

COMMENTARY

Medico-legal implications of off-label iodinated contrast media use in contrast-enhanced mammography: Between regulatory status and emerging clinical evidence

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Abstract

Contrast-enhanced mammography (CEM) has emerged as a high-performance diagnostic tool, showing comparable accuracy to breast magnetic resonance imaging. However, a clinical-regulatory gap persists: although international guidelines increasingly support CEM, most iodinated contrast agents used for CEM may lack product-specific regulatory approval for breast imaging applications in certain jurisdictions; their use in those settings is therefore off-label. This commentary explores the medico-legal implications of this discrepancy, emphasizing the necessity of rigorous clinical protocols, enhanced informed consent, and institutional governance. Rather than proposing ready-to-use operational documents applicable in all jurisdictions, the manuscript outlines the essential elements that should be incorporated into standardized safety pathways and dedicated informed consent procedures to support risk management and medico-legal compliance. By integrating current clinical evidence—including the RACER trial—with ethical and legal considerations, this commentary proposes a practice-oriented medico-legal framework that may assist institutions in developing jurisdiction-specific protocols for the safe implementation of CEM. The adoption of CEM as an increasingly evidence-supported imaging technique should therefore be accompanied by appropriate regulatory awareness, explicit informed consent, and standardized institutional procedures.

Keywords: Contrast-enhanced mammography; Iodinated contrast media; Off-label use; Medico-legal implications; Patient safety; Informed consent; Breast cancer diagnosis; Clinical governance

Contrast-enhanced mammography (CEM) has become an established functional breast imaging technique by combining digital mammography with the intravenous administration of iodinated contrast media (ICM), enabling the simultaneous assessment of breast morphology and tumor neoangiogenesis.¹⁻⁶ Diagnostic studies, systematic reviews, and randomized clinical trials have demonstrated that CEM provides high diagnostic accuracy for lesion detection, characterization, and preoperative staging, with performance approaching that of breast magnetic resonance imaging, while offering advantages in terms of accessibility, examination time, and cost-effectiveness.¹⁻⁸

Although these data have supported the rapid clinical adoption of CEM, the widespread implementation of the technique has also highlighted an important clinical-regulatory gap. Unlike computed tomography (CT), where the administration of ICM is supported by well-established regulatory indications and consolidated clinical pathways, the use of ICM in CEM remains predominantly an off-label application in many jurisdictions because currently available contrast agents are approved for intravascular radiological procedures but not specifically for mammographic imaging.⁹⁻¹¹

This discrepancy is particularly relevant because the expansion of CEM has been considerably faster than the development of dedicated recommendations governing contrast administration in this setting. Consequently, issues related to the appropriate selection of iodinated contrast agents, injection protocols, patient eligibility, prevention and management of adverse reactions, informed consent, professional liability, institutional governance, and clinical risk management have become increasingly important components of routine clinical practice.¹¹⁻¹⁴

Recent evidence has further supported the use of CEM for assessing tumor extent, multifocality and multicentricity, image-guided biopsy, structured reporting, quantitative imaging biomarkers, and artificial intelligence-based risk stratification models, supporting its integration into modern breast imaging pathways.^{7,8,13,14}

However, technological progress alone is insufficient to ensure the safe and legally appropriate implementation of CEM. The administration of ICM represents not only a technical component of the examination but also a pharmacological act subject to regulatory requirements, safety standards, and medico-legal responsibilities.¹⁵⁻¹⁸

The off-label nature of contrast administration in CEM therefore requires clinicians to reconcile the growing scientific evidence supporting the technique with national regulations, professional standards, and institutional governance policies.^{9-14,18}

This issue has important practical implications. Physicians must ensure that off-label administration is supported by robust scientific evidence, that patients receive comprehensive information regarding benefits, risks, and available alternatives, and that institutional protocols adequately address emergency preparedness, documentation, and quality assurance. These aspects are consistent with the principles of clinical risk management and patient safety promoted by contemporary healthcare systems and scientific societies.^{12,15-19}

Accordingly, the present commentary does not primarily revisit the diagnostic performance of CEM, which is already supported by extensive literature.¹⁻⁸ Instead, it focuses on the unresolved regulatory and medico-legal challenges associated with the use of ICM in CEM, discussing the implications of off-label prescribing, informed consent, professional liability, institutional governance, and standardized safety pathways. While the discussion is framed within the Italian legal system, the proposed considerations provide a broader conceptual framework that may be applicable to other healthcare settings facing similar clinical-regulatory challenges.¹⁵⁻²³

