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Contrast-associated risks of iodine-based contrast media administration in breast imaging: Tips and overview of existing evidence – A narrative review

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ABSTRACT

Background: Contrast-enhanced mammography (CEM) and dedicated breast computed tomography (dBCT) are advanced breast imaging techniques that utilize iodine-based contrast media (ICM) to improve the visualization of tumor vascularity. This review explores key challenges related to ICM use in these imaging modalities, focusing on hypersensitivity reactions (HR), acute kidney injury (AKI), and risk screening.

Methods: A narrative review was conducted to summarize the available evidence based on guidelines, recommended questionnaires, and relevant recent research. A literature search using PubMed and Embase identified guidelines on the safe use of ICM from January 2017 to February 2025, along with studies on CEM and dBCT. Keywords included (synonyms of) "iodine-based contrast media," "hypersensitivity reactions to ICM," "kidney function tests," "contrast-associated acute kidney injury," "contrast-induced acute kidney injury," and "contrast-enhanced mammography," "dedicated breast CT." Guidelines related to subspecialties, intra-arterial contrast administration, and outdated versions were excluded.

Results: Nine guidelines from international medical and radiological associations were included. While the majority of evidence comes from studies on contrast-enhanced computed tomography (CECT), the findings are applicable to CEM and dBCT as they use similar non-ionic low-osmolar ICM. HR with ICM is rare (0.3 %–0.7 %) but can be severe, with some requiring treatment (e.g., H1-antihistamines or intramuscular adrenaline). Any patient experiencing a mild HR should be observed for at least 30 min after administration. AKI occurs in at least 5 % of cases, which may rise to 30 % in patients with chronic kidney disease (CKD). Current guidelines suggest targeted testing for CKD risk using patient questionnaires, which is applicable to breast imaging, given the low prevalence of advanced CKD in this population.

Abbreviations: ACR, American College of Radiology; ADR, Adverse drug reaction; AI, Artifical intelligence; CA-AKI, Contrast-associated acute kidney injury; CECT, Contrast-enhanced computed tomography; CAR, Canadian Association of Radiologists; CEM, Contrast-enhanced mammography; CI-AKI, Contrast-induced acute kidney injury; CKD, Chronic kidney disease; CM, Contrast medium/media; dBCT, Dedicated breast computed tomography; DL, Deep learning; DRESS, drug reaction with eosinophilia and systemic symptoms; eGFR, estimated glomerular filtration rate; ESUR, European Society of Urology; GAN, Generative Adversarial Network; GBCM, Gadolinium-based contrast medium/media; HR, Hypersensitivity reaction; ICM, Iodine-based contrast medium/media; IV, Intravenous; IHR, Immediate hypersensitivity reactions; LOCM, Low-osmolar contrast media; NICE, National Institute for Health and Care Excellence; NIHR, Non-immediate hypersensitivity reactions; NSF, Nephrogenic systemic fibrosis; RANZCR, Royal Australian and New Zealand College of Radiologists (RANZCR); RSTN, Radiological Society of The Netherlands; SFMR, Swedish Society of Radiology.

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Conclusion: ICM risks in breast imaging are similar to CECT but tend to occur less often due to the lower-risk, non-urgent outpatient population. Both HR and AKI are infrequent, and at-risk patients can be identified through questionnaires.

1. Introduction

Contrast-enhanced mammography (CEM) and dedicated breast computed tomography (dBCT) are innovative techniques for evaluating breast tumour vascularity, providing valuable insights into tumour perfusion and enhancing breast cancer diagnosis accuracy [1]. CEM consists of a combination of low-energy (comparable to standard digital mammography [2]) and high-energy mammography images used to generate recombined images showing areas of contrast enhancement in a fashion comparable to breast MRI [3]. dBCT produces high-resolution, three-dimensional images of the uncompressed pendant breast [4–6] at radiation-dose in the range of mammography [7]. Recent studies have demonstrated that dBCT delivers high-quality imaging and holds promise as a viable alternative to mammography, particularly for patients reluctant to undergo the discomfort associated with breast compression [8]. Both CEM and dBCT require intravenous (IV) administration of iodine-based contrast media (ICM).

ICM administration introduces new challenges to breast imaging in the form of contrast-medium (CM)-associated risks such as hypersensitivity reactions (HR) and acute kidney injury (AKI). This necessitates risk screening, including kidney function determination, prior to contrast-enhanced imaging. Extensive experience using intravenous ICM exists in the field of radiology, especially for computed tomography. However, ICM administration for breast imaging is relatively new. The aim of this narrative review is to explore challenges related to ICM administration in breast imaging, based on evidence obtained from current (inter)national guidelines and original scientific studies pertinent to CEM/dBCT.

2. Methods

In this narrative, we address CEM and dBCT, which are similar to contrast-enhanced computed tomography (CECT) in terms of ICM administration. Specifically, both modalities use iso- or low osmolar non-ionic ICM, require similar iodine load (CM volumes of 90–150 ml with concentrations of 300–400 mg iodine/ml), and use an intravenous contrast administration route. Despite being a relatively new application for breast imaging, ICM in CEM and dBCT can therefore benefit from extensive evidence-based knowledge from CECT, supported by established and regularly updated guidelines on safe use of contrast media (Table 1).

Patient populations undergoing CEM and dBCT generally differ from those undergoing CECT. Breast imaging is not typically performed in high-risk, emergency, or inpatient settings, thus reducing some risk factors for adverse drug reactions (ADR) from CM.

2.1. Guideline search and inclusion

A literature search was conducted using the PubMed and Embase databases with keywords such as (synonyms of) “iodinated contrast media,” “hypersensitivity reactions to ICM,” “kidney function tests,” “contrast-associated acute kidney injury,” “contrast-induced acute kidney injury,” and “guideline.” The search was focused on identifying guidelines published between January 2017 and February 2025 addressing safe use of iodinated contrast media, to ensure the inclusion of the most recent advancements in this area. Guidelines from specific medical subspecialties, such as thyroid or cardiac associations; guidelines focused solely on intra-arterial contrast media administration; outdated versions of updated guidelines; non-English publications; and duplicate entries were excluded. Additional literature on ICM adverse effects was identified by cross-referencing included guidelines and seeking input from experts.

