Clinical Applications of Gadopiclenol in Breast MRI

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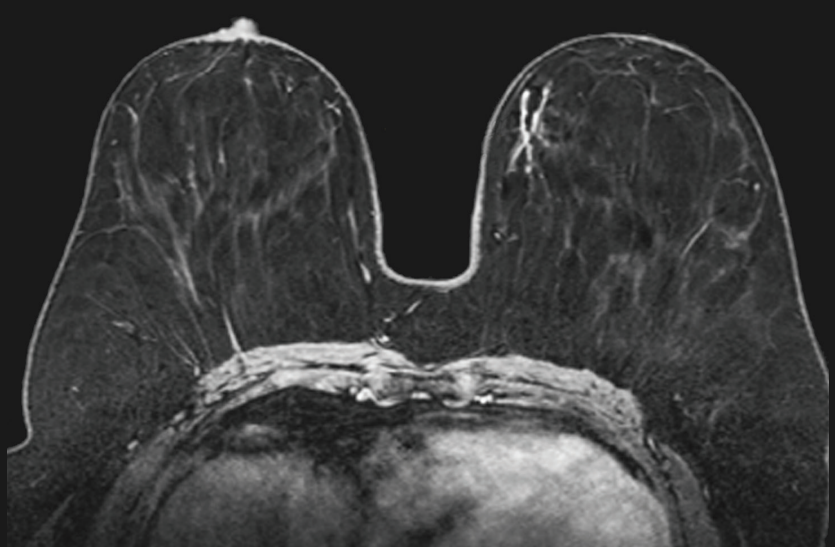

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LIFE FROM INSIDE

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Introduction

Breast cancer is the second most common cancer diagnosed in women, affecting millions globally.[1] The higher sensitivity of MRI for breast cancer detection depends on gadolinium-based contrast agents (GBCAs).[2-4] With more than 700 million doses administered worldwide, GBCAs are considered safe; however, the risk of serious conditions like nephrogenic systemic fibrosis (NSF) warrants their prudent use.[5] Furthermore, mounting evidence on the long-term, albeit trace amounts of gadolinium retention in human tissue, has led to more thoughtful practices around GBCA use and has generated interest in the development of low-dose agents, the most recent of which is gadopiclenol.[6-8]

In breast MRI, minimizing gadolinium exposure is particularly important, as many healthy women at elevated risk of breast cancer undergo repeat screening MRI with GBCAs, increasing the cumulative dose of gadolinium during their lifetime.[9] This article discusses considerations for GBCA use in breast MRI, with a focus on gadopiclenol.

Applications of Contrast-Enhanced Breast MRI

Breast MRI has the highest sensitivity for breast cancer detection among currently available imaging modalities. Since effective mammographic assessment can be difficult in women with dense breast tissue or breast implants, contrast-enhanced breast MRI is often preferred for identifying tumors.[3,10] Breast MRI is also recommended as a supplemental screening modality for women with an elevated lifetime risk of breast cancer.[10] Owing to its exceptional sensitivity, contrast-enhanced breast MRI can aid in the surveillance of breast cancer survivors with mammographically dense breasts or those diagnosed before age 50, and in assessing tumor response to neoadjuvant chemotherapy to help guide treatment decisions and surgical planning.[10]

The utility of GBCAs in imaging relies on the paramagnetic properties of gadolinium (Gd^{3+}).[11] Gadolinium shortens the T1 relaxation time of nearby protons, resulting in increased signal intensity on T1-weighted images.[11] This higher signal, which quantitatively differs across GBCAs based on their relaxivity, facilitates the detection and characterization of breast lesions by increasing the image conspicuity of areas with increased vascularity, such as tumors, while suppressing normal breast tissue.[12] Currently, 2 GBCAs are approved by the US Food and Drug Administration (FDA) for use in breast MRI (**Table 1**), with gadopiclenol being the most recent addition and exhibiting the highest relaxivity.[13] In breast imaging, the use of a high relaxivity GBCA that is administered at half the dose of standard extracellular fluid (ECF) agents can allow for lower gadolinium exposure while ensuring an efficacious exam.

