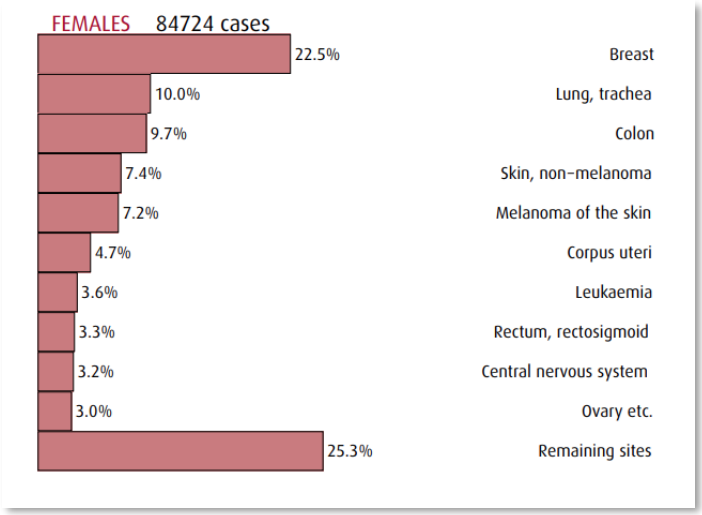


Figure 1: The most frequent cancer types for women between 2018-2022 (Cancer Registry of Norway, 2023a, p. 24)

1.2 Assessment of breast cancer

Breast diagnostics is the assessment of whether lumps and other clinical symptoms are normal or not (The Norwegian Directorate of Health, 2023, p. 21). Symptomatic patients should be referred to a breast diagnostic centre (BDS). For women (50-69 years) participating in the national mammography program, who indicates symptoms that rise suspicion of breast cancer, or where there is suspicious findings on the screening images, must be recalled to BDS for further investigations (Bjørndal et al., 2019, pp. 10-11).

A breast investigation consist of breast imaging, a clinical examination performed by a breast radiologist or a -surgeon, and (where appropriate) a histopathological needle sample – called *triple assessment* (The Norwegian Directorate of Health, 2023, p. 25). To ensure a standardized patient pathway of good and equal quality, there has been developed a national guideline for the assessment, treatment, and follow-up of patient with- or suspicion of breast cancer (The Norwegian Directorate of Health, 2023).

1.3 The role and modalities of breast imaging

From early attempts in the 1920s until today, breast imaging has developed into a separate speciality in medical imaging (Joe & Sickles, 2014, p. 23). Which modality and/or method being used will vary in each individual patient case.

The right treatment for the right patient requires continuous optimization in all stages of the patient pathway (Cancer Registry of Norway, 2023b, p. i). Optimized breast imaging modalities and techniques are vital in patient-management decisions made by breast cancer surgeons and -oncologists. In assessment of breast cancer, the imaging modalities must be able to accurate visualize the presence, type, and extent of disease (Nori & Kaur, 2018, p. 3).

Full field digital mammography-system (FFDM) with a selection of imaging methods is the primary modality (The Norwegian Directorate of Health, 2023, p. 26);

- Digital mammography (DM) with conventional 2D- and magnified images.
- Digital breast tomosynthesis (DBT) – a 3D-tecnique where angled 2D low-dose images are reconstructed to a series of thin slides throughout the breast (The Norwegian Directorate of Health, 2023, p. 28).
- Contrast-enhanced mammography (CEM) combining DM with the use of iodine-based contrast agent (see section 1.3.2).

X-ray-guided interventional breast procedures can also be performed with FFDM (Kuzmiak, 2019).

Ultrasound (US) is a supplementary modality to FFDM, and must be performed if FFDM shows any sign of pathology (The Norwegian Directorate of Health, 2023, p. 26). Where needle sampling is required, it is the primary modality.

Breast magnetic resonance imaging (BRMI) is also a supplementary modality to FFDM (The Norwegian Directorate of Health, 2023, p. 27). Due to its high sensitivity, BRMI is the next step in a breast cancer investigation where there, among other, is inconclusive results from FFDM and US (see section 1.3.1.).

1.3.1 Breast magnetic resonance imaging

Research on BRMI was conducted and published already in the mid-80s, but the modality had no clinical significance before 1990s when gadolinium-based contrast agent was introduced (Mann et al., 2015, p. 3670; Nori & Kaur, 2018, p. 47). As of today, BRMI is considered as the most sensitive modality in breast imaging, and it applies to both the detection of cancer and the assessment of the extent of disease (The Norwegian Directorate of Health, 2023, p. 27). BRMI requires an intravenous contrast injection, and assumes that the patient has normal renal function. A BRMI-examination is performed as a multiparametric protocol, consisting of T2-weighted sequences, diffusion sequences and dynamic T1-weighted sequences before and after IV-contrast.

Even if it outperforms FFDM-methods and US, limitation such as a high false positive rate, relatively long acquisition- and interpretation time, and limited access must be taken in to consideration (The Norwegian Directorate of Health, 2023, p. 27). Technical development, such as better coil designs, higher magnetic field strength and optimized sequences, has improved BRMIs diagnostic performance (Nori & Kaur, 2018, p. 47). BRMI is used as a part of the triple assessment test only on certain indication (fig. 2).

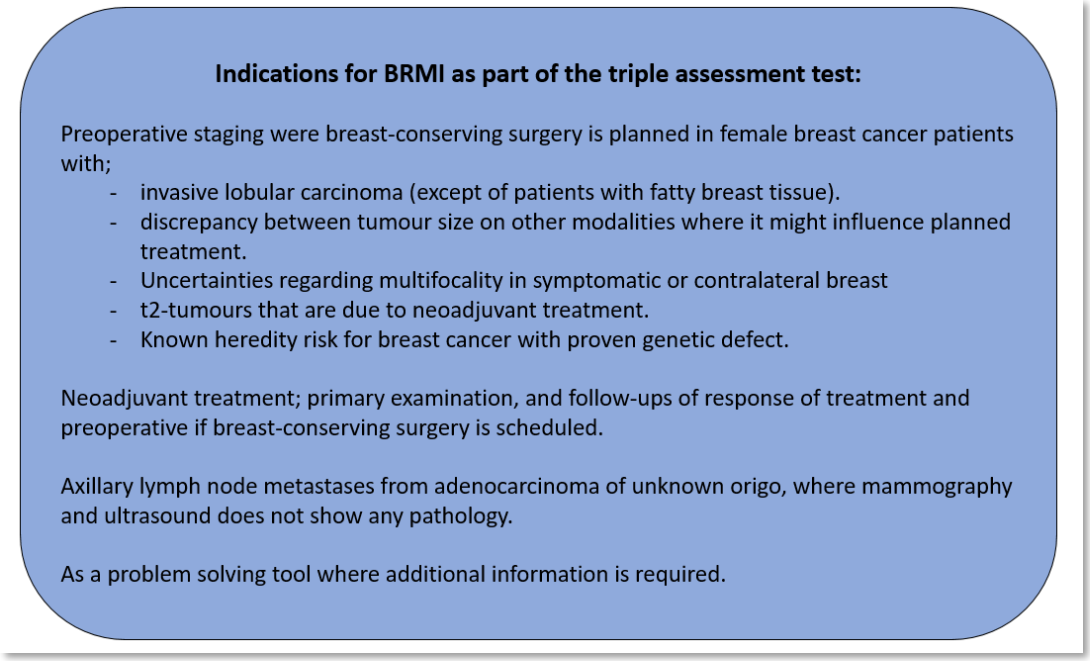


Figure 2: Indication for BRMI (The Norwegian Directorate of Health, 2023, p. 27)

1.3.2 Contrast-enhanced mammography

BRMIs success in breast imaging was the primary stimuli for the development of CEM (Lobbes & Jochelson, 2019, p. 77). The first commercial CEM-system got CE- and FDA- approval in 2010 and 2011 (Lobbes & Jochelson, 2019, p. 18), and as of today, all major vendors are offering CEM on their FFDM-systems. CEM is the only method in FFDM that provides images with morphological and functional information similar to BRMI (Nori & Kaur, 2018, p. 3). The dual energy-technique used in CEM, utilizes the inherent difference between iodine and breast tissue (Nori & Kaur, 2018, p. 18). A low-energy (LE) acquisition of 25-34 kVp (below the *k*-edge of iodine) and a high-energy (HE) acquisition of 45-49 kVp (above the *k*-edge of iodine) during one compression of the breast. The system software creates a recombined (R) image, that highlights the contrast-enhanced areas from the background parenchyma (fig. 3). The LE-image is equivalent to a DM-mammogram, so there is no need for an additional exposure (Lobbes & Jochelson, 2019, pp. 61-62). CEM has potential to reduce the challenges with breast tissue overlap and the similarity in contrast between healthy breast- and tumour tissue, seen on other FFDM-methods (Lobbes & Jochelson, 2019, pp. 1-2). CEM is an emerging tool in breast imaging (Jochelson & Lobbes, 2021). It is fast, easy, and cost-effective, and it may increase access to vascular imaging. Although, the slight increase in radiation dose and the small risk of adverse reactions of contrast media must be taken into consideration (Jochelson & Lobbes, 2021, p. 44).