Off-label prescribing is generally accepted within medical practice when supported by robust scientific evidence and when aligned with the patient's best interest. However, it entails an increased level of professional responsibility, requiring clinicians to base their decisions on up-to-date evidence, validated clinical indications, and a rigorous individualized risk-benefit assessment.¹⁷⁻¹⁹

In this context, ICM administration in CEM represents a paradigmatic example of off-label use embedded in routine clinical imaging practice, where pharmacological, diagnostic, and medico-legal dimensions intersect, in line with current evidence and regulatory frameworks governing off-label prescribing and patient safety.^{11-14,18,19}

While the growing body of literature supports the clinical effectiveness of CEM, such evidence should be interpreted primarily in terms of diagnostic applicability rather than as an automatic redefinition of the standard of care, which remains dependent on regulatory approval and guideline endorsement.^{5,7,10}

From a safety perspective, ICM used in CEM exhibits a well-established risk profile consistent with its use in CT. A comprehensive systematic review has shown that the most widely used contrast agents worldwide include iohexol, iopromide, iomeprol, ioversol, and iopamidol, all low-osmolality non-ionic agents with consolidated safety profiles.²⁰ A dedicated meta-analysis focusing on iopromide confirmed its widespread adoption and favorable safety and tolerability profile in CEM.²¹

In Italy, iomeprol is among the most commonly used iodinated contrast agents in clinical radiological practice and is approved by the Italian Medicines Agency (AIFA) for multiple diagnostic indications within cross-sectional imaging; however, no iodinated contrast medium currently holds a specific authorization for use in mammographic applications, thereby confirming the off-label nature of contrast administration in CEM within the Italian regulatory framework.^{10,15,16}

This regulatory status implies that its use in breast imaging must be justified on the basis of scientific evidence, clinical necessity, and adherence to professional standards of care, and must be accompanied by appropriate documentation and informed consent procedures in accordance with national medico-legal requirements.¹⁵⁻¹⁹

Prospective evidence from the TOCEM trial has further demonstrated that both acute and delayed hypersensitivity reactions remain uncommon, even in patients undergoing multiple CEM examinations, with adverse events generally mild and comparable to those observed in CT contrast administration.²²

A crucial medico-legal aspect concerns informed consent. Patients must be explicitly informed that the use of iodinated contrast in CEM may be off-label, and should receive clear information regarding potential risks, expected benefits, and alternative imaging modalities such as magnetic resonance imaging.^{15,16, 24-26}

Furthermore, the rapid dissemination of CEM underscores the need for structured institutional governance and standardization. Recent literature emphasizes the importance of harmonized imaging protocols and safety pathways to ensure quality assurance and patient safety in clinical practice.^{13,14,27}

In this context, we propose a practice-oriented medico-legal framework based on current evidence and available guidance. This framework includes (i) a dedicated informed consent process specifically designed for CEM and (ii) institutional safety pathways aligned with recommendations from scientific societies such as the Italian Society of Medical and Interventional Radiology (SIRM) and the Italian Society of Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI).^{12,22,23}

Given the rapid expansion of CEM and the heterogeneity in contrast protocols, there is a compelling need for harmonized recommendations addressing technical and clinical aspects such as contrast agent selection, injection protocols, and patient selection criteria.¹⁻⁶

Pre-examination screening practices remain heterogeneous, particularly regarding renal function,

allergy history, and comorbidities.^{4,5,20,22}

Another key issue is the absence of harmonized protocols for the prevention and management of adverse reactions in CEM workflows, especially in standalone breast units with limited immediate access to emergency or resuscitation support.²²⁻²⁴

From a regulatory perspective, the off-label use of ICM underscores the importance of procedure-specific informed consent and standardized governance structures.^{11,15-19,27}

In conclusion, CEM represents a significant advancement in breast imaging supported by high-quality evidence,^{1-6,20} but its reliance on off-label iodinated contrast administration requires structured medico-legal and safety frameworks. Harmonized guidelines, institutional protocols, and explicit informed consent are essential to ensure safe and legally appropriate implementation.^{1-6,11-23,27-37}

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