Considerations for GBCA Selection: Gadopiclenol for Breast MRI

Weighing the benefits of a GBCA against its risks is critical in ensuring patient safety and appropriateness of contrast-enhanced breast MRI studies.[14] Three key factors can help guide contrast selection — efficacy, stability, and safety. All currently available GBCAs differ in

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Table 1. Indications and Relaxivities of US Food and Drug Administration-approved Extracellular Fluid Gadolinium-based Contrast Agents.[7,8,13,17-21]

	GENERIC NAME	TRADE NAME	INDICATIONS	RELAXIVITY AT 1.5T	RELAXIVITY AT 3.0T
Macrocyclic	Gadoteridol	ProHance	CNS (adults + children aged >2 years); head and neck (adults)	4.1	3.7
	Gadobutrol	Gadavist	CNS (adults + children, including term neonates); breast; coronary artery disease; MRA for supra-aortic or renal artery disease (adults and pediatrics, including term neonates)	5.2	5.0
	Gadoterate meglumine	Dotarem/ Clariscan	CNS (brain [intracranial], spine and associated tissues; adults + children, including term neonates)	3.6	3.5
	Gadopiclenol	Vueway/ Elucirem	CNS and body (head and neck, thorax*, abdomen, pelvis, and musculoskeletal system; adults + children aged ≥2 years)	12.8	11.6
Linear	Gadobenate dimeglumine	MultiHance	CNS (adults + children, including term neonates); MRA for renal or aorto-ilio-femoral occlusive vascular disease (adults)	6.3	5.5

CNS = central nervous system; MRA = magnetic resonance angiography.
*Inclusive of breast MRI.

terms of efficacy and indications for use, and the choice of an agent in favor of others is often based on its safety profile in addition to its ability to improve lesion conspicuity relative to background and produce high image quality. GBCAs with high relaxivity can increase image enhancement and potentially improve lesion detection, which has been proven in imaging the central nervous system.[11] Gadopiclenol exhibits approximately 2 to 3 times higher relaxivity than other approved ECF linear and macrocyclic GBCAs in water and serum and at all field strengths.[13]

Chelate structure and ionicity influence overall GBCA stability and are thus important considerations in selecting an agent. In general, linear GBCAs have lower stability than macrocyclic agents, with nonionic linear agents being the least stable and linear ionic agents being moderately stable.[15] The higher stability of macrocyclic agents is credited to their cage-like structure that binds Gd^{3+} more tightly than linear chelates.[15] In the setting of renal impairment, dissociation of the Gd^{3+} ion from the GBCA chelate has been linked to the development of NSF.[16] In response, the American College of Radiology (ACR) has classified GBCAs relative to the number of NSF cases associated with each agent.[14] According to the groupings, gadopiclenol is classified as a Group II agent for which the risk of NSF among patients exposed to standard or lower than standard doses is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration.[14]

Lastly, ensuring patient comfort during an MRI exam is critical to achieving an adequate study, especially in breast imaging given the prone positioning of patients and the length of the exam if an abbreviated protocol is not used. In terms of GBCA use, those associated with lower rates of immediate adverse reactions, such as nausea, injection site, or allergic reactions, are preferred. The safety profile of gadopiclenol resembles that of other available GBCAs, with most adverse reactions being mild and self-limited.[7,8] In addition, the high relaxivity of gadopiclenol ensures lower gadolinium exposure, with the use of an approved dose that is half that of other ECF agents (ie, 0.05 mmol/kg for gadopiclenol vs 0.1 mmol/kg for other ECF agents approved in the US for similar indications).[7,8,17-21] This aligns with the ACR's guidance to administer a GBCA only if deemed necessary and at the lowest dose needed for diagnosis.[14]