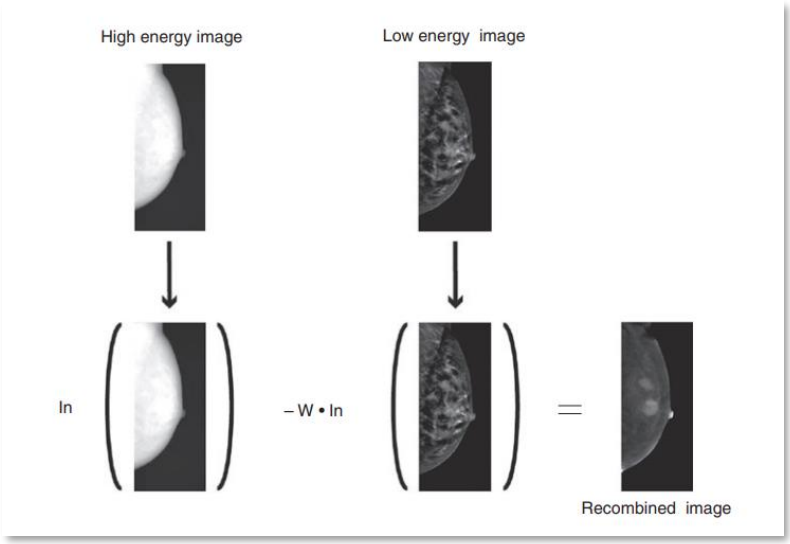


Figure 3: Visual presentation of the post-processing done by the system software, to obtain the recombined image out of the low- and high-energy image acquisitions (Lobbes & Jochelson, 2019, p. 29)

1.4 Research on the topic

CEM is mentioned in the national guideline as an option for additional imaging in primary FFDM-mammography (The Norwegian Directorate of Health, 2023, p. 26).
Despite the fact that CEM has been an approved method in Europe for many years, it is not widespread used in Norway. As of today, there are approximately five CEM-systems in clinical use, but several installations are being planned (Larsson H. (GE Healthcare), Lyseng J. (Tromp Medical), and Schuster A. (Fuji Film), personal communication, spring 2023).
Neither is there, to my knowledge, done any scientific research on this method in Norway.

Internationally, research has been done on CEM in comparison with BRMI (Lobbes & Jochelson, 2019, pp. 78-91; Nori & Kaur, 2018, pp. 47-56), including some meta-analysis' (Cozzi et al., 2022; Neeter et al., 2023; Xiang et al., 2020).
Based on known issues within breast diagnostics, the methods have been compared on their diagnostic performance. The reason is that the principle for doing a CEM is the same as for BRMI (Nori & Kaur, 2018, p. 47). Tumours need sufficient nourishment to grow. To secure this, adjacent blood vessels will form new capillaries to the tumour, and these are unable to retain contrast agents. By utilizing tumours neovascularity, dedicated imaging protocols can increase breast cancer detection (fig. 4).

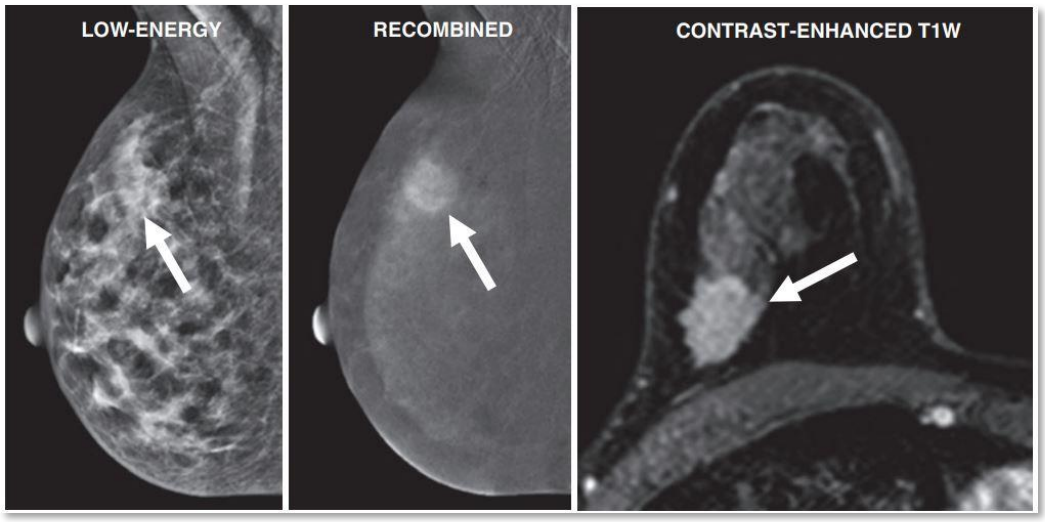


Figure 4: An invasive breast cancer shown on CEM as an irregular mass on the LE-image (left), shown as an enhanced mass in the R-image (middle) and on the T1W-image from the BMRI (right) (Nori & Kaur, 2018, p. 53).

Fallenberg et al. compared the diagnostic performance and size estimation of BRMI, DM and CEM, and their conclusion was that CEM, alone or in combination with DM, was as accurate as BRMI (Fallenberg et al., 2014).

Kamal et al. investigated the feasibility of replacing BRMI with CEM in the assessment of sonomammograpic indeterminate lesions (Kamal et al., 2020). Their study showed a sensitivity and specificity of 94% and 65% for CEM and 100% and 67% for BRMI. They concluded that CEM may replace BRMI as a problem-solving tool in the characterization of indeterminate breast lesions.

Sumkin et al. did a comparison of the estimation of extent of disease between BRMI, CEM and molecular breast imaging versus the histopathological result (Sumkin et al., 2019).

They concluded that all modalities had similar cancer detection rate, but they led to overestimate the tumour size.

Łuczyńska et al's. main goal was to compare BRMI and CEMs sensitivity, accuracy, and predictive values (Łuczyńska et al., 2015). They concluded that CEM has a potential as a valuable diagnostic method with high sensitivity, accuracy, and negative predictive value and a false-positive rate similar to BRMI.

1.5 Background and aim of this study

1.5.1 Purpose and motivation

BDS at Oslo University hospital (OUS) is specialized in the assessment of breast cancer and follow-up of breast cancer patients. BDS is also responsible for breast cancer screening in Oslo municipally on behalf of BreastScreen Norway. Approximately 200 clinical- and 650 screening patients are handled each week. For 2022, a total of 543 new breast cancer cases were detected at BDS (Cancer Registry of Norway, 2023b, p. 4).

The main goal for BDS is to be able to deliver the best service to OUSs breast surgeons and -oncologists within the financial, technological, and legal framework provided. This, to be able to give breast cancer patients the best possible outcome of their treatment.

Therefore, a three-part project was planned and carried out to acquire more knowledge about CEM and what opportunities this method could offer, before moving on to purchasing necessary software and equipment.

From a personal point of view as a radiographer at BDS since 2016, increased knowledge among radiographers is an important part of to securing this service. This led me to participating in the Master of clinical healthcare-program at the University of South-Eastern Norway. Based on this, I was given the opportunity to participate in the project as a coordinator for both the planning and the implementation. It was natural to include results from this project in my final thesis. In addition to this study – cost effectiveness and patient satisfaction were assessed in the project.

1.5.2 Aim and research questions

The aim of this study was to investigate CEM's diagnostic performance in breast cancer detection and characterization compared to BMRI, in a specific patient group where BRMI is the standard patient pathway. In addition to the BRMI, the participants underwent a CEM-examination.
Based on this, the goal for this study is to answer the following two research questions;

1. *Does Contrast-enhanced mammography show the same diagnostic performance as Breast magnetic resonance imaging in patients with indeterminate findings after triple assessment?*
2. *In assessing the extent of disease; is there a correlation between Contrast-enhanced mammography and Breast magnetic resonance imaging in that same patient group?*

2 Theoretical framework, materials and methods

2.1 Theory and research design

This study was performed as a prospective clinical intervention trial with a quantitative approach. Clinical trials are a type of research that studies new methods, including radiological ones, and assesses their effect on human health outcome (World Health Organization, 2022).
Quantitative research originates from natural sciences, with positivism as a theoretical starting point (Drageset & Ellingsen, 2009, p. 101). Such research must relate to facts that can be observed and recorded, with the aim of explaining, predicting, and controlling events.
Hypothetical-deductive method is widely used in this type of research (Drageset & Ellingsen, 2009, p. 101). Based on a theory, a hypothesis is formed or tested, and by the results, one can either disprove or confirm the relevant hypothesis/claim.

A quantitative approach was an obvious choice for this study, as it includes the collection of numerical data where the aim is to provide knowledge about a new imaging method to relevant stakeholders (Bjørnnes & Gjevjon, 2019).
A clinical diagnostic test used in patient care must be guided by evidence (StatPearls Publishing, 2023). Most of these tests classifies patients as positive or negative depending on presence or absence of disease, and this can be used to calculate essential indicators to assess the diagnostic performance of a test (see 3.4.1).

2.2 Study population

Participation was voluntary, and a written consent was mandatory (annex 4). A refusal to participate did not affect the standardized patient pathway, planned investigation or treatment.
All participants had to review OUS' checklist (annex 5) regarding use of contrast agents ahead of the CEM-examination. This checklist is based on ESUR guidelines on contrast agents (European Society of Urogential Radiology, 2018). Inclusion and exclusion criteria are shown in fig.5.