A total of 9 guidelines were selected for final inclusion in this narrative review, as determined by the authors (Fig. 1). These guidelines were developed by the European Society of Urogenital Radiology (ESUR); the American College of Radiology (ACR); the English National Institute for Health and Care Excellence (NICE); the Royal Australian and New Zealand College of Radiologists (RANZCR); Italian medical societies (SIRM, SIN, AIOM); the Japanese Society of Nephrology, Japan Radiological Society, Japanese Circulation Society (JSN, JRS, JCS) Joint Working Group; the Canadian Association of Radiologists (CAR); the Radiologic Society of The Netherlands (RSTN); and the Swedish Society of Radiology (SFMR). Additionally, extant questionnaires designed to assess risk of reduced kidney function prior to administering ICM were reviewed. These were selected based on the included guidelines and literature analysed in this narrative, with final selection made through consensus among all authors. In cases where guidelines lack comprehensive information on specific topics, such as the risk of contrast-related hypersensitivity reactions, scientific evidence based on published studies was used as reference in accordance with all authors of the present study.

2.2. Contrast-enhanced breast imaging literature review

In addition to reviewing the guidelines, we expanded our literature search by including keywords such as “contrast-enhanced mammography” and “dedicated breast CT.” This search focused on original studies related to contrast-enhanced breast imaging, specifically targeting research on CEM and dBCT to investigate the use of ICM in breast imaging.

3. Contrast-related hypersensitivity reactions

Acute ADR to intravenous ICM are classified into two types: Type A reactions (chemotoxic or physiologic reactions) and Type B reactions (HR). HR can be either allergic (immunologic mechanism, via IgE), or non-allergic (direct stimulation of other mast cell receptors). Based on the onset of symptoms, HR can be divided into two categories: immediate hypersensitivity reactions (IHR), developing within the first hour after administration (rarely up to 6 h), and non-immediate hypersensitivity reactions (NIHR), which can occur from one hour up to several days after administration [19,20]. HR can be further categorized into three general levels of severity using the ACR-classification: mild (isolated nausea/vomiting, mild urticaria/edema, scratchy throat, mild naso-ocular symptoms), moderate (severe vomiting, extensive urticaria, dyspnea without hypoxia, throat tightness or hoarseness); severe or anaphylaxis (laryngeal edema with stridor, bronchospasm with hypoxia, persistent hypotension with tachycardia, and generalized symptoms due to low cardiac output, cardio pulmonary arrest) [11]. NIHR often present as exanthems, particularly maculopapular rashes of mild to moderate severity and are usually self-limiting [19,21]. However, potentially life-threatening delayed severe HR can occur, such as acute generalized exanthematous pustulosis, DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome, Stevens-Johnson syndrome, or toxic epidermal necrolysis [22]. There are also very rare, case-based ADRs, including Kounis syndrome, SDRIFE (Symmetrical Drug-Related Intertriginous and Flexural Exanthema), Sweet Syndrome, iododerma, iodide sialadenitis, leukocytoclastic vasculitis and bowel angioedema. Among these, Kounis syndrome is a severe HR involving coronary vasospasm, atheromatous plaque rupture, or stent thrombosis,

Table 1
Indications for Renal Testing Prior to Imaging with Iodine-based Contrast Media and Recommendations from Published Guidelines on Safe Use of Contrast Media.

Guideline	Kidney Testing	Time for test	Identification of high-risk patients	Recommended mitigating strategies for high-risk patients
ESUR 10.0 (2018) [9,10]	eGFR; (a) In all patients or (b) In patients who have a history of; • Renal disease (eGFR < 60 ml/min/1.73 m2) • Kidney surgery • Proteinuria • Hypertension • Hyperuricemia • Diabetes mellitus	Within; −7 days (patients with an acute disease, acute deterioration of a chronic disease or inpatients) −3 months (all other patients)	−Consider patients as high risk for AKI if; • eGFR less than 30 ml/min/1.73 m2 • Known or suspected acute renal failure	−Prophylactic IV hydration methods are recommended. −Oral hydration is not supported. −Stopping nephrotoxic drugs before administering contrast agents is not generally recommended −Stop taking metformin from the time of ICM administration. Measure eGFR within 48 h and restart metformin if renal function has not changed significantly
ACR Committee on Drugs and Contrast Media (2024) [11]	eGFR; Only for patients with any of the risk factors; −Personal history of renal disease, including; −History of diabetes mellitus (optional) −Metformin or metformin-containing drug combinations[1] • Known chronic kidney disease • Remote history of AKI • Dialysis • Kidney surgery • Kidney ablation • Albuminuria	Within; −30 days (outpatients) −Shorter (inpatients)	−eGFR < 30 mL/min/1.73 m2 is relative but not absolute contraindication for ICM administration.	−Prophylactic IV hydration methods are recommended −N-acetylcysteine is not supported. −Stopping Metformin is not recommended (for IV).
NICE guideline NG148 (2023) [12]	eGFR; Only for high-risk patients determined with questionnaires including; • chronic kidney disease • diabetes but only with chronic kidney disease • heart failure • renal transplant • age 75 years or over • hypovolaemia • increasing volume of contrast agent • intra-arterial administration of contrast medium with first-pass renal exposure.	Within; −3 months	−Consider patients as high risk for AKI if; • eGFR less than 40 ml/min/1.73 m2	−Re-evaluating risk versus benefit of contrast media, particularly for patients with lower eGFRs when the risk is manageable. −Prophylactic IV hydration methods are recommended −Consider temporarily stopping ACE inhibitors and ARBs.
RANZCR(2018) [13]	eGFR; Only for high-risk patients with; • known kidney disease (including kidney transplant) • presence of diabetes • currently taking a drug containing metformin.	Decision based on clinical judgment	−Consider patients as high risk for AKI if; − The risk ofAKI is likely to be non-existent for patients with eGFR greater than 45 mL/min/1.73 *m* • eGFR less than 30 ml/min/1.73 m2	−-Prophylactic IV hydration methods are recommended −N – acetyl cysteine is not recommended. −Cease metformin for at least 48hrs
JSN, JRS, and JCS Joint Working Group** (2018) [10]	eGFR; All patients	Refers ESUR recommendations	−Consider patients as high risk for AKI if; eGFR less than 60 ml/min/1.73 m2 −	−-Prophylactic IV hydration methods are recommended −Oral hydration is not supported
Radiological Society of the Netherlands (2017) [14,15,9]	eGFR; All patients	Within; −7 days (acute disease or an acute deterioration of a chronic disease) −3 months (a known chronic disease with stable kidney function) −12 months (all other patients)	−Consider patients as high risk for AKI if; • eGFR less than 30 ml/min/1.73 m2	−Prophylactic IV hydration methods are recommended-For eGFR ≤ 15 ml/min/1.73 m2 or congestive heart failure consider alternative imaging without ICM.
SIRM-SIN-AIOM* (2022) [16]	eGFR; All patients	Within; − 7 days (unstable or	−Consider patients as high risk for AKI if;	−Prophylactic IV hydration methods are recommended −N-acetylcysteine is not supported.