In terms of clinical experience, gadopiclenol 0.05 mmol/kg has been compared with gadobutrol 0.1 mmol/kg in the randomized, double-blind, crossover, phase 3 PROMISE study that enrolled 273 adults with at least 1 suspected focal lesion in 1 of 3 body regions (head and neck; breast, thorax, abdomen, or pelvis; or musculoskeletal system).[22] Among the study population were 76 patients with suspected breast lesions. Despite the half dose of gadolinium administered, gadopiclenol was comparable to

Figure 1. A 45-year-old woman undergoing annual screening MRI. Axial dynamic early bilateral contrast-enhanced MRI images obtained with 0.05 mmol/kg gadopiclenol in 2024 (**A**) demonstrate higher enhancement in the heart and vessels compared with the same contrast phase with 0.1 mmol/kg gadobutrol in 2023 (**B**).

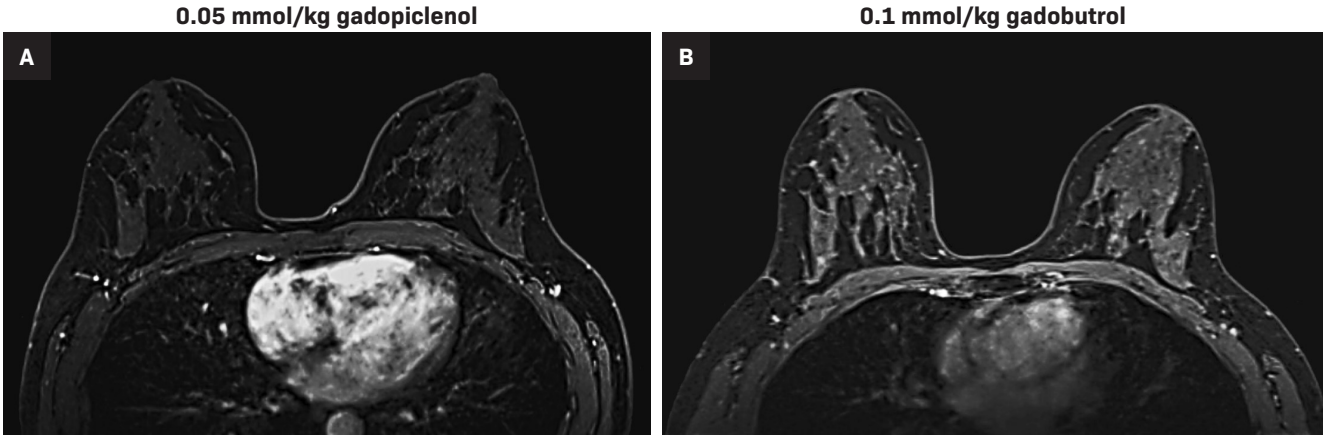


Figure 2. A 56-year-old woman with known intermediate-grade ductal carcinoma in situ in the medial left breast, initially diagnosed in 2022. The patient elected observation. Axial dynamic early bilateral contrast-enhanced MRI image obtained with 0.1 mmol/kg gadobutrol in 2023 demonstrates segmental clumped enhancement (**A**, arrow). Follow-up MRI using 0.05 mmol/kg gadopiclenol in 2024 shows the cancer extent is stable (**B**, arrow). No significant difference in enhancement rate or visibility was observed.