Inclusion criteria:
Patients who;

- were 18 years and older
- had undergone the triple assessment test with uncertain findings and/or extent of disease
- were referred to further investigation with BRMI

Exclusion criteria:
Patients who;

- did not consent or were not competent to consent
- had allergy or sensitivity for contrast agent containing iodine
- had diabetes requiring insulin
- had reduced renal function
- had acute mastitis/abcsess
- had medical – or cosmetic implants
- were breast feeding
- were undergoing chemotherapy treatment

Figure 5: Inclusion- and exclusion criteria.

A total of 36 patients accepted to participate. 30 did consent, passed the inclusion criteria, and performed both BRMI and CEM, and are included in this study. One patient consent, but due to diabetes not accepted to participate. Two did consent, passed the inclusion criteria, but did not complete the CEM-examination. Three patients withdraw their consent before the CEM-examination. Patients referred to further investigations with a BRMI are by the conducting radiologist, informed that there is a suspicion of a malignant diagnosis. How patients react varies greatly, and several of these patients were assessed as "not competent to consent".
A step-by-step overview of the recruitment process is shown in the flowchart below (fig. 6).

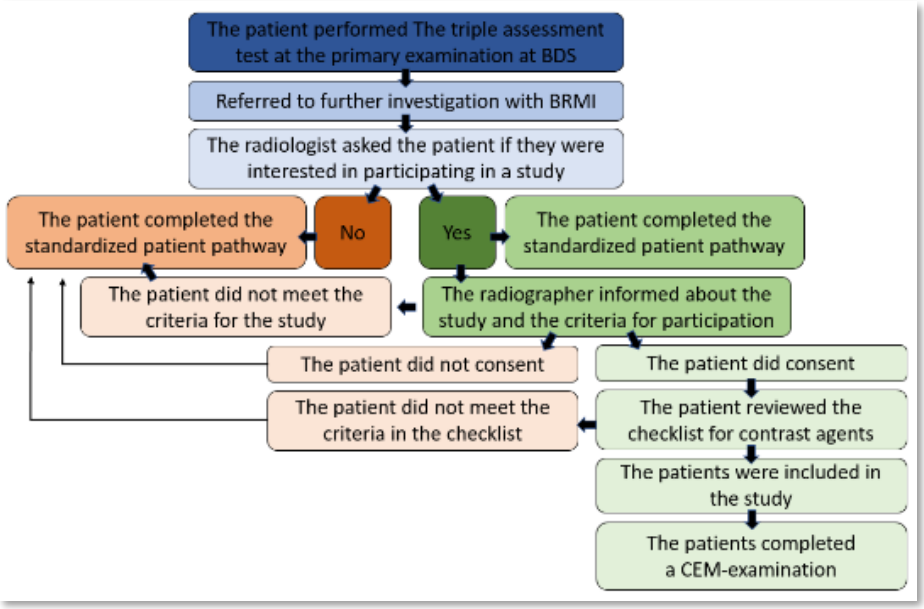


Figure 6: Flowchart with an overview of the recruitment process

2.3 Equipment and protocols

The BDS is not equipped with a dedicated MRI-scanner. All patients, including the participants in this study, are referred to the general radiology department at The Radium hospital[4] for a BRMI. The examination is performed according to their current protocols, recommended by the national guideline (The Norwegian Directorate of Health, 2023, p. 28). Except from image interpretation, BDS is not involved in the conduct of these examinations.

To enable CEM, one FFDM-system at BDS needed an upgrade with a software (SenoBright™ HD, GE Healthcare) and a copper filter. This upgrade was made following an agreement for a one-year loan of a demo license, concluded by the Radiology Account Manager at GE Healthcare Diagnostic Imaging Norway and the section manager for radiography at BDS.

Our chosen protocol for CEM was four dual-energy acquisitions in an order recommended by the vendor. There is no evidence-based research that recommends a specific order, as long as they are acquired within the time (up to 10 minutes) the contrast media is present in the breast tissue (Jochelson & Lobbes, 2021, p. 37).

Neither is there an optimized guideline for imaging parameters on CEM, including the use of contrast media. A general accepted one does exist, and our chosen setup was within these recommendations (Jochelson & Lobbes, 2021, p. 37).

Due to the risk of adverse reactions from the contrast injection, each participant was observed for 30 minutes after the injection before they were allowed to leave. This according to OUSs policy based on the European guideline (European Society of Urogential Radiology, 2018).

2.4 Criteria for interpretation of the examinations

Three radiologists at BDS performed the interpretation of the BRMI- and CEM-examinations. They have experience in all modalities used in breast diagnostics, except CEM (fig. 7). Prior to the project they visited two centres that performs CEM and were introduced to the method by radiologists with experience in interpretation of CEM-images. They also updated themselves on available literature.

The interpretations were done as in an everyday clinical practice, with support in previous FFDM- and US-images. BRMI was always prioritized as it is the standard patient pathway.

[4] The Radium hospital is incorporated in the Oslo University hospital's organization.

Radiologist	Experience in breast diagnostics	Experience in BRMI
1	30 years	25 years
2	10 years	6 years
3	8 years	3 years

Figure 7: The three radiologists that performed image interpretations, with year in breast diagnostics in general and BRMI in specifically indicated.

A study-specific interpretation form, based on BI-RADS® (American College of Radiology, 2022a), was filled out during interpretation for each examination. The Breast Imaging Reporting & Data System (BI-RADS®) was developed by the American College of Radiology, and is a standardized system for a common terminology, assessment structure and classification for the modalities used in breast imaging. The head radiologist developed the interpretation forms for BRMI (annex 6) and CEM (annex 7) based on this system. A review of the interpretations forms was subsequently carried out, in order to rule out obvious errors and omissions.

A dedicated BI-RADS®-atlas for CEM was not published before 2022 (American College of Radiology, 2022b). The regular BI-RADS®-atlas for FFDM was used to interpret the LE-image. For the recombined images the radiologist used available literature on CEM, such as part two in the book *Contrast-enhanced mammography* (Nori & Kaur, 2018, pp. 139-254).

2.4.1 Assessment of the diagnostic performance

The number of assessment factors the radiologists use to determine a conclusion on an examination is many, and they emerge from the interpretation forms. The given conclusions can be either negative, benign, and likely benign, uncertain, likely malignant and malignant.

To determine if a case is a true or false, positive- or negative, the given conclusions was compared against the histopathological result. These results were extracted from DIPS Arena, OUSs digital journal system (DIPS, 2023), and are defined as the gold standard for the participants final diagnosis. To be able to calculate the standard diagnostic indices' (sensitivity and accuracy) in this study, the conclusions was divided in two groups:

1. Negative, benign, and likely benign
2. Uncertain, likely malignant, and malignant

2.4.2 Assessment of the extent of disease

Due to the large number of participants that received neoadjuvant treatment (systemic therapy given before local treatment) assessment of the extent of disease was only done between BRMI and CEM, because the histopathological results does not reflect the initial size (annex 8).
The definition of the extent of disease is the longest distance between the outer edges of suspicious finding(s), regardless of if it is unifocal of multifocal mass, a group of micro-calcifications or an area with non-mass enhancement, and are listed in millimetres (American College of Radiology, 2022a). Non-mass enhancement is area of enhancement that does not have a distinct feature of a mass, and is characterized by its distribution (Nori & Kaur, 2018, p. 113).

2.5 Data analysis

2.5.1 Assessment of the diagnostic performance

Sensitivity and accuracy are among indicators used to determine diagnostic performance (Baratloo et al., 2015). Sensitivity is a tests ability to correctly identify an individual with a disease, and accuracy is the ability to differentiate those with and without a disease.

2.5.2 Assessment of the extent of disease

To assess the agreement on the extent of disease between BRMI and CEM, Pearson product-moment correlation coefficient was chosen (Pallant, 2020, pp. 135-147). This is a parametric test that describes the strength of the relationship and the linearity between to continuous variables.

2.6 Ethics and data protections

2.6.1 Applications and approvals

This study was approved by the Regional Committee for Medical & Health Research Ethics (annex 9), the Research Committee for the Division of Radiology and Nuclear Medicine (annex 10) and by the Data Protection Officer (annex 11) at OUS.

2.6.2 Anonymization of participants, images, and data

The project coordinator at BDS was responsible for all anonymization of patient data in images, files, and forms used in this study. All participants were given a unique study number in Medinsight, a research tool used at OUS (Medinsight). A separate work list was created in Sectra Patient Archive and Communication System (PACS) for storing images from the BRMI- and CEM-examination (Sectra, 2023). All images were anonymized.

2.6.3 Radiation dose

The additional CEM-examination leads to a small increase in radiation dose for the participants. When the LE-image is used as the routine mammogram, the HE-image gives an increased radiation dose varying from 20% to 80% depending on system and -settings and breast thickness (Jochelson & Lobbes, 2021, p. 44). Mammography, in general, has low radiation doses (Norwegian Radiation and Nuclear Safety Authority, 2020).

3 Results

In 3.1 and 3.2 relevant original tables from SPSS are shown.

3.1 Calculations of diagnostic performance

The following tables and clinical information, such as the conclusion given by the radiologist (annex 8) are used to calculate the diagnostic indices found in table 3 in the article manuscript.