(*continued on next page*)

Table 1 (*continued*)

Guideline	Kidney Testing	Time for test	Identification of high-risk patients	Recommended mitigating strategies for high-risk patients
		hospitalized patients) −3 months (other patients)	• eGFR less than 30 ml/min/1.73 m2	
Canadian Association of Radiologists guidance on contrast associated acute kidney injury (2022) [17]	eGFR; (Outpatients) Only if 'yes' to this question (Inpatients) Current eGFR should not delay emergent imaging examination • Do you have kidney problems or a kidney transplant? • Have you seen, or are you waiting to see a kidney specialist or urologist (kidney surgeon)?	Within; − 3–6 months (outpatients) − 7 days (inpatients)	−Consider patients as high risk for AKI if; • eGFR less than 30 ml/min/1.73 m2	−There is a lack of evidence on benefit of volume expansion −N-acetylcysteine is not supported.
Swedish Society of Radiology – contrast agent (2018) [18]	eGFR; (a) In all patients or (b) In patients with; Hospital inpatients • Known or suspected renal disease • Decreased kidney function (eGFR < 60 ml/min/1.73 m2) • Non renal risk factors • Age ≥ 65 years	Within; * 3 months is acceptable if no history of disease that may have affected kidney function • 12 days in hospital inpatients or patients with an acute disease that may affect kidney function • 7 days in all other patients	−Consider patients as high risk for AKI if; Non-renal risk factors: Diabetes, congestive heart failure (NYHA III/IV), dehydration, sepsis, hypoxia, liver cirrhosis, NSAID or nephrotoxic medication, and patients on dialysis with residual kidney function. • eGFR less than 45 ml/min/1.73 m2 irrespective of route of administration, especially if combined with multiple non-renal risk factors	−Prophylactic IV hydration methods are recommended. −Oral hydration alone is not recommended −Stop taking metformin from the time of ICM administration. Measure eGFR within 48 h and restart metformin if renal function has not decreased significantly

Abbreviations:
ESUR: European Society of Urogenital Radiology; ACR: American College of Radiology; NICE: National Institute for Health and Care Excellence; RANCZR: The Royal Australian and New Zealand College of Radiologists; CIN: Contrast-Induced Nephropathy; eGFR: Estimated Glomerular Filtration Rate; AKI: Acute Kidney Injury; ICM: Iodine-based Contrast Media.* Italian College of Radiology (SIRM), Italian College of Nephrology (SIN) and Italian Association of Medical Oncology (AIOM).
**Japanese Society of Nephrology, Japan Radiological Society, and the Japanese Circulation Society.
1 Metformin does not confer an increased risk of CI-AKI. However, patients who develop AKI while taking metformin may be susceptible to the development of metformin-associated lactic acidosis (MALA).

all of which can lead to myocardial ischemia [23].

Since the early discoveries of opaque mediums in roentgenography by Donald F. Cameron in the 1918s and the development of radiocontrast agents by Dr. Osborne in the 1920s, developments in ICM have enabled a shift from ionic high osmolar to non-ionic low-osmolar contrast media (LOCM), which cause fewer undesirable adverse effects [24–27]. Currently, LOCM are the most commonly used ICM in both CECT and CEM, and are most represented in available data [28]. Although these ICM cause fewer HR than the older high-osmolar contrast media, they are not risk-free, with overall HR frequency of varying between 0.3 %-0.7 % [19,11,29]. Mild IHR occur after 0.7 % to 3 % of intravenous administrations, and severe reactions after 0.02 % to 0.04 %. NIHR frequencies are estimated to range from 0.5 % to 14 % [11,30]. Similar incidences of HR in contrast-enhanced breast imaging were confirmed in a systematic review on CEM, with eight reported cases of ICM-related HR among 1022 patients, representing a rate of 0.8 % (0.7 % to 1.4 %) [31].

The occurrence of Type A reactions following the administration of ICM, though rare (0.01 %–0.04 %), typically presents with mild symptoms such as limited nausea/vomiting, transient flushing, warmth, chills, or hypotension with bradycardia. However, they may occasionally be serious, including cardiac arrhythmias, reduced myocardial contractility, cardiogenic pulmonary edema, and seizures [11]. Contrary to HR reactions, type A reactions are often dose- and concentration-dependent: iodine load − CM volume- as low as possible should be administered in any diagnostic imaging modality.

