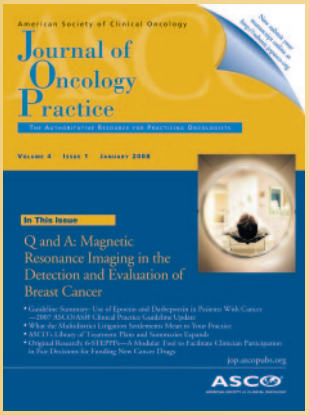


Q and A: Magnetic Resonance Imaging in the Detection and Evaluation of Breast Cancer

By Dana S. Wollins, MGC, and Mark R. Somerfield, PhD

A recent guideline from the American Cancer Society (ACS) recommends the use of magnetic resonance imaging (MRI) for annual screening of women at high risk for breast cancer.[1] Additionally, a study of breast MRI in women with newly diagnosed breast cancer by Lehman and colleagues suggests that MRI may also play a role in this population.[2] The guideline and the study have raised many questions in the oncology community regarding how MRI should be implemented in clinical practice, or regarding ". . . the responsible use of MRI for the evaluation of the breast."[3]

According to the ACS guideline, annual breast cancer screening with mammograms and MRI is recommended for women at high risk for breast cancer. High-risk features include a *BRCA1* or *BRCA2* gene mutation, a strong family history of breast or ovarian cancer, a 20% or greater lifetime risk of breast cancer (cumulative lifetime risk of breast cancer for an American woman is estimated to be approximately 13%), and radiation therapy to the chest for the treatment of Hodgkin's disease.

In the study conducted by Lehman et al,[2] 969 women with unilateral breast cancer underwent a breast MRI in the contralateral breast soon after diagnosis. Although no abnormalities were found by clinical examination or mammography, MRI detected abnormalities in the unaffected breast in 135 (13.9%) of 969 women. In follow-up biopsies of 121 of the 130 women with positive MRI findings, 30 specimens were positive for cancer or carcinoma in situ (24.8% of those receiving biopsies; approximately 3% of the total study group), of which 18, or 60%, were positive for invasive breast cancer. The sensitivity of MRI in this study was 91%, and the specificity was 88%.

More recently, a prospective observational study conducted by Kuhl et al[4] compared the sensitivity of mammography and breast MRI in the diagnosis of ductal carcinoma in situ (DCIS). Kuhl and colleagues found that the sensitivity of MRI for DCIS is considerably higher than that of either film screen or digital mammography. The sensitivity of breast MRI increased with higher nuclear grade of DCIS; the sensitivity of mammography decreased with higher nuclear grade.

Some in the oncology community consider the recent guideline and study results to be valuable resources for clinical practice; they argue that the diagnosis of breast cancer in high-risk women can occur at an earlier stage when combining the two technologies rather than using mammography alone. As discussed by Lehman et al,[2] information from MRI of the contralateral breast in women with breast cancer can be helpful to patients and their physicians in treatment planning around prophylactic mastectomy. However, the guideline and the recent studies have raised significant questions among some others in terms of implementing the recommendations in clinical practice, especially with respect to access to high-quality MRI and MRI-guided biopsies for women,[4] effects of MRI on survival,[5] overdiagnosis of breast cancer with the potential for increase in mastectomy rates, and false-positive rates and associated psychological morbidity.[6]

In this article, several national experts, representing a broad range of clinical interests, respond to questions raised by the

recent guidelines and studies and offer their perspectives on these important issues.

Q and A

Question: The authors of the ACS guideline are clear on the point that the evidence base was "not sufficient to form a solid basis for many of the recommendations." Specifically what kind of evidence was considered and what does this mean for implementing the recommendations in clinical practice?

Barnett Kramer, MD, MPH

Barnett Kramer, MD, MPH: It's not clear. None of the guidelines is based on randomized controlled trials. The authors state that the recommendations labeled as "Based on Evidence" rest on nonrandomized trials and observational studies. They list a second category of recommendations as "Based on Expert Consensus Opinion," but are not explicit about the process. It is not clear what threshold of evidence was required to place a recommendation into the first versus second category. Even within the first category, the open-ended recommendation for screening women "for as long as a woman is in good health," is not based on direct empirical clinical evidence. The balance of benefits and harms is likely to change as a woman ages. With regard to implementing the recommendations, there is insufficient information provided. The authors state that "there is evidence of a learning curve for radiologists conducting MRI breast screening. . . ," but do not give criteria by which referring physicians and women can judge the competency of a given screening center. This learning curve can have important effects on the balance of potential benefits and risks of screening.

Question: Many screening tests are associated with some degree of "overdiagnosis" of lesions that would lead to morbidity but nevertheless trigger unnecessary treatment. To what extent is this anticipated with screening breast MRI?

Gabriel Hortobagyi, MD

Gabriel Hortobagyi, MD: All screening tests are associated with overdiagnosis. MRI is a highly sensitive test, especially in expert hands. As the *New England Journal of Medicine* article would indicate,[2] MRI would find abnormalities in at least 12.5% of patients with normal physical exam and mammography. Four biopsies were performed for every malignant lesion diagnosed. Therefore, there is substantial overdiagnosis that leads to utilization of additional diagnostic techniques, including biopsy. There is probably a lot of additional anxiety associated with true-positive and false-positive findings. There is no evidence that treating noninvasive breast cancer earlier (or treating noninvasive breast cancer at all) leads to improved survival. Therefore, one is left with 18 of 969 women in whom screening MRI is potentially of benefit.