Descriptives for age

			Statistic	Std. Error
Age in years	Mean		55,80	1,902
	95% Confidence Interval for Mean	Lower Bound	51,91	
		Upper Bound	59,69	
	5% Trimmed Mean		55,57	
	Median		54,00	
	Variance		108,510	
	Std. Deviation		10,417	
	Minimum		40	
	Maximum		76	
	Range		36	
	Interquartile Range		17	
	Skewness		,278	,427
	Kurtosis		-,914	,833

Figure 8: Results of the descriptive analysis for age (Pallant, 2020, pp. 53-58).

Histopathological diagnosis

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	IDC	5	15,6	15,6	15,6
	IDC + DCIS	12	37,5	37,5	53,1
	ILC	4	12,5	12,5	65,6
	ILC + LCIS	1	3,1	3,1	68,8
	ILC & ITC	1	3,1	3,1	71,9
	ILC & ITC + DCIS	1	3,1	3,1	75,0
	IMC + DCIS	1	3,1	3,1	78,1
	DCIS	2	6,3	6,3	84,4
	FA	1	3,1	3,1	87,5
	NEGATIVE	4	12,5	12,5	100,0
	Total	32	100,0	100,0	

Figure 9: Summary of histopathological diagnosis of all included core needle biopsies (Pallant, 2020, pp. 53-58).

3.2 Calculations of extent of disease

The following tables and clinical information, such as measurement (annex 8) form the basis for carrying out the Pearson coefficient correlation test found in the article manuscript.

Descriptives for total extent of disease

			Statistic	Std. Error
BRMI_total extent of disease	Mean		49,14	5,607
	95% Confidence Interval for Mean	Lower Bound	37,64	
		Upper Bound	60,65	
	5% Trimmed Mean		47,77	
	Median		45,00	
	Variance		880,201	
	Std. Deviation		29,668	
	Minimum		5	
	Maximum		120	
	Range		115	
	Interquartile Range		43	
	Skewness		,680	,441
	Kurtosis		,137	,858
CEM_total extent of disease	Mean		47,75	6,164
	95% Confidence Interval for Mean	Lower Bound	35,10	
		Upper Bound	60,40	
	5% Trimmed Mean		45,94	
	Median		45,50	
	Variance		1063,972	
	Std. Deviation		32,619	
	Minimum		5	
	Maximum		125	
	Range		120	
	Interquartile Range		42	
	Skewness		,757	,441
	Kurtosis		,065	,858

Figure 10: Results of the descriptives analysis for total extent on disease (Pallant, 2020, pp. 53-58)

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BRMI_total extent of disease	,167	28	,044	,945	28	,146
CEM_total extent of disease	,150	28	,107	,932	28	,070

a. Lilliefors Significance Correction

Figure 11: Results of the Shapiro-Wilk's test of normality, p>0.05 indicates normality (Pallant, 2020, pp. 59-65)

Correlations

		BRMI_total extent of disease	CEM_total extent of disease
BRMI_total extent of disease	Pearson Correlation	1	,872**
	Sig. (2-tailed)		<,001
	N	29	28
CEM_total extent of disease	Pearson Correlation	,872**	1
	Sig. (2-tailed)	<,001	
	N	28	29

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 12: Results on the Pearson correlation coefficient on total extent of disease between BRMI and CEM, from SPSS (Pallant, 2020, pp. 135-141)

4 Discussion

The discussion section for this master thesis is divided between the one found in the article manuscript and the one below in this supplementary thesis. In the article manuscript, the discussion is mainly narrowed down to cover the results of the study. While this section has a broader approach that aims to discuss study limitations, CEMs role in a clinical perspective (on a macro, meso and micro-level) and further research.

4.1 Comparison with research – study limitations

This study aimed to compare the diagnostic performance of CEM versus BRMI, on the basis of gaining knowledge about the method and what role it could have in our department. For our selected patient group, CEM showed a high diagnostic performance, but slightly lower than BRMI. Measurements of extent of disease had a strong positive correlation between CEM and BRMI.

Thru existing research, CEM has demonstrated high performance in assessment of breast cancer (Cozzi et al., 2022; Neeter et al., 2023; Xiang et al., 2020), and there seems to be a consensus about CEM being an emerging tool in breast imaging and may become a viable alternative to BRMI (Jochelson & Lobbes, 2021). The result from this study are in agreement with what is known on the topic. However, in a larger meta-analysis where 60 studies (10605 patients and 11049 CEM-examinations) are included, it is pointed out that it is not always appropriate to directly compare diagnostic indices' from a single study against a pooled results in meta-analysis (Cozzi et al., 2022). High heterogeneity among the studies is in a general a limitation for existing research on CEM, such as differences in study designs, study population and methodology.
Our study consists of a very homogenous group of patients where there were a high likelihood of a malignant diagnosis', which may have affected the outcome. When the results are compared to other studies, it should be ensured that it is done to studies with similar subgroups of participants. Cozzi et al. also show that there is great variation in the number of participants in existing CEM-studies with a range of 15-953. Our study, with 30 participants, is in the lower range and this affected the choices of methodology and the results. If we had chosen an approach where each of the three radiologists involved, interpreted both examinations and compared these in a ROC-curve, we could have a more liable result with the same amount of participant. Nevertheless, with the

background of the aim of this study, we found the prospective approach and the interpretation as close to a normal clinical setting as possible more beneficial.
It should also be noted that interpretation of the CEM-examinations were done before the BI-RADS®-atlas for CEM was published (American College of Radiology, 2022b). This may have led to some bias in the results.
The limited sample size also affected our approach to the methodology for measuring the extent of disease. We chose to use the measurement for the entire extent of the disease, without taking into account whether there were one or more masses, an area of non-mass enhancement or calcifications. With this method, we achieved one uniform measurement and were able to carry out a statistical test for the entire study population.

4.2 Interpretation of results in clinical perspective

The requirements for efficiency and better utilization of the resources are central in today's healthcare system. In order to achieve a sustainable health services, it is required to use the opportunities that technology provides and the knowledge and skills of the employees to be able to solve the tasks as efficiently as possible (Meld. St. 7 (2019-2020), p. 3).
To acquire knowledge about CEM and assessing its diagnostic performance and efficacy against existing modalities and methods, may improve breast imaging and gain better utilization of the available resources. This is also pointed out in the Norwegian Directorate of Health's proposal for a strategy for rational use of diagnostic imaging, which states that; «different approaches regarding a rational utilization of existing and future resources in diagnostic imaging should be described» (The Norwegian Directorate of Health, 2019, p. 4).

In a clinical perspective, it is perhaps the utilization of BRMI and CEM the main challenge – when to use whom? This issue is addressed by Kamal et al., and they point out that both techniques has their advantages and limitations (Kamal et al., 2021). CEMs advantages lies in the potential high accessibility, and how easy and fast it is to perform and interpret. These factors make CEM an easy method to implement in the daily workflow. For BRMI, these topics are limitations. BRMI still has a slightly superior diagnostic performance, especially in the assessment of inflammatory lesions, and for lesion close to pectoralis major or outside the mammographic field of view. The key point is to choose the most appropriate imaging technique(s) for the current issue of each individual patient.

According to the national guideline (The Norwegian Directorate of Health, 2014), patients with indeterminate suspicious findings must be referred to BRMI in a fixed timeline, which means they will follow a patient pathway with recommended progression times. There is a limited number of MRI-appointments available at the Radium hospital for assessment of breast cancer, so it is vital they are used on the right patients. Where CEM is an alternative, it should be used. This may affect the progression times, not only for the patient in question, but also for patients with other issues.

Based on the original project at BDS, where the results in this study originates from, there was a desire to assess what role CEM could have in our department. The knowledge gained by carrying out this project, together with already known literature and research, contributed to BDS being granted funds to acquire the necessary equipment for CEM.
As of today, CEM is implemented in the clinical practice and the examination is carried out regularly. In most cases CEM has been used as a problem-solving tool of indeterminate suspicious findings. Instead of being scheduled for a BRMI, potentially several days ahead, they perform a CEM-examination at their primary visit (fig. 13).

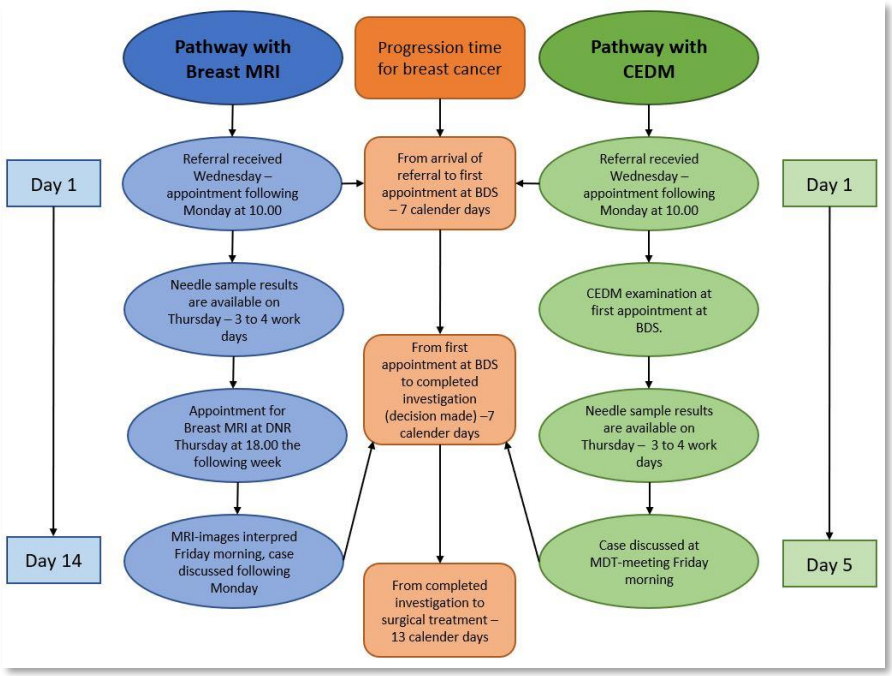


Figure 13: Flowchart [own work, (MRAD630)] showing the investigation phase in a "worst-case scenario", for a patient with indeterminate suspicious findings at BDS. Progression times from the national guideline (The Norwegian Directorate of Health, 2014)

This makes the investigation phase shorter, and the patients are either quicklier clarified or -diagnosed. This is very beneficial for the patients. Raised anxiety during the investigation phase is known, and can be very demanding for some (Drageset & Lindstrøm, 2005).
This is a subgroup Cozzi et al. also highlights to be beneficial to perform CEM on instead of BRMI, related to the economic and psychological costs (Cozzi et al., 2022).