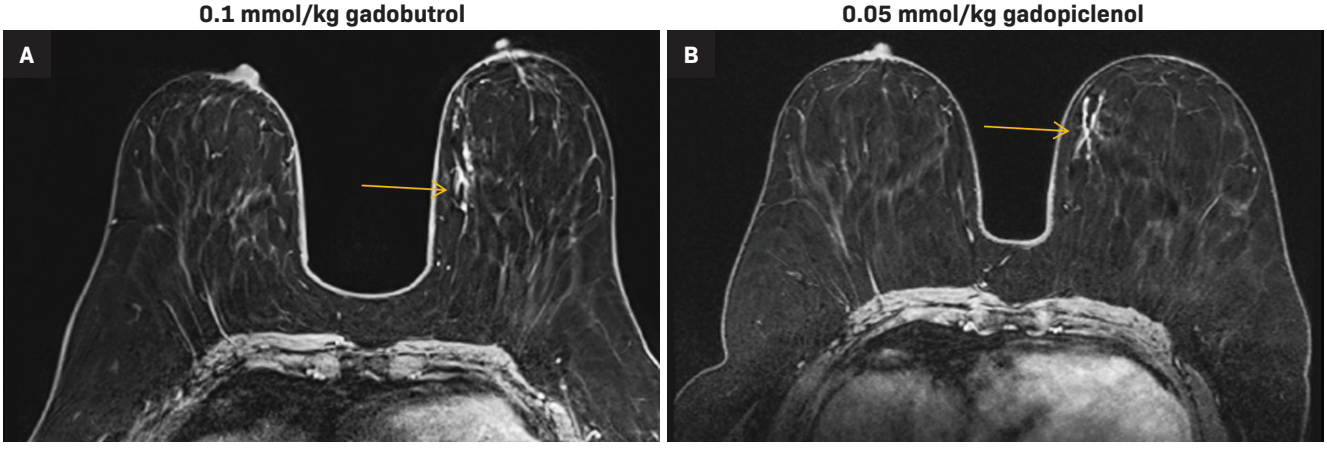
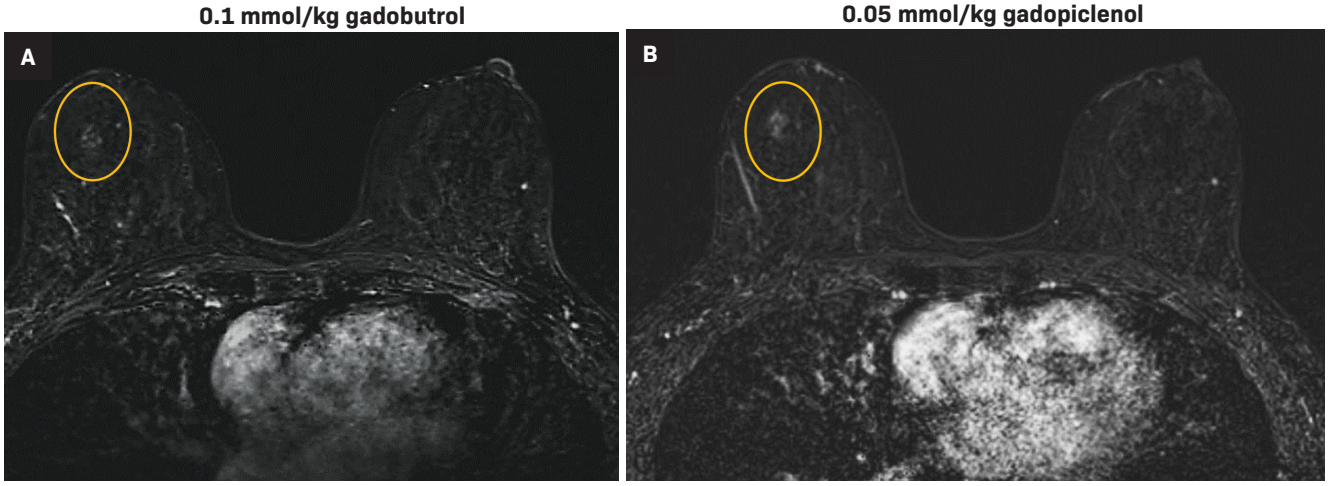


Figure 3. A 49-year-old mutation carrier with increased lifetime risk of breast cancer (>20%) undergoing screening MRI. Early subtraction axial image in an April 2023 (**A**) screening MRI exam performed using 0.1 mmol/kg gadobutrol shows known fibroadenoma in the lateral right breast as a low-grade enhancing mass. In an April 2024 (**B**) MRI obtained with 0.05 mmol/kg gadopiclenol, the lesion shows higher enhancement and increased conspicuity compared with the 2023 exam.