Mild immediate adverse drug reactions (ADRs), whether Type A or Type B, generally do not require treatment. Mild symptomatic urticarial reactions can usually be managed effectively with H1-antihistamines. However, mild reactions can progress to moderate or severe forms, and any patient experiencing a mild HR should be observed for at least 30 min to ensure clinical stability or recovery. It is also important to monitor vital signs repeatedly: hypotension may be clinically silent when a patient is supine. Most moderate reactions and all severe reactions require prompt treatment (such as intramuscular adrenaline) based on the specific type of reaction: guidelines on safe use of contrast agents provide detailed prevention and treatment strategies [20,11,13,32,33]. Updated ESUR Contrast Media Safety Committee guidelines provide detailed, severity-based treatment recommendations for hypersensitivity reactions; the current summary highlights the key decision points and immediate management steps drawn from these recommendations (Fig. 2) [20,33].

3.1. Risk screening and mitigation

The strongest predictor of future HR is a prior hypersensitivity or unknown type reaction to the same class of contrast agent [11]. Other antecedents, such as a history of sensitization to inhalants, foods, or drugs, or a previous allergic contact dermatitis, have been previously considered as risk factors [32]. However, current evidence does not support these conditions as established risk factors [34–36]. On the other hand, certain patient comorbidities should be considered, as they may increase the likelihood of HR as well as increasing HR severity. These conditions include uncontrolled urticaria or asthma, a diagnosis of idiopathic anaphylaxis, or systemic mastocytosis [36].

European guidelines [14] and recent ACR consensus statement [37] emphasize the importance of proper documentation of HR related to ICM in electronic health records (EHR) to improve the safety of contrast

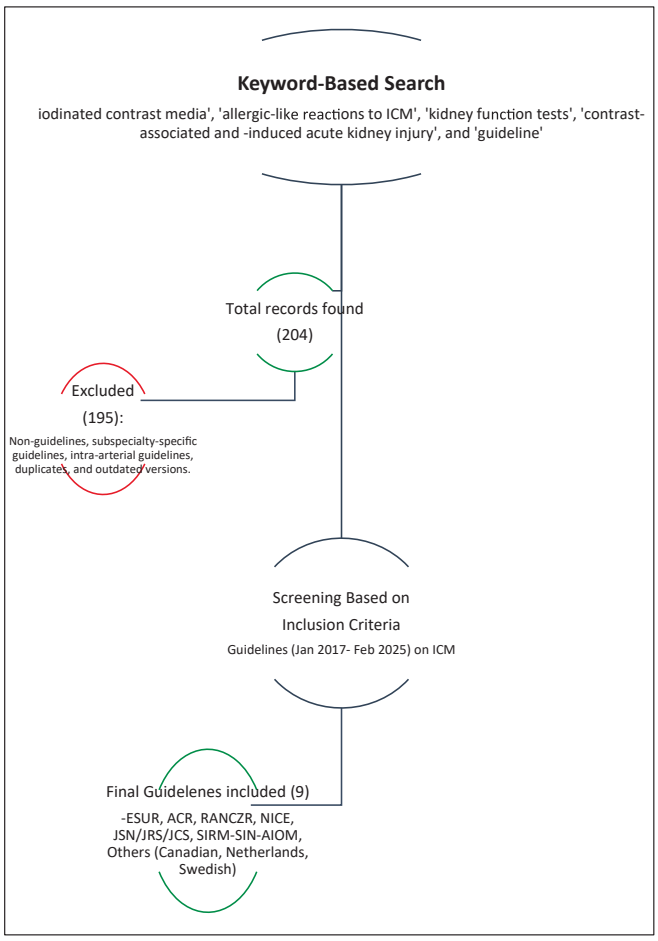

Fig. 1. Flowchart of "Guideline selection and inclusion process".

media use in at-risk patients. This includes documenting the date and location of the reaction, the specific contrast media used, the dose, the type of HR (immediate or non-immediate), symptoms, vital signs, treatments administered, patient response, consultation notes from a drug allergy specialist, clinical follow-up, and advice to see an allergy specialist. However, studies have shown that HR documentation in EHRs is often incomplete and insufficient [38]. While a questionnaire to detect previous hypersensitivity reactions cannot replace proper documentation, in the absence of detailed records, the following screening questions can help identify patients at risk for HR reactions to ICM: "Have you ever had a reaction after receiving a contrast injection (e.g., itching, rash, breathing difficulties, or hospitalization)?"; "Are you currently experiencing an exacerbation of your asthma or urticaria?"; "Have you experienced any prior episodes of anaphylaxis?"; and "Have you been diagnosed with mastocytosis?".

The high risk of HR in patients with a history of previous reactions presents a challenge when making recommendations for future imaging studies with ICM. For breast imaging, it may be preferable to consider alternative imaging modalities that do not require the administration of ICM, especially in patients with a history of severe HR in accordance with the latest recommendations from the ACR consensus [37] and updated ESUR guidelines [33].

For many years, premedication has been used before administering ICM in these patients [39,40]; however, there is growing consensus in Europe and the USA/Canada regarding its inefficacy [32,35,41,42]. Recently, a joint consensus statement by ACR and the American College of Radiology and the American Academy of Allergy, Asthma & Immunology, revised previous recommendations by stating that premedication is not necessary for patients with a history of mild immediate hypersensitivity reactions to ICM [37]. Currently, premedication appears to be considered only in emergency situations for patients with prior anaphylactic-type HR [34,43,44].

A more appropriate approach would be an empirical switch to another ICM [37,45–47], following one of the published classifications [48,49], or, when feasible, the selection of an alternative ICM based on the results of an allergy workup that includes skin testing, as recommended by RSTN guideline [14,15,9] and also supported by recent publications on the subject [34,50–52]. If the latter approach is considered, allergy evaluation may be completed by confirming tolerance through a controlled provocation test prior to administering the ICM that yielded a negative skin test result [20,32].