4.3 Further research

The meta-analysis by Cozzi et al. points out a need for larger and more powerful studies with more homogeneous subgroups with specific breast cancer related issues (Cozzi et al., 2022). Randomized studies are currently being carried out, and will hopefully add valuable knowledge about the utilization of CEM. Neeter et al.'s aim is to study CEMs role in the work up with recalled women from screening (Neeter et al., 2019), while Åhsberg et al. are studying the role CEM could have in preoperative staging (Åhsberg et al., 2021).
An ongoing prospective randomized-controlled study at Maastricht University Medical Centre, aims to investigate the diagnostic accuracy of CEM in terms of size measurements and degree of lesion enhancement when reducing the volume of contrast media (Van Nijnatten et al., 2023). A reduction in the amount of contrast media may be beneficial for patients as the risk for adverse reactions is reduced.
From a radiographer's perspective, there are several current topics that requires further research, that radiographers also could be involved with. As of today, there is no scientific evidence for an optimized order for image acquisitions (Jochelson & Lobbes, 2021). As an example, it is known that different breast cancer types has different enhancement patterns dependent on time (Kuhl et al., 2007). Longer time delay between contrast injection and image acquisition may result in stronger enhancement. An optimized protocol will be able to better utilize the time where contrast media is present in the breast. Assessment of radiation dose is another topic of interest. In an everyday clinical use, it is the radiographers who has first-hand information on the technical parameters used and how they affect the radiation dose. A recent two-centre study concluded that a two-view bilateral CEM had an average dose 30% higher than DM (Gennaro et al., 2022).
However, with the expected increase in the use of CEM, it is nevertheless important to assess the radiation dose – at least nationally and/or locally. This is supported by Norwegian legislation (The Radiation Protection Regulations, 2016, p. §40).

4.4 In conclusion

CEM showed a high diagnostic performance, but slightly lower than BRMI for our selected patient group. Measurements of extent of disease had a strong positive correlation between CEM and BRMI. CEM has potential to improve efficiency in the daily workflow, which will be beneficial for the utilization of available resources. In assessment of breast cancer where CEM is an available method, may lead to a shorter investigation phase and less psychological distress for the patients, associated with a breast cancer assessment. Larger multicentre randomized studies comparing CEM with BRMI for various indications are needed.

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List of tables and charts

Manuscript title:

Contrast-Enhanced Mammography versus Breast Magnetic Resonance Imaging: Comparison of diagnostic performance and assessing correlation of extent of disease.

Author's name: incl. address, fax/e-mail

Anne Synnøve Bakken, Jakslandveien 81, 3440 Røyken, Norway
e-mail: anne.s.bakken@gmail.com

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Figures and images referred to in this article manuscript, required to be attached in an annex' upon submission, can be found at the very back of the document.

Total number of words excl. reference list, tables, images and figures: ***2914***

Abstract:

Background:

Breast Magnetic Resonance Imaging (BRMI) is the most sensitive method of breast imaging, which provides both morphological and functional images. It is an indispensable tool where conventional imaging does not provide conclusive answers. However, it is known to be time consuming, with high cost and limited accessibility. Contrast-enhanced mammography (CEM) is the latest method in mammography and can provide images similar to BRMI, with comparable result in diagnostic performance. It is known as a fast and cost-effective, with potentially higher accessibility than BRMI.

Purpose:

To compare the diagnostic performance and to assess the correlation on extent of the disease between BRMI and CEM.

Material and Methods:

In this prospective study 30 participants were included and performed both BRMI and CEM. All suspicious findings were evaluated independently based on BI-RADS®-classifications. The given conclusion on BRMI and CEM were compared to the histopathological result and the correlation between measured size of extent of disease were assessed.

Results:

32 lesions from 30 participants were identified and biopsied. Histopathology confirmed 27 malignant, 1 benign and 4 negative diagnoses. Sensitivity was 96.3% on BRMI and 92.6% on CEM and accuracy was 93.6% on BRMI and 87.5% on CEM. The correlation test showed no statistically significant difference in measurements of extent of disease (Pearson's $r = 0.868$ $p < 0.001$).

Conclusion:

The overall diagnostic performance was slightly better for BRMI than CEM. There was a strong correlation in assessment of extent of disease. CEM has potential to become a valuable problem-solving tool.

Trial registration: *Contrast-enhanced digital mammography in assessment of breast cancer*, Regional Committee for Medical & Health Research Ethics, https://rekportalen.no/#hjem/home, reg.no.: 139114.

Keywords: Breast cancer, breast imaging, contrast-enhanced mammography, breast magnetic resonance imaging, diagnostic performance

Introduction:

A biological active breast cancer tumour needs to acquire sufficient nutrients to grow (1). Small ones depend on simple diffusion. Larger ones angiogenesis, and these newly and rapidly formed vessels tends to be leaky to contrast media. Consequently, injected contrast media will extravagate into the tumour and causing it to enhance on dedicated imaging techniques.

BRMI in combination with the use of gadolinium-based contrast media, is the most sensitive technique in breast imaging (2). Among others, it is an indispensable tool for problem-solving when 2D/3D mammography and/or ultrasound gives indeterminate answers. According to the Norwegian guideline, BRMI is the standard pathway for this patient group (3). However, BRMI can be limited by long acquisition– and interpretation time, high cost and low accessibility. BRMI has been the only modality in breast imaging with dedicated protocols for enhanced images, until the first commercial contrast-enhanced mammography system (CEM) was approved in 2010 (4).

CEM involves a dual-energy technique that enables to do two exposures during one projection – a low-energy (LE) image (kVp < the K-edge of iodine) and a high-energy (HE) image (kVp > the K-edge of iodine) (5). By utilizing the inherent difference between breast tissue and iodine, this technique creates a third, image that highlights the contrast-enhanced areas from the breast parenchyma, called recombined image (R). The LE-image is equivalent to a standard 2D-mammogram (6). CEM requires an intravenous injection with a low osmolar iodine-based contrast media two minutes prior to the first image acquisition (7). One cranio-caudal (CC) and one mediolateral oblique (MLO) acquisition of each breast is the standard protocol. CEM is fast and cost-effective due to short examination- and interpretation time and potentially higher accessibility than BRMI.

Internationally, a lot of research on CEM has been done and it is an emerging technique (8). However, in Norway it is not widespread used. To acquire knowledge about CEM, and assess it to existing techniques may improve breast imaging and lead to better utilization of resources – this according to the Norwegian Directorate of Health's strategy on medical imaging (9).

Based on this, the purpose of this study was to evaluate the diagnostic performance of CEM, and the aim is two-fold: (1) To assess CEMs ability to detect malignancy suspect changes compared to BRMI and the histopathological results, and (2) to compare the correlation between extent of disease measured on CEM and BRMI, in patients referred to BRMI due to indeterminate findings after triple assessment.

Material and Methods:

Study design

This prospective clinical intervention study was performed at the Breast diagnostic centre (BDS) at Oslo University hospital (OUS), as a part of a project assessing the role CEM may have in breast diagnostic at the hospital. This study is approved by the Regional Committee for Medical & Health Research Ethics, and the Research Committee for the Division of Radiology and Nuclear Medicine and the Data Protection Officer at OUS.

Patient selection

From October 2020 to November 2021, participants were recruited among patients who were referred to BRMI for further investigation after the primary examination, where triple assessment including a core needle biopsy of suspicious lesions were performed (fig. 1).

Patients were excluded if they were under 18 years old, did not/could not consent, had allergy to iodine, diabetes, reduced renal function, acute mastitis/abscess, medical- or cosmetic implants, were breast feeding or undergoing chemotherapy treatment.
All participants completed a written informed consent before they underwent the additional CEM-examination. A refusal to participate did not affect the standard patient pathway.

