AJR FOCUS ON:

Gadolinium Retention and Breast MRI Screening: More Harm Than Good?

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OBJECTIVE. The purpose of this article is to describe the risk-benefit balance of contrast-enhanced breast MRI (CE-BMRI) screening.

CONCLUSION. CE-BMRI confers risk of effects associated with administration of gadolinium-based contrast agents (GBCAs), including nephrogenic systemic fibrosis and gadolinium retention. The risk-benefit balance of CE-BMRI screening is favorable for carriers of *BRCA*, *TP53*, or other deleterious mutations women who have undergone thoracic irradiation; and women at 20% or greater lifetime risk of breast cancer. The balance is uncertain, however, for women at intermediate to average risk. Women must always receive detailed information regarding possible GBCA-associated effects.

Someone's intelligence can be measured by the quantity of uncertainties that he can bear.
—Attributed to Immanuel Kant

Since the 1970s, the diagnosis of neoplasms in humans [1], breast neoplasms in particular [2], has inspired the use of nuclear MR in medicine, promoting its evolution into MRI. Although unenhanced MRI has had high diagnostic performance in the CNS and musculoskeletal system since the early 1980s, breast applications have been disappointing. In 1986, the IV administration of the first gadolinium-based contrast agent (GBCA) opened a new chapter of breast imaging [3].

Contrast-Enhanced MRI Before and After *BRCA* Gene Discovery

The following factors favored breast applications of contrast-enhanced MRI (CE-MRI): high sensitivity, absence of ionizing radiation exposure, avoidance of breast compression, and absence of known relevant adverse effects of GBCAs. In particular, when GBCAs were compared with iodinated contrast agents, the frequency of all immediate adverse effects (especially hives and nausea) was reported to be 0.04% versus 0.13% and of adverse effects necessitating treatment, 0.01% versus 0.03% [4]. From 2004 to 2009 in the United States, the incidence of GBCA-associated deaths was reported to be 0.2–2.7 per million doses [5]. Nonnegligible disadvantages of breast CE-MRI were need to enter a closed MRI unit, the long examination time, high cost, and—last but not least—the axiom about low specificity of breast MRI. Low specificity was attributed to breast MRI for several reasons, mainly lack of standardized interpretation criteria, such as BI-RADS for MRI, which was not introduced until 2003 [6], and the fact that studies reporting low specificity of breast MRI for small series of lesions managed surgically [7] received more attention than very large studies showing high specificity [8].

In the mid-1990s, while the debate on indications for breast MRI was ongoing, the discovery of *BRCA1* and *BRCA2* mutations and increased general knowledge of breast cancer risk stratification encouraged studies of MRI screening of women at high risk. Results were strongly in favor of the new modality, which had a huge advantage over mammography and sonography in terms of sensitivity and also had high specificity, evidence against the aforementioned axiom. In 2007, the American Cancer Society issued the first guideline [9] recommending breast CE-MRI as an adjunct to mammography for women at 20–25% or greater lifetime risk (LTR), including those with a strong family history of breast or ovarian cancer or previous thoracic irradiation. Other guidelines on this topic followed in many countries, some

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of which adopted a higher LTR threshold for breast MRI screening. For example, the National Institute for Clinical Excellence (United Kingdom) suggests breast MRI screening in the presence of LTR of 30% or greater [10]. Conversely, if the LTR cutoff is 20% or greater, breast MRI screening should be considered also for women with pathogenic variants detected in moderate-risk genes or with newly discovered suspect genes [11].

Therefore, while further indications to breast MRI were being discussed (and still are, as in the case of preoperative imaging), the medical community accepted breast MRI screening of woman at high risk in the absence of outcome data, considering the huge sensitivity gap in the population at high risk as self-sustaining evidence. Studies [12–18] showed that mammography and ultrasound give no additional diagnostic power to screening MRI, supporting the MRI-alone approach and avoiding mammography, especially for *BRCA* and *TP53* mutation carriers who have a higher radiosensitivity and radiosusceptibility [19]. Even though this advice has translated into a guideline [20] only for *BRCA* mutation carriers younger than 35 years and for *TP53* mutation carriers without age limitations, this is a general issue to be taken into consideration.