gadobutrol for overall lesion evaluation, signifying that a GBCA with high relaxivity can reduce gadolinium exposure while maintaining image quality.[22] In terms of safety, 12 of 288 (4.2%) participants receiving gadopiclenol and 16 of 290 (5.5%) receiving gadobutrol experienced adverse events related to contrast; however, they did not differ in frequency, intensity, or type.[22]

Our practice at the University of Texas Southwestern Medical Center has successfully introduced gadopiclenol in screening breast exams with minimal workflow interruption and protocol changes. Administering half the gadolinium dose with 0.05 mmol/kg gadopiclenol yields images with at least the same conspicuity and level of enhancement as that achieved with a full 0.1 mmol/kg dose of gadobutrol (**Figures 1-3**). By comparing breast exams from the same patient using different GBCAs, we have been able to gain a better understanding of how gadopiclenol behaves and how it can be leveraged to serve our patient population best.

Summary

Contrast-enhanced breast MRI is a mainstay in the diagnostic armamentarium for breast cancer detection and characterization. With its high sensitivity, multiplanar and multiparametric imaging capability, breast MRI can help guide clinical decision-making across various clinical scenarios. Despite safety considerations associated with GBCA administration, the benefits of contrast-enhanced breast MRI continue to outweigh the risks, offering invaluable insights into breast pathology and facilitating personalized patient care. Gadopiclenol is the latest macrocyclic GBCA with a robust safety profile and can help decrease the gadolinium dose needed for breast MRI.

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VUEWAY® (gadopiclenol) solution for injection

Indications
VUEWAY injection is indicated in adults and children aged 2 years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

IMPORTANT SAFETY INFORMATION
WARNING: RISK ASSOCIATED WITH INTRATHECAL USE and NEPHROGENIC SYSTEMIC FIBROSIS

Risk Associated with Intrathecal Use
Intrathecal administration of gadolinium-based contrast agents (GBCAs) can cause serious adverse reactions including death, coma, encephalopathy, and seizures. VUEWAY is not approved for intrathecal use.

NEPHROGENIC SYSTEMIC FIBROSIS
Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR < 30 mL/min/1.73 m^2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age > 60 years, hypertension, diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**
- **For patients at highest risk for NSF, do not exceed the recommended VUEWAY dose and allow a sufficient period of time for elimination of the drug from the body prior to any re-administration.**

Contraindications
VUEWAY injection is contraindicated in patients with history of hypersensitivity reactions to VUEWAY.

Warnings and Precautions
There are **risks associated with intrathecal use** of GBCAs that can cause serious adverse reactions including death, coma, encephalopathy, and seizures. The safety and effectiveness of VUEWAY have not been established with intrathecal use and VUEWAY is not approved for intrathecal use.

Risk of **nephrogenic systemic fibrosis** is increased in patients using GBCA agents that have impaired elimination of the drugs, with the highest risk in patients with chronic, severe kidney disease as well as patients with acute kidney injury. Avoid use of GBCAs among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

Hypersensitivity reactions, including serious hypersensitivity reactions, could occur during use or shortly following VUEWAY administration. Assess all patients for any history of a reaction to contrast media, bronchial asthma and/or allergic disorders, administer VUEWAY only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, and observe patients for signs and symptoms of hypersensitivity reactions after administration.

organs (brain, skin, kidney, liver and spleen). Minimize repetitive GBCA imaging studies, particularly closely spaced studies, when possible.

Acute kidney injury requiring dialysis has occurred with the use of GBCAs in patients with chronically reduced renal function. The risk of acute kidney injury may increase with increasing dose of the contrast agent.

Extravasation and injection site reactions can occur with administration of VUEWAY. Ensure catheter and venous patency before the injection of VUEWAY.

VUEWAY may **impair the visualization of lesions** seen on non-contrast MRI. Therefore, caution should be exercised when VUEWAY MRI scans are interpreted without a companion non-contrast MRI scan.

The most common adverse reactions (incidence ≥ 0.5%) are injection site pain (0.7%), and headache (0.7%).

POST-MARKETING EVENTS
Acute pancreatitis within 48 hours of GBCA administration has been reported.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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