Equipment and protocols

BRMI was performed with a 1.5T-scanner (Magnetom Sola, Siemens Healthineers, Erlangen, Germany) with one Breast 18 (bilateral) and Body 18 – 36 channels in total, in prone position. The contrast agent (Clariscan™, GE Healthcare, Freiburg, Germany) was administered as an intravenous injection with a power injection system (Medrad® MRXperion, Bayer, Leverkusen,

Germany) with a dose of 0.5 mmol/ml, 0.1 mmol/kg, 3 ml/s followed by 30 ml NaCl-flush (9 mg/ml). Following sequences were used; Tra 2D SE T2W Dixon, Tra DWI and Tra dyn 3D GE T1W.

CEM was performed on a full-field digital system (Senographe^{TM} Pristina, GE Healthcare, Freiburg, Germany), installed with a software enabling CEM (SenoBright^{TM} HD). The contrast agent (Omnipaque^{TM}, GE Healthcare, Freiburg, Germany) was administrated as a one-shot intravenous injection with a power injection system (Medrad® Stellant, Bayer, Leverkusen, Germany) with the dose of 300 mg/ml, 1.5 ml/kg, 3 ml/s followed by 10ml NaCl-flush (9 mg/ml). With a two-minute delay a LE-image (26-34 kVp) and a HE-image (49 kVp) were acquired directly after each other during one compression in the following order: CC of the contralateral breast, CC and MLO of the symptomatic breast and MLO of the contralateral breast. All images were acquired within the recommended 10 minutes (7).

Interpretation of examinations and image analysis

Images from both examinations were interpreted once, randomly by one of three experienced breast radiologists. As CEM was a new method, they received an introduction to the method ahead of the study. The radiologists interpreted BRMI and CEM separately to avoid bias', but with support in previous mammography- and ultrasound examinations. Interpretations were done with a Dell Precision Tower 5820 with Nvidia Quadro 2200 and two Eizo GX550 monochrome screens, in Sectra Radiology PACS.

One study-specific form, based on the 5th edition of BI-RADS®-atlas (10), for each examination was filled out during interpretation. The histopathological results of the core needle biopsies were use as the reference standard. For BMRI and CEM, presence or absence of malignancy suspect finding(s) were assessed, then classified as mass and/or non-mass and further assessed with characteristics.

Each finding was given a conclusion on a six-category scale: negative, benign, likely benign, uncertain, likely malignant or malignant. The cut-off that divides examined subjects with and without malignancy suspicion are as shown in table 1.

To be able to compare the total extent of disease between BRMI and CEM, each malignancy suspect finding were measured at its longest distance of the outer edges. Measurements were done after the biopsies were taken.

Table 1
Criteria for cut-off positive and negative cases

True positive (TP)	Malignant histopathological analysis, classified as uncertain, likely malignant or malignant on BRMI and/or CEM.
False positive (FP)	Negative or benign histopathological analysis, classified as uncertain, likely malignant or malignant on BRMI and/or CEM.
True negative (TN)	Negative or benign histopathological analysis, classified as negative, benign and or likely benign on BRMI and/or CEM.
False negative (FN)	Malignant histopathological analysis, classified as negative, benign and or likely benign on BRMI and/or CEM.

Statistical analysis

All data were anonymised and coded in a dedicated codebook and calculated in IBM® SPSS® Statistics (version: 28.01.1 (14)), stored on OUS's encrypted research server. Data were summarized using descriptives.

Standard diagnostic indices were used to compare BRMI and CEM's performance compared to the histopathological result. Sensitivity and accuracy was calculated by the following formulas;

- Sensitivity = [TP/(TP + FN)] × 100%
- Accuracy = [(TP + TN)/(TP + TN + FP +FN)] X 100%

To test the correlation of total extent of disease, Pearson correlation coefficient (PCC) was used, visualised with a correlation-scatterplot. Test of normality with Shapiro-Wilk.

Results:

30 participants were included in this study, 29 females and one male, range 40-76 years (mean age 55.8 years (±10.4 years)).

Detection of malignancy suspect lesions on BRMI and CEM

A total of 32 core needle biopsies were taken of malignancy suspect lesions and analysed. 30 from index lesion of each participant, as well as one additional finding in the contralateral breast in two participants (table 2). The histopathology analysis showed 27 of 32 (84.4%) biopsies with malignant diagnosis and 5 of 32 (15.6%) were negative/benign. One of the negative cases and a fibroadenoma was the findings in the contralateral breasts.

Table 2
Histopathological diagnosis of study population

Total of included core needle biopsies	**32**	
Malignant diagnosis (%)	*27 (84,4)*	
IDC		*5*
IDC+DCIS		***12***
ILC		*4*
ILC + LCIS		*1*
ILC&ITC		*1*
ILC&ITC + DCIS		*1*
IMC + DCIS		*1*
DCIS		*2*
Negative/benign diagnosis (%)	*5 (15,6)*	
Negative		*4*
FA		*1*

Note: ICD = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, ILC = invasive lobular carcinoma, LCIS = lobular carcinoma in situ, ITC = invasive tubular carcinoma, IMC =invasive mucinous carcinoma, FA= fibroadenoma

The number of positive and negative cases can be found in table 3. BRMI was found to have a slightly higher sensitivity than CEM, 96,3% versus 92,6%. The accuracy for the BRMI and CEM were 93,6% and 87,5% respectively. The FN-case on BRMI was a DCIS stage 1&2, detected on the LE-image on CEM due to microcalcifications (fig. 2). The first FN on CEM was a DCIS stage 1 without microcalcifications, only seen on BRMI as non-mass enhancement (fig. 3). The second FN on CEM was an IMC + DCIS. A lesion interpreted as likely benign on the LE-image and without enhancement on
the R-image, appeared with rim-enhancement on BRMI (fig. 4). A fibroadenoma with contrast enhancement on both examinations was classified as false positive (FP) on CEM, but as true negative (TN) on BRMI due to a type 1 kinetic enhancement curve on BRMI (fig. 5). One case was FP on both BRMI and CEM (fig. 6). This finding was intraductal hyperplasia (without atypia) in the contralateral breast where breast cancer surgery previously has been performed.

Table 3
2x2-tables for BMRI and CEM compared to the histopathological results

		Histopathological
	Malignant	Negative/benign
BRMI	*True positive*	*False positive*
	26 (81.25%)	**1** (3.125%)
	False negative	*True negative*
	1 (3.125%)	**4** (12.5%)
CEDM	*True positive*	*False positive*
	25 (78.125%)	**2** (6.25%)
	False negative	*True negative*
	2 (6.25%)	**3** (9.375%)

Note: Number in parentheses = % of total number cases.

Assessment of total extent of disease

29 measurement was registered om BRMI and CEM, of which 28 on both examinations. On BRMI, mean size was 49.9mm (range 5-120mm) and on CEM, 29 (range 5-125mm). Test for normality showed $p = 0.146$ for BRMI and $p = 0.70$ for CEM.

The correlation-test (PCC) showed that there was a strong positive correlation between the variables, $\boldsymbol{r} = 0{,}872$, $\boldsymbol{n} = 28$, $\boldsymbol{p} = < 0.001$ (fig.7).

Discussion:

This study showed a better diagnostic performance for BRMI than CEM. Compared with the pooled sensitivity from two meta-analysis (11, 12). CEMs result is lower and BRMI is on the same level. Xiang et al. (11) analysed 13 studies published between 2011 – 2018, using QUADAS-2, a tool for a systematic evaluation of diagnostic performance studies (12). The pooled sensitivity were 97% for both BRMI and CEM, and they concluded that both techniques are effective in breast cancer detection. Neeter et al. (13) also used QUADAS-2 including 6 studies with participants from the same subgroup – recalled women with suspicious breast lesions, published between 2015 – 2020. They found a slightly lower pooled sensitivity for CEM than BRMI (96% vs. 97%).
Kamal et al. (14) investigated a comparable subgroup as in this study – indeterminate lesions, and found that BRMI performed slightly better with a sensitivity of 97% and accuracy of 90.6% versus CEM with 94,2% and 85,4%. Łuczyńska et al. (15) on the other hand found the results from CEM more reliable than from BRMI, with an accuracy of 79% vs. 73%, but this was not found statistically significant. However, results between different studies cannot necessarily be generalized. The designs of these studies are different to our, which hampering a direct comparison between them.

Before implementing of a new breast imaging method, the false negatives and false positives should be investigated to get an understanding of the implication of an implementation. To achieve a high sensitivity score, the proportion of FN examinations must be low. A FN examination could lead to delayed or even missed diagnosis, that may put a patient's health and survival at risk. Nevertheless, FN-cases will occur on both BRMI and CEM even if their sensitivity is very high (>90%). Causes for FN can be technical, perceptual or cognitive (16, 17, 18). Technical errors, such as artifacts, patient motions, incomplete visualization of finding (outside field of view) may occur during the examination.

Perceptual errors are when abnormalities, such as atypical appearance, small lesions or poor lesion conspicuity, are not identified or detected at the primary interpretation (prospective). Fatigue is an example of human error that can cause perceptual errors. Cognitive errors are e.g., misinterpretation of suspicious lesions as benign or as secondary to postsurgical changes. Incorrect clinical information and lack and lack of experience can also result in cognitive errors.