4. Contrast-associated acute kidney injury

ICM have been considered to pose a risk to renal function for a long time, as a decline in renal function is frequently observed following intravascular administration. To date, a direct causal relationship between ICM and renal impairment has not been definitively established. This lack of evidence has prompted a shift in terminology, favouring "contrast-associated" over "contrast-induced" to reflect the current understanding of the condition more accurately.

While there is a clear terminological distinction between contrast-associated acute kidney injury (CA-AKI) and contrast-induced acute kidney injury (CI-AKI) [11,32], separate clinical biochemical definitions enabling differentiation between the two are lacking. This is complicated further by the fact that distinguishing between CA- and CI-AKI requires studies with a control group receiving similar treatment but without intravascular ICM, which is not ethically feasible. For clinical practice it suffices to know that CI-AKI is considered a subset of CA-AKI [11]. Both CA- and CI-AKI refer to AKI, a sudden decline in kidney function that occurs within 48–72 h following the intravascular administration of ICM, and both are associated with poorer clinical outcomes. Where CA-AKI is a correlative diagnosis and can occur regardless of whether ICM is administered, CI-AKI, previously termed contrast-induced nephropathy (CIN), is a causative diagnosis and is directly caused by the administration of ICM.

4.1. Risk screening

Not all patients are at risk of developing AKI, with kidney function being the most important risk factor. There are minor patient-related risk factors, including advanced age, chronic kidney disease, diabetes mellitus, cardiovascular diseases, anaemia, and dehydration [11,28,32].

Additionally, there are procedure-related factors that contribute to the development of CA-AKI, such as the type of ICM, osmolality, administered volume (iodine load), route of administration (intravenous versus arterial), recent exposure to ICM, history of CA-AKI and emergency settings [53].

The risk of CA-AKI markedly increases in patients with chronic kidney disease (CKD). According to consensus statements from the American College of Radiology and the National Kidney Foundation [28], patients with an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 or higher, when receiving intravenous contrast media, have low risk of CA-AKI, with incidences approximately 5 %. This rises to 10 % for patients with eGFR levels between 45–59 mL/min/1.73 m^2, to 15 % for patients with eGFR between 30–44 mL/min/1.73 m^2, and up to 30 % for individuals with an eGFR below 30 mL/min/1.73 m^2 [28]. Most guidelines agree that there is currently little evidence to suggest that intravenously administered ICM is an independent risk factor for AKI in patients with an eGFR $\geq$ 30 mL/min/1.73 m^2 (Table 1). Therefore, eGFR $<$ 30 mL/min/1.73 m^2 is most often recommended as a threshold for AKI risk [11,28,32,36,9].

Because there is no treatment once AKI has occurred, prevention is important [28,17]. The first step is to consider alternative contrast-free imaging strategies for those with severely impaired kidney function.

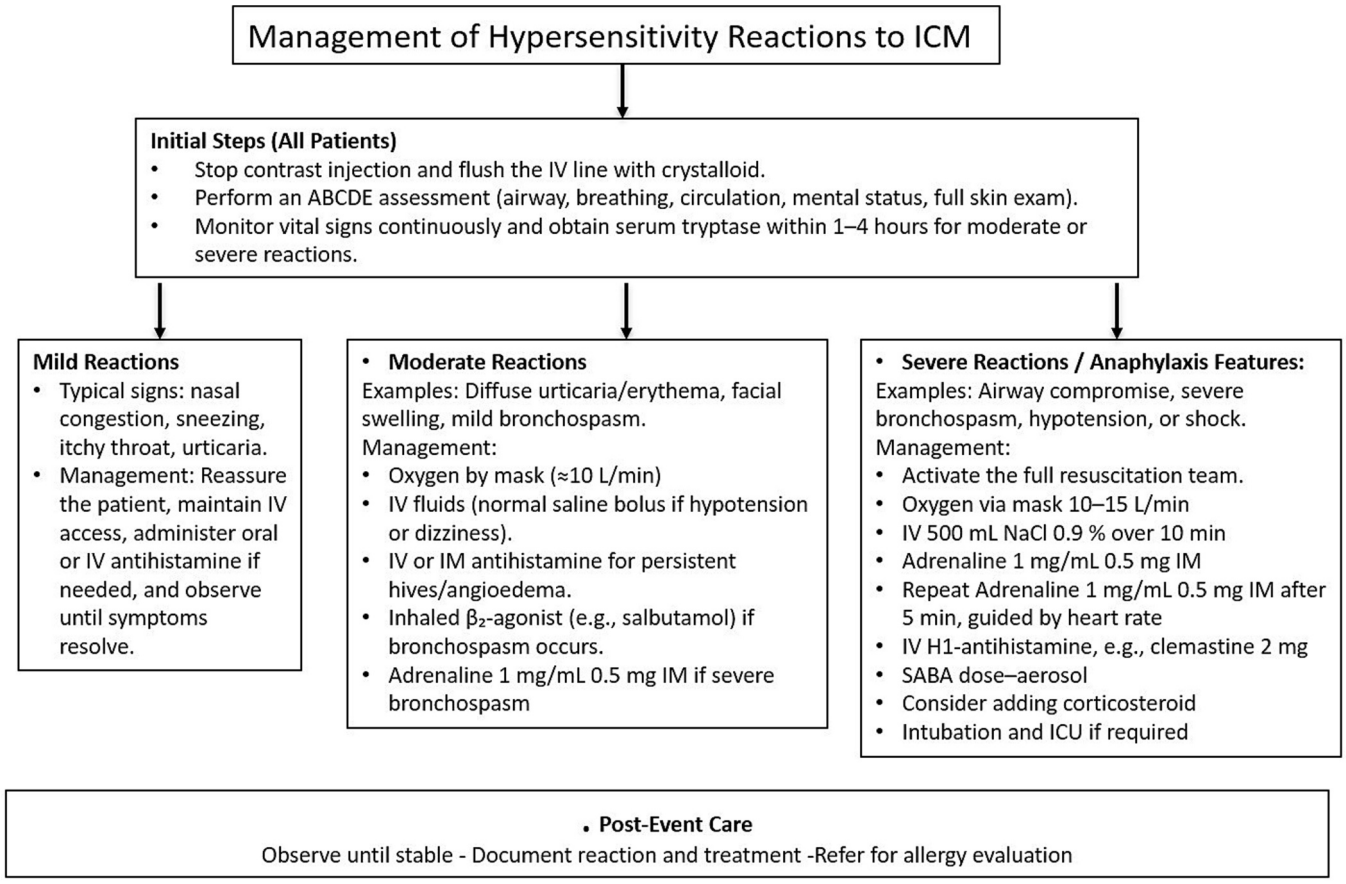

Fig. 2. Flowchart of "Management for hypersensitivity reactions".