Nephrogenic Systemic Fibrosis: A Vanishing Concern

In 2006, the association between GBCA administration and nephrogenic systemic fibrosis (NSF), a sclerodermalike disease, was first reported [21]. NSF is a late adverse reaction to GBCA injection in patients with acute or chronic renal failure, mainly related to dissociation of Gd^{3+} ions from ligands and subsequent formation of new insoluble precipitates. As a consequence, use of GBCAs was discouraged for imaging of patients with a glomerular filtration rate less than 30 mL/min × 1.73 m^2, and the higher risk of NSF associated with some linear GBCAs, such as gadodiamide and gadopentetate dimeglumine, as opposed to other linear (gadobenate dimeglumine) and macrocyclic (gadobutrol, gadoterate meglumine, gadoteridol) GBCAs came into evidence. The incidence of NSF decreased dramatically with implementation of screening of renal function and avoiding the use of double and triple GBCA doses. A systematic review [22] reported a total of 639 biopsy-confirmed NSF cases, only seven after 2008.

NSF has been an important lesson. In 2008, it was rightly defined as a "perfect storm" [23], one major factor being the supposed evidence from the 1980s to mid-2000s was in favor of GBCA safety even for patients with renal failure. This was not the case. Today, after renal function assessment, breast MRI screening can be performed without any known risk of NSF.

Brain Gadolinium Retention: The Great Fear

Starting in 2014, an association was reported between previous GBCA administration and increased signal intensity in deep cerebral and cerebellar nuclei on unenhanced T1-weighted MR images [24]. This was confirmed by assessing the presence of gadolinium in the brain through postmortem studies of humans [25] and animals [26]. Although macrocyclic GBCAs had a less pronounced effect than linear GBCAs, some degree of increase in signal intensity and of gadolinium presence correlated with progressive GBCA exposure was nevertheless observed in many tissues for all GBCAs [27]. Research is ongoing on several issues, including cofactors prompting the phenomenon, the route of gadolinium from CSF to gray and white matter, and the gadolinium washout rate. In particular, studies of gadolinium washout in animal models [28] presented a new perspective, in which the more physiologic phenomenon of retention (with significant differences also among linear GBCAs) is proposed as an alternative to deposition, although the latter term is still used more often in the literature.

Retention in tissues and organs other than the brain, such as bone, has been clearly documented. However, because brain is brain, its possible clinical relevance became a public concern. In 2017, the European Medicines Agency suspended marketing authorization of four linear GBCAs, leaving only macrocyclic agents for clinical use, including breast MRI, with few exceptions (use of gadobenate dimeglumine is still authorized only for liver imaging and use of low-concentration gadopentetate dimeglumine only for intraarticular injection). In the United States, the Food and Drug Administration and the National Institutes of Health emphasized the need for a thorough review of GBCA indications, administration policies, and general admissibility of serial injections in a number of follow-up or screening protocols. They also advocated a specific patient-tailored approach, in which each radiologist should carefully appraise the risk-benefit ratio between GBCA effects (including retention) and the possibility of missing clinically relevant abnormalities. This view was also supported by the safety committee of the International Society for Magnetic Resonance in Medicine [27].

Only long-term studies will properly address this matter. In 2016, Welk et al. [29] compared 99,739 patients who had undergone at least one CE-MRI examination with 146,818 who underwent only unenhanced MRI. They investigated the possible correlation between extrapyramidal disorders and gadolinium retention in basal ganglia and the dentate nucleus. They found no significant difference in new diagnoses of parkinsonism (the most expected effect of a possible impairment of the extrapyramidal system) between patients exposed and those unexposed to GBCA. Other studies [30, 31] have likewise shown no evidence of clinical effects of gadolinium retention in the brain, in particular in patients with multiple sclerosis, who regularly undergo CE-MRI. In patients with Crohn disease, who also regularly undergo CE-MRI and have gadolinium-related dentate nucleus hyperintensity on T1-weighted images, no resting-state functional connectivity changes were found [32]. Therefore, to our knowledge, there is no evidence of clinical effects of gadolinium retention independent of the chemical structure (linear or macrocyclic) of the administered GBCA.