The two cases of pure DCIS in this study are both classified as FN, but on opposite examinations. The FN on CEM is a non-calcified DCIS g. 1 and the FN on BRMI showed no enhancement on either examination, but visible as calcifications on the LE-image. This is consistent with what is associated with DCIS (17). The higher grade of the DCIS more likely is it to enhance on BRMI (19), and this probably applies to CEM too (17). A plausible cause for lack of enhancement is absence of angiogenesis in DCIS (19). Limited is data available on CEMs role in detection of DCIS (20), but Yang et al. experienced similarities in enhancement pattern between the techniques in their recent study (17). Assessment of both the LE-image and the RI-image is important to prevent FN DCIS' on CEM, as these two images complement each other (20).

The second FN on CEM was a mucinous carcinoma (MC), a rare subtype of invasive ductal carcinoma (21, 22) . MC often appear as homogenous lobular masses with rim-like or heterogenous internal enhancement on BRMI. The presence of aqueous mucin; gives high signal in T2W-seqiences, and round well-defined masses with low density on the LE-image (up to 20% can be occult). MC may show weak or no enhancement on the RI-images (7). This correspond to our finding. MC can be overlooked or as in this case, misinterpreted as benign, and be a potential pitfall on CEM.

A high FP-rate is not desirable either. This can lead to the unnecessary use of diagnostic imaging, unnecessary interventions and, not least, it could lead to psychological distress in patients awaiting results of the additional examinations. FN-findings are not uncommon for BRMI or CEM (18, 20). Typical appearances of benign lesions are well known, but cases still could be hard to differentiate from malignant lesions. Fat necrosis, radial scar and fibroadenomas are typical benign lesions that may enhance. Doubtful cases should still be biopsied to rule out malignancy, even if they may result in FN-cases.

In this study two FP are observed on CEM, both as additional findings in the contralateral breast where the index findings was invasive cancers. One of these is also classified as a FP on BRMI. The histopathology analysis for this FP-lesion showed usual ductal hyperplasia, which can be associated with benign radial scars (23). This FP-lesion was observed in a breast previously undergone breast-conserving surgery. The last FP-case, a fibroadenoma was classified as uncertain on CEM, but likely benign on BRMI due to the added information the kinetic enhancement curves provides on BRMI.

There was a strong positive correlation between measured extent of disease on BRMI and CEM. This result can be supported by Fallenberg et al. (24) that showed a correlation between BRMI and CEM of PCC 0.943. They also observed a slightly higher correlation for CEM to histopathological result than BRMI to histopathological result (PCC 0.733 vs. 0.654).

Extent of disease is a factor that is taken into consideration in preoperative staging, and can be decisive for the choice of surgical method (3). Studying correlation between BRMI and CEM has some inherent bias'. The positioning of a pliable breast – prone position in a coil during BRMI and compressed in in two views during CEM, makes it challenging to measure the exact same planes (25). Underestimation may increase the risk residual disease and a reoperation, while overestimation may increase the mastectomy rates (3, 26).

Overall, our experience from this study is that both BRMI and CEM has their advantages and limitations. It is important to recognize them to be able to optimize their use in a clinical practice. CEM has potential to become a valuable problem-solving tool in cases with indeterminate findings.

This study has some limitations that must be taken into consideration. It is a single centre study with few participants from a homogenous patient group, and this may have influenced the results. The radiologists were not completely blinded during the interpretation of the examinations. This could have affected the results; due to the additional information they may have gained from previous mammography- and ultrasound examinations. However, in an everyday clinical setting a final conclusion in a breast cancer investigation is based on all available information (10). This study was conducted before the standardized BIRADS lexicon for CEM was published in 2022 (10). Interpretation according to a standardized lexicon with morphological descriptors seen on CEM, could provide a more optimal analysis and reporting of the examination.

In conclusion

There were registered false positives and false negatives on both techniques, but the overall diagnostic performance was slightly better for BRMI than CEM. There was a strong correlation in assessment of extent of disease. CEM has potential to become a valuable problem-solving tool in cases with indeterminate suspicious findings.

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Images and figure:

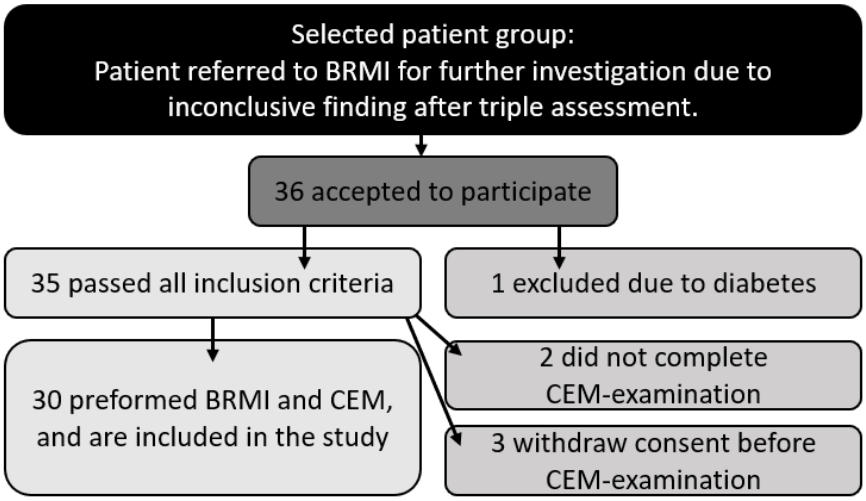

Figure 1: Overview of recruited participant.

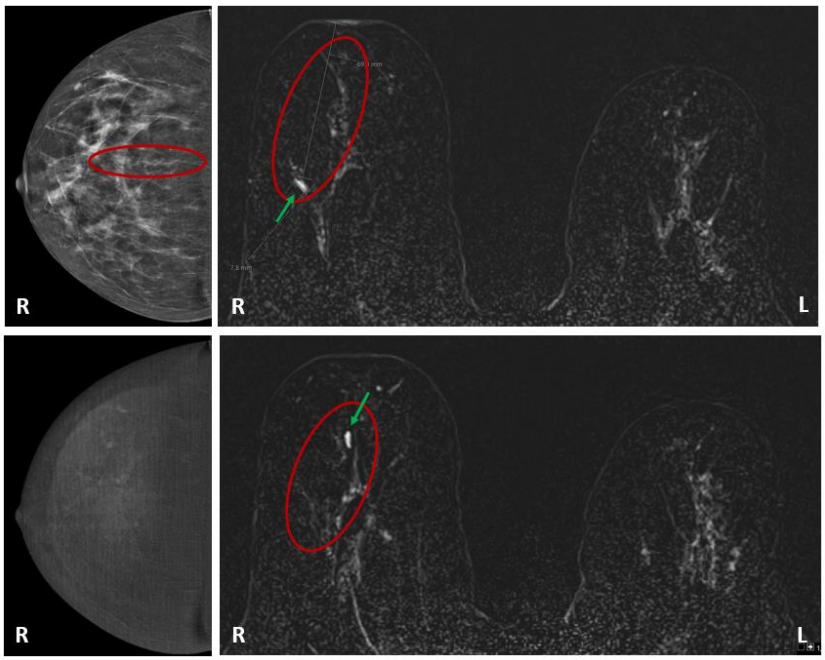

Figure 2: False negative case on BRMI. On the BRMI T1W-images (upper and lower right) the area (red circles) between two known fibroadenomas (green arrows) represent the location of the DCIS, but without any enhancement. CEM RCC LE-image (upper left) shows the microcalcifications (red circle), CEM RCC HE-image (lower left) shows no enhancement.

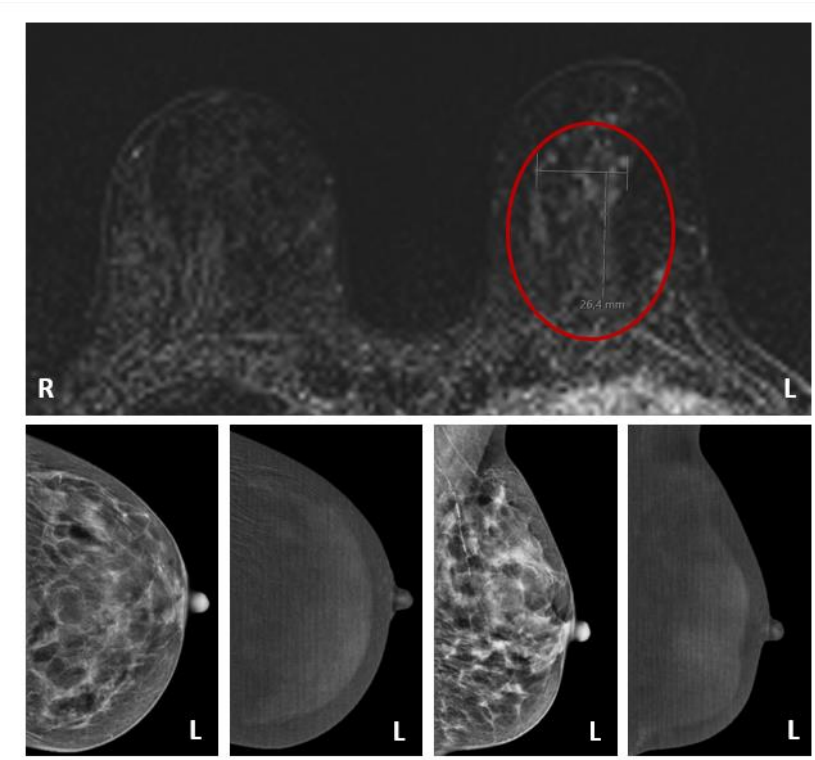

Figure 3: False negative case on CEM. DCIS is not visible on any LE- and HE-images of CEM (lower images). On the BRMI T1W-image is visible as area of non-mass enhancement (upper image).