This is especially relevant for patients referred for breast-imaging where other (well-established) breast imaging modalities can relatively easily be prioritized over imaging with ICM administration [54].

4.1.1. Kidney function testing prior to ICM administration in women scheduled for contrast-enhanced breast imaging

Identifying patients at risk of AKI is crucial for safe use of ICM. To date, comprehensive testing of kidney function before ICM administration was standard practice [9,55]. However, unlike emergency or inpatient procedures where patients have higher risk profiles, contrast-enhanced breast imaging is typically performed for breast cancer screening in outpatient settings among otherwise healthy women [53]. Additionally, compared to patients with advanced breast cancer or systemic diseases requiring other contrast-enhanced procedures, the risk of AKI is lower in women undergoing CEM or dBCT for screening, symptom evaluation, or localized breast cancer [10]. Also, the prevalence of advanced CKD (stages 4 and 5) is low in both the general population and among referrals for breast-screening. A large cohort study conducted in Ontario, Canada, between 2002 and 2013, to identify patterns and predictors of breast and cervical cancer screening in women with CKD included 141,326 participants and found prevalence of advanced CKD (stages 4 and 5) to be 0.7 %. The study results also highlighted that women with advanced CKD, particularly in older age groups, were significantly less likely to undergo breast screening compared to those without CKD [56]. Given this low prevalence, breast imaging may be suited for targeted kidney function testing instead of comprehensive kidney function assessment [10].

4.1.2. Use of questionnaire prior to ICM administration for targeted kidney function testing

Current international guidelines, including ESUR [32] and ACR [11], advocate targeted kidney function testing in patients at high risk of CKD, rather than universal assessment as suggested by the RSTN guideline (Table 1) [14,15,9]. This approach is supported by a validation study that found only 1.1 % of outpatients had an eGFR < 30 mL/min/1.73 m^2. Targeted testing strategies suggested by guidelines, based on CECT, can identify over 92.6 % of severe renal insufficiency cases, with a high negative predictive value (>99.9 %), reducing kidney testing from comprehensive to 16.9 % (ACR) and 38.8 % (ESUR) [57]. Considering these findings, targeted kidney function screening in breast imaging is expected to be an effective and efficient approach, minimizing unnecessary testing while ensuring patient safety.

Selecting patients for kidney function tests before administering ICM requires clear characterization. However, there is currently no consensus on which risk factors should necessitate pre-contrast media kidney function testing, aside from known kidney disease and diabetes [13]. Table 2 presents guideline recommendations—ESUR, ACR and RANZCR—aimed at CKD risk assessment to determine the need for kidney testing prior to contrast-enhanced imaging using ICM [11,32,13]. Two examples of structured questionnaires are provided in Appendix 1; the Choyke [58] questionnaire, which is generalized for all contrast-enhanced imaging with ICM, and the Parillo et al. [10] questionnaire, developed by systematic analysis of the literature. Both questionnaires contain six questions and are designed to enhance patient safety, minimize imaging delays, and reduce unnecessary testing and resource consumption [59].

CEM and dBCT are considered cost-effective breast imaging alternatives to breast MRI [1,60]; however, renal testing prior to these ICM-based modalities adds extra costs, potentially diminishing their cost-effectiveness. Some studies have explored point-of-care (PoC) creatinine tests using finger-stick sampling for renal assessment, which is cheaper and quicker than laboratory assays, but the method proved

Table 2
Patient questionnaires assessing the need for kidney function testing before imaging with iodine-based contrast media.

Reference	Question(naire)	Additional Information
ESUR (2018) [32]	−History of; −Currently using medications (metformin, IL-2, NSAIDs, Aminoglycosides, beta blockers) • Heart Failure • Diabetes Mellitus • Renal disease • Renal surgery • Proteinuria • Hypertension • Gout • Most recent measurement of creatinine	Provides a questionnaire for ICM that referral clinicians can complete, also featuring questions to assess the risk of allergy
ACR (2024) [11]	−History of; • Known chronic kidney disease • AKI • Dialysis • Kidney surgery • Kidney ablation • Albuminuria • Diabetes mellitus (optional) • Metformin or metformin-containing drug combinations	Not established questionnaire but recommends questioning some risk factors
RANZCR (2018) [13]	Do you have ANY of the following; • Kidney disease (acute or chronic) or kidney transplant? • Current dialysis −– permanent dialysis? • Current dialysis −– temporary dialysis? • Diabetes? • Currently taking metformin?	−Recommendation based on systematic reviews and international guidelines, emphasizing their lack of consensus on which risk factors necessitate pre-contrast media kidney function testing, aside from known kidney disease and diabetes. −Questionnaire focuses on a few risk factors identified in multiple studies

Abbreviations:
ESUR: European Society of Urogenital Radiology; ACR: American College of Radiology; RANCZR:The Royal Australian and New Zealand College of Radiologists; AKI: Acute Kidney Injury; ICM: Iodine-based Contrast Media. NSAID: Non-Steroidal Anti-Inflammatory Drug.

unreliable for detecting renal impairment in patients recalled for CEM [61]. A recent comparative cost-analysis study including 447 patients from a single center found that using a risk-stratified pathway with a questionnaire before renal testing could lead to estimated 5-year savings of £69,620 for this population [59].