Self-Reported Gadolinium Toxicity

A new entity named gadolinium storage condition [33], gadolinium deposition disease [34], or probably more appropriately self-reported gadolinium toxicity [35] has been proposed, especially by gadolinium toxicity support groups, as a possible immediate or late effect of GBCA administration. A list of chronic symptoms ascribed to the contrast injection includes: clouded mentation; headache; central, peripheral, and bone pain; leg and arm skin thickening; and vision or hearing change [33–35]. Even though lawsuits have been filed against manufacturers, no evidence has been found that any GBCA actually causes these symptoms.

Risk-Benefit Balance for Breast MRI Screening

What is the balance between the benefit of CE-MRI breast screening (high sensitivity) and the possible risks associated with yearly repeated GBCA injections? A specific patient-tailored approach should take into account breast cancer risk as estimated with

a variety of tools and models and also considering breast density. An LTR of 20% or greater is commonly accepted as a threshold for CE-MRI breast screening, but some countries, such as the United Kingdom, have adopted a threshold LTR of 30% or greater [10]. However, *BRCA* or *TP53* mutation carriers and women who have undergone thoracic irradiation are at 40–50% or greater LTR, which is very high. For *BRCA* mutation carries, especially *BRCA1* mutation carriers, not only yearly breast CE-MRI but also prophylactic mastectomy is justified, even more so when the breast is contralateral to one with a first breast cancer diagnosis.

Indirect evidence of a positive effect of MRI (combined with modern therapies) on patient outcome has been reported [36, 37]. We are in favor of extending a breast MRI screening strategy to women at 20% or greater LTR (even if *BRCA* or *TP53* wild-type), in agreement with the results of a 2019 randomized controlled trial [38]. Considering both the available evidence and repeated injections, preference always has to be given to macrocyclic versus linear GBCAs, and among the former, possible differences in diagnostic power and washout rate have to be taken into account.

Below the 20% LTR threshold, we enter a largely unexplored territory where the sensitivity gap may not be wide enough. For women at intermediate or average risk (10–19% LTR), including patients with a history of sporadic breast cancer, the risk-benefit balance estimation is uncertain. On one side, abbreviated breast CE-MRI protocols have been found to reduce test duration and costs without impairing the high sensitivity [39]. On the other side, as we know from the rules of evidence-based medicine [40], large-scale application of a screening practice requires evidence in terms of patient outcome. Increased sensitivity is not enough (overdiagnosis is a concern), especially in the presence of the aforementioned uncertainties.

In a 2019 study, Wernli et al. [41] reported on over 13,000 women with a history of breast cancer who underwent approximately 34,000 mammographic and 2500 breast MRI examinations. Breast MRI was associated with a significantly higher cancer detection rate (odds ratio [OR], 1.7) and biopsy rate (OR, 2.2) than was mammography alone. However, no significant differences were found for sensitivity or interval cancer rate. Further studies are necessary to address uncertainty about extending breast MRI screening to women at average risk. For woman at high risk, the use of macrocyclic GBCAs is preferred. New insights on this matter will come from the Dense Tissue and Early Breast Neoplasm Screening (DENSE) trial, which randomized women with extremely dense breasts and negative mammography to undergo additional MRI or current practice [42].

Conclusion

Various new approaches must be investigated, potentially driving plot twists in this story. To our knowledge, only two major examples of such approaches exist. The first is GBCA dose reduction, which can be achieved with artificial intelligence to generate virtual full-dose images from very-low-dose images, as already reported for brain applications [43]. The second example is use of unenhanced breast MRI for cancer detection, mainly with DWI [44]. While we await clinical application of these techniques, we must accept a word of caution about the introduction of breast MRI screening for women who are not at high risk. Regarding possible late effects of dozens of GBCA injections, we need to remember that the absence of evidence is not evidence of absence and that evidence of presence is not evidence of harm. When offering breast MRI screening, we inform women about the risk-benefit balance. For women not at high risk, we must also strive to communicate a higher grade of uncertainty as a transparent approach fostering patient empowerment.

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