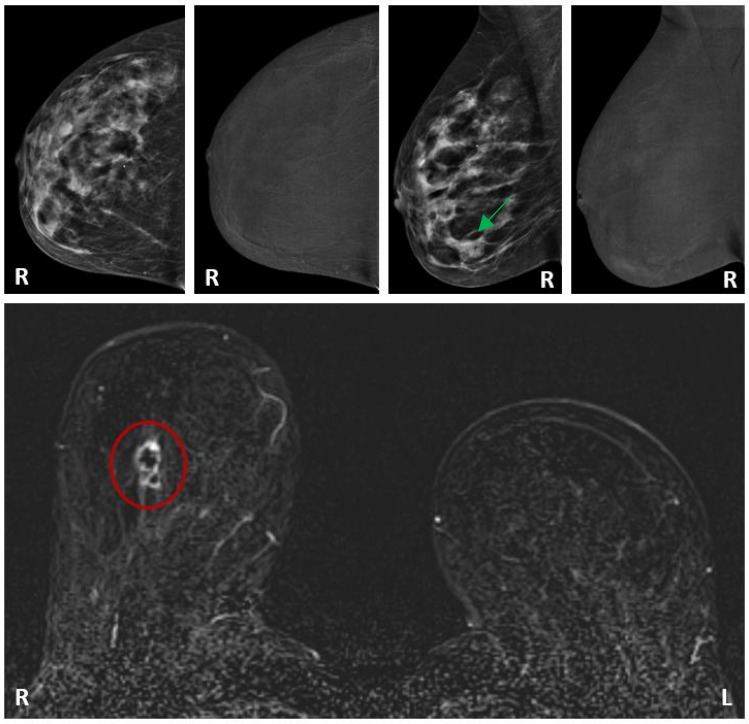

Figure 4: False negative case on CEM. Mucinous carcinoma interpreted as likely benign on CEM (upper images), shown as a well-defined lesion on the LE-image (green arrow), but with no enhancement on either HE-images. On BRMI T1W-image (lower image) observed with the typical rim-enhancement.

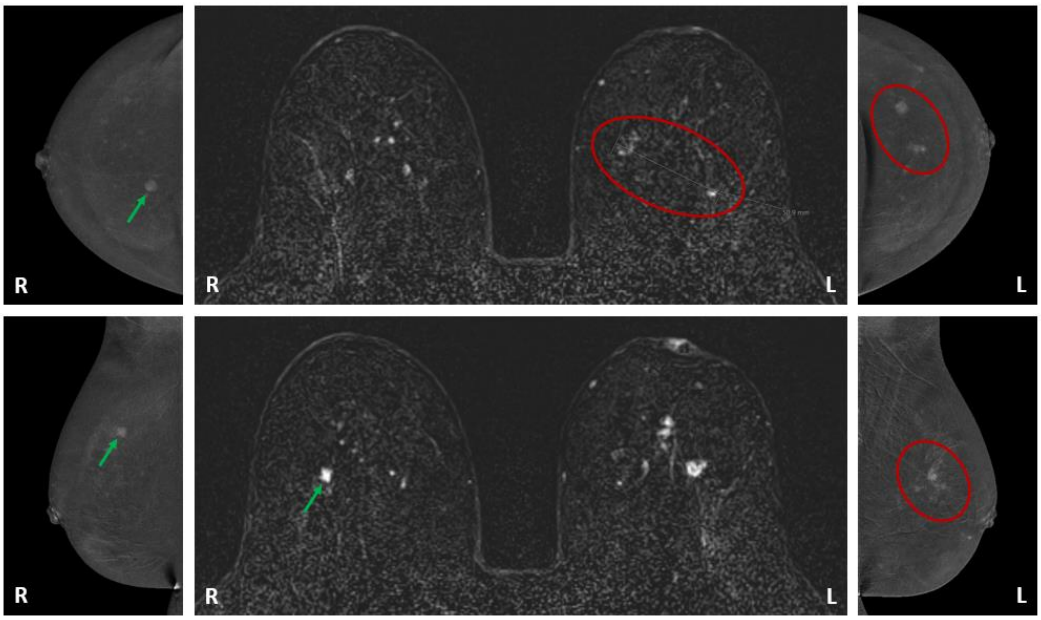

Figure 5: False positive case on CEM. The index finding (ITC + ITC/ILC) in the left breast is visible on both examinations (red circles). The additional finding (fibroadenoma) is also seen on both examinations (green arrows). Classified as uncertain on CEM, but likely benign on BRMI due to a type 1 kinetic enhancement curve. Biopsied to rule out malignancy.

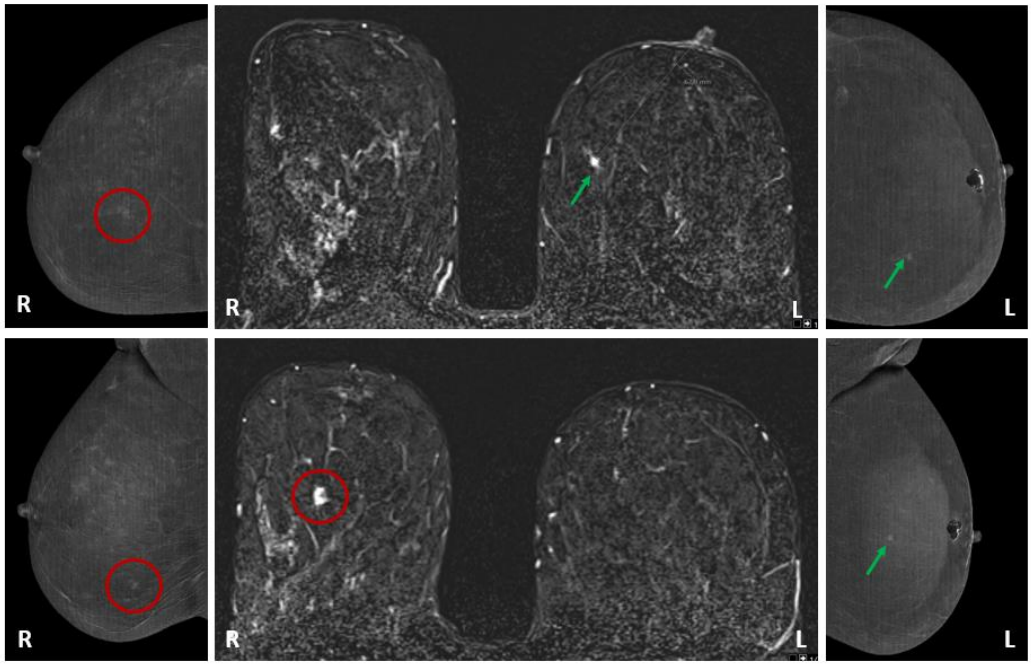

Figure 6: False positive case on both BRMI and CEM. The index finding (IDC + DCIS) in the right breast is visible on both examinations (red circles). The additional finding (intraductal ductal hyperplasia without atypia) in the left breast (that previously underwent breast conserving surgery) is also observed on BRMI and CEM (green arrows). Classified as uncertain and biopsied to rule out malignancy.

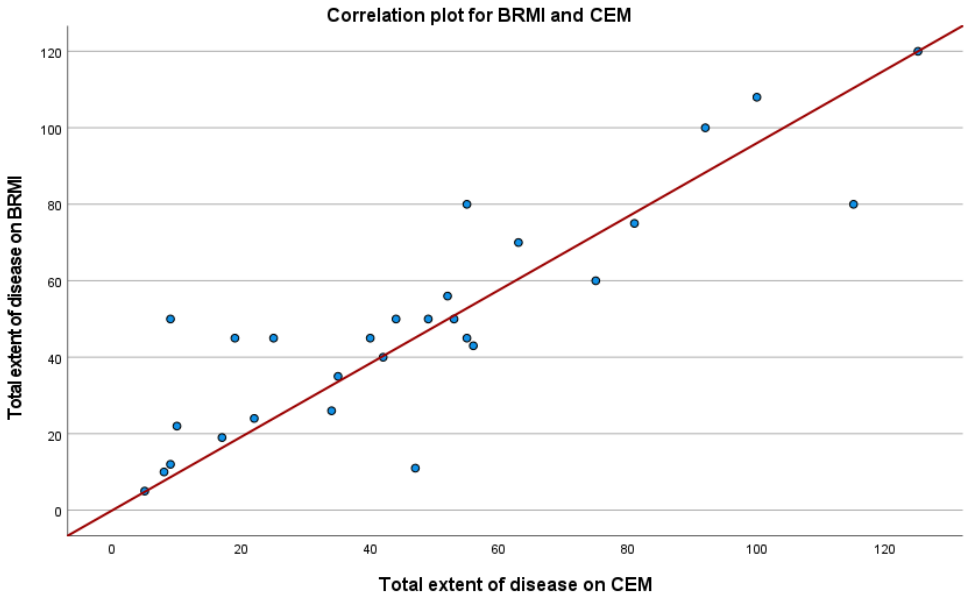

Figure 7: Scatter plot of correlation between BRMI and CEM.