Referral pathways for contrast-enhanced breast imaging with iodinated contrast media are summarized in a flowchart in Fig. 3.

4.2. Risk mitigation

Patients with eGFR > 45 mL/min/1.73 m^2 are not considered at risk of developing CA-AKI, and contrast-enhanced breast imaging is deemed safe for this group. Even for patients with eGFR between 30–45 mL/min/1.73 m, IV administration of ICM is generally considered non– or only minimally nephrotoxic. Most guidelines do not categorize this group as high-risk for CA-AKI, and therefore contrast-enhanced breast imaging can also be considered safe (Table 1) [11,32,13,9].

For patients with eGFR < 30 mL/min/1.73 m^2 or actively declining renal function (as in acute renal insufficiency), a careful risk–benefit analysis is essential. As contrast-enhanced breast imaging with ICM is not typically urgent or irreplaceable, alternative breast imaging methods should be considered. If contrast-enhanced breast imaging with ICM is planned for this patient group, guidelines recommend prophylactic hydration (Table 1) [11,32,13]. For instance, ESUR recommends IV hydration either by: (a) administering sodium bicarbonate (1.4 % or 154 mmol/L in 5 % dextrose water) at 3 mL/kg/hour for 1 h prior to the contrast medium, or (b) using saline (0.9 %) at 1 mL/kg/hour for 3–4 h before and 4–6 h after the contrast medium administration [32].

5. Contrast-induced thyrotoxicosis

Administration of ICM may lead to thyroid function disturbances in at-risk patients due to the presence of free iodide in the contrast solution, but it does not affect thyroid function in individuals with a normally functioning thyroid gland [11]. According to recent guidelines, including those of the European Thyroid Association [62] and ESUR [12] iodinated contrast–related thyrotoxicosis is classified as a very late adverse reaction. Reported frequencies of ICM-induced thyroid dysfunction vary widely, ranging from 0.05 % to 22 % [16]. Routine thyroid function testing before ICM injection is not necessary in patients with normal thyroid function. The risk group for iodine-induced thyrotoxicosis includes individuals with untreated Graves' disease and those with multinodular goiter with thyroid autonomy. For patients suspected to be at risk of thyrotoxicosis, TSH measurement can be helpful [32]. ICM should not be administered to patients with manifest hyperthyroidism. Routine prophylaxis is generally unnecessary, but endocrinology follow-up is advised for individuals at risk. In selected high-risk cases—particularly in regions with dietary iodine deficiency—prophylactic treatment may be considered under endocrinologist supervision [12]. A recent prospective investigation from the Swedish CArdioPulmonary bioImage Study (SCAPIS) evaluated 422 randomly selected adults aged 50–65 years who underwent contrast-enhanced coronary CT angiography. The findings indicate that, in iodine-sufficient countries, iodinated contrast–related thyroid dysfunction is uncommon, typically mild, self-limiting, and largely oligo- or asymptomatic in this age group [16].

These considerations, while derived from experience with CECT, apply equally to ICM-based breast imaging techniques. Before the procedure, patients should be asked directly, "Do you have a hyperfunctioning thyroid or have you been diagnosed with hyperthyroidism?" Individuals identified as being at risk should then be evaluated appropriately. For patients who are not in a risk group, routine thyroid function testing is unnecessary, and breast imaging using ICM can proceed without additional screening.

6. Comparison of gadolinium-based contrast media and ICM

When comparing ICM used in CEM or dBCT with GBCM used in breast MRI, the overall pattern of acute hypersensitivity reactions is similar, although the incidence is slightly higher with ICM [11,32]. Clinical doses of GBCM (0.1–0.2 mmol/kg) are associated with very low overall adverse event rates, ranging from 0.07 % to 2.4 %. Typical reactions are mild and physiologic, such as transient warmth or coldness at the injection site, nausea, headache, paresthesias, or dizziness. Allergic-like reactions are uncommon (≈0.004 %–0.7 %) and resemble those seen with iodinated contrast agents. Severe, life-threatening anaphylaxis is exceedingly rare, reported at only 0.001 %–0.01 % [11]. Importantly, there is no cross-reactivity between iodinated and gadolinium-based agents, and patients with prior reactions to one do not have an increased risk for the other [11].

In terms of renal safety, ICM are primarily linked to AKI, whereas GBCM have been implicated in nephrogenic systemic fibrosis (NSF)—a very rare but potentially severe condition, observed almost exclusively in patients with advanced chronic kidney disease (CKD stage 4–5, eGFR < 30 mL/min/1.73 m^2) or on dialysis [32,13]. With modern macrocyclic group II GBCAs, the estimated NSF risk is extremely low (<0.07 %), while AKI remains a relevant consideration for iodine-based agents, especially in volume-depleted or high-risk patients. Although emerging data have raised awareness of possible long-term tissue deposition and environmental accumulation of gadolinium, the clinical implications

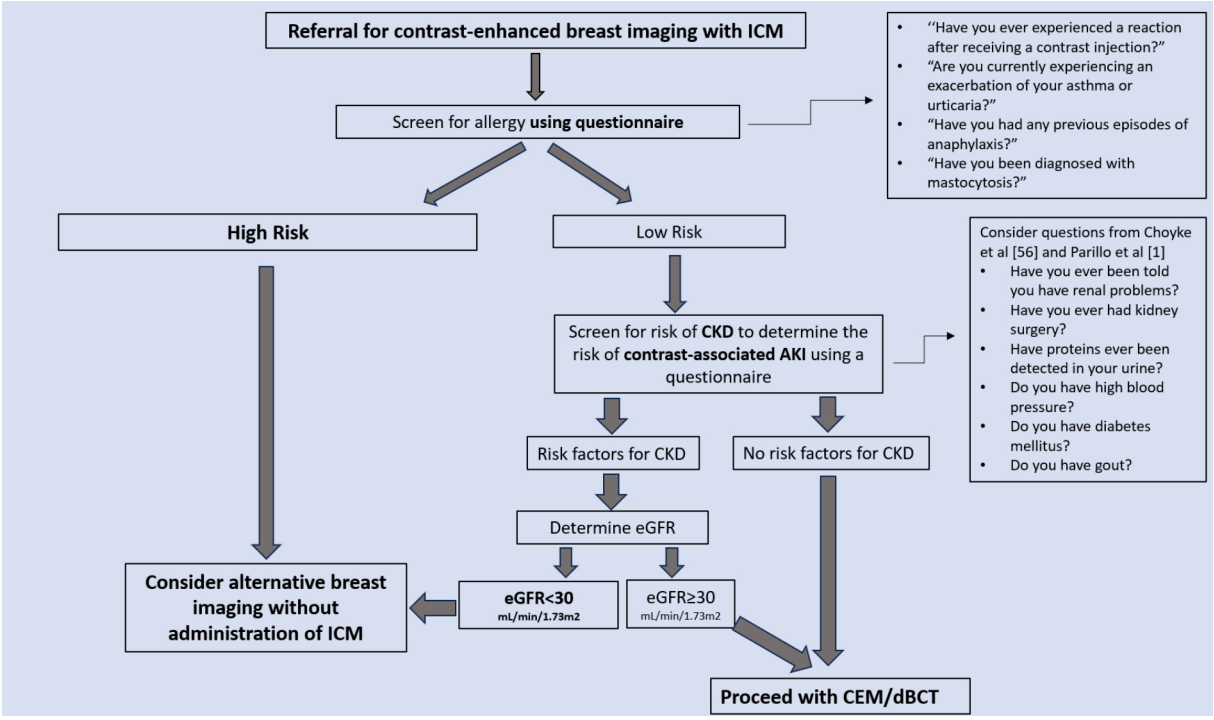

Fig. 3. Flowchart of "Referral for contrast-enhanced breast imaging".

remain uncertain [18,63,64]. In practice, these distinctions primarily influence patient selection, pre-scan counselling, and risk mitigation strategies, while a detailed comparison of diagnostic performance between both contrast types is beyond the current scope of this review.

7. Future directions: Artificial intelligence for contrast reduction

While iodinated contrast media currently remain the standard for CEM and dBCT and gadolinium-based contrast media for breast MRI, recent advances in artificial intelligence (AI)—particularly deep learning (DL) methods—have sparked growing interest in reducing or even replacing contrast media through AI-based, contrast-free imaging approaches. For instance, a study applying DL for virtual contrast enhancement in CEM demonstrated that Generative Adversarial Networks (GANs), particularly CycleGAN, were highly effective in generating synthetic recombined images, underscoring the potential of AI techniques for virtual contrast enhancement in this setting [65]. Likewise, multiple studies using DL-based reconstruction have reported significant reductions in the required dose of injected contrast agent [66–68]. Similarly, promising results from GAN-based breast MRI research suggest the feasibility of achieving diagnostic image quality with reduced contrast agent doses [69].

Although these approaches are still largely confined to early research and small pilot studies, their potential adaptation to contrast-enhanced breast CT warrants further investigation. Robust prospective validation in larger cohorts, technical standardization, and regulatory approval will be essential before clinical implementation. For now, iodinated contrast media remain the standard for CEM and dBCT, and therefore our review's focus on hypersensitivity and acute kidney injury risk screening remains clinically relevant.

8. Summary

Contrast-enhanced mammography and dedicated breast computed tomography are new breast imaging techniques using intravenous ICM. Due to their novelty, there is a lack of evidence on ICM-based breast imaging studies, including risks and potential complications such as contrast-related HR reactions, and AKI. Given their similarities to contrast-enhanced CT, existing ICM guidelines apply to these methods. Consequently, there is currently no reason to deviate from existing guideline-recommendations on intravenous ICM administration for contrast-enhanced breast imaging.

HR is one of the first concerns when using ICM, which may be unfamiliar to breast imagers since ICM is not commonly used in other breast imaging modalities. Although HR are uncommon (0.3 % to 0.7 % in recent series), rare cases can be severe. It is advisable to identify patients at risk through pertinent questions before ICM administration, to consider alternative imaging without ICM for patients at risk of HR, and to keep patients under observation for at least 30 min after ICM administration.

A second concern is risk of AKI, although consensus is that this applies only to patients with advanced kidney disease (eGFR $<$ 30 mL/min/1.73 m^2) whose prevalence is low (0.7 %). While some guidelines recommend routine kidney function testing, recent guidelines (ESUR, ACR, RANZCR) suggest a more selective approach, testing only patients with CKD risk factors. This reduces unnecessary testing while maintaining high accuracy, identifying over 92.6 % of severe renal insufficiency cases with a negative predictive value $>$99.9 %. Given the low prevalence of advanced CKD in the target population, this approach is well-suited for breast imaging with ICM.

To conclude, challenges associated with ICM in breast imaging are similar to those encountered in CECT. Risks of both HR and AKI are low, and patients at risk can be identified through patient questionnaires.

CRediT authorship contribution statement

T.J.A. van Nijnatten: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **E. Meltem:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **A.J. van der Molen:** . **M. Parillo:** Writing – review & editing, Methodology, Conceptualization. **C.A. Mallio:** Writing – review & editing, Methodology, Conceptualization. **C.C. Quattrocchi:** Writing – review & editing,

Methodology, Conceptualization. **F. Vega:** Writing – review & editing, Methodology, Conceptualization. **M.N.J.M. Wasser:** Writing – review & editing, Methodology, Conceptualization. **J.E. Wildberger:** Writing – review & editing, Methodology, Conceptualization. **E.C. Nijssen:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2025.112481.

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