In generic terms, for a screening procedure to be considered useful, it should not only find lesions at an earlier stage, but also demonstrate that earlier diagnosis results in some clinical benefit, preferably a reduction in breast cancer mortality. This will be a tall order for MRI, since mammography is pretty good, and the incremental benefit from MRI in the population at standard risk would require many thousands of patients to document a reduction in mortality. Whether clinical benefit can be documented from a screening procedure will depend not only on the sensitivity and specificity of the procedure, but also from the prevalence of the condition for which screening is being used. For this reason, I don't believe MRI is ready to be used for screening standard-risk women. For women at high risk, the indications look more acceptable, because MRI-detected abnormalities are much more likely to represent a true-positive finding. I, therefore, support the use of MRI screening for women with a strong family history of breast cancer, or in a more generic sense, those with a high risk for developing breast cancer. A 20% risk is about twice the standard risk, so it should make the cut. However, women undergoing screening MRI need to be informed of the odds of false-positive findings and the consequences of those findings.

Barnett Kramer, MD, MPH: The guideline does not mention the possibility of overdiagnosis, even though I agree that it is a realistic possibility that would be an important consideration in judging benefits versus harms. Mammography alone is associated with overdiagnosis (estimates vary from approximately 5% to 30% of tumors), and MRI + mammography may increase the frequency. Current nonrandomized study designs, in which every woman gets both MRI and mammography, don't provide a reliable estimate of overdiagnosis. The proportion of additional cancers that are potentially lethal versus those that are overdiagnosed can't be ascertained from that design. All we can tell is that MRI picks up "cancers" missed by mammography. A recent MRI study showed that 40% of MRI-detected cancers were DCIS, and the natural history of MRI-detected DCIS is not known. Without describing supporting evidence, the guideline simply says, "It is reasonable to extrapolate that detection of noninvasive (DCIS) and small invasive cancers will lead to mortality benefit." However, the history of medicine provides many examples in which extrapolations have misled us.

Question: How should women be advised regarding what we know and the remaining uncertainties about overall benefits and harms of MRI?

Gabriel Hortobagyi, MD: Women at standard risk for developing breast cancer should be informed that the probability of deriving benefit from the procedure for them is around 1.85% of 0.3%. This is my calculation, and is derived from assuming that standard-risk women have about a 3 in 1,000 probability of having breast cancer found at screening, and from the Lehman paper one would find about 1.85% detection of invasive breast cancer for those with negative mammograms. That would be about 0.0055%, while their false-positive rate would be about 12.5%. For women at high risk, the potential benefits are much higher because of the estimated prevalence and because high risk women tend to be young, and have dense breasts where mammography is least useful. They also need to be informed of the odds of false-positive findings and the consequences of those findings. In our institution, we use both MRI and mammography alternating every 6 months for women with *BRCA* mutations or those who have a quantifiable high risk using standard calculations.

Harold Burstein, MD, PhD

Harold Burstein, MD, PhD: It is important for patients and clinicians to realize that the recommendations of the American Cancer Society apply to women with twice the risk of breast cancer as the average woman in the US. These women typically have strong family histories of breast cancer (two or more relatives) or known inherited gene abnormalities that predispose to breast cancer. Fortunately, such women constitute only a small part of the general population. As with any screening test given to large numbers of people, the usefulness of MRI is determined by the prevalence of the disease in the population. Because of the higher risk of breast cancer in women with family history or gene predisposition, a more sensitive technique such as MRI is warranted and provides valuable information. By contrast, in women with lower risk of breast cancer, the chance that MRI would result in a meaningful finding is much lower. The "price" to be paid for this extra screening includes both the cost difference between MRI and mammogram, and the increased risk of biopsy for benign breast disease. In fact, even in high-risk women, MRI-directed biopsies that proved benign outnumbered the cancer diagnoses by 3 to 1.

There are several important caveats to the ACS recommendations. First, screening MRI was endorsed for high-risk women, but not for average-risk women, nor for women with personal history of breast cancer. Many women overestimate their risk of developing breast cancer and are not necessarily at the elevated risk of the women with hereditary predisposition to the disease. Second, screening MRI should only be performed in experienced centers with ready availability of MRI-directed biopsy. This does not describe all imaging centers. Patients and clinicians should inquire about the experience of the facility at screening breast MRI and MRI-guided biopsy before they allow imaging to be done. Third, the experience with high-risk women receiving MRI screening typically involved very short (roughly 3 years on average) surveillance periods. It is not clear that such women would need annual MRI for the duration of their lives. Finally, MRI is not a substitute for mammography. There is still a tremendous need across the country to encourage women to get screening mammograms.

Question: Should MRI be used routinely in the evaluation of newly diagnosed breast cancer patients?

Monica Morrow, MD

Monica Morrow, MD: No, I believe that this is inappropriate and leads to unnecessary mastectomies. It is clear that MRI identifies additional cancer, not evident clinically or mammographically, in 10% to 20% of patients. Despite this, only 3% to 8% of women selected for breast conserving therapy (BCT) without MRI experience local recurrence at 10 years. These high rates of local control indicate that much of the disease found on MRI is controlled with radiation. Pathology studies from the 1970s using serial subgross sectioning documenting additional foci of carcinoma in 30% to 60% of patients with clinically localized cancer, were used to argue that all breast cancer required treatment with mastectomy, something clearly proven to be incorrect. With MRI, we now have a technology capable of detecting some of this disease. Its routine adoption has resulted in increased numbers of mastectomies in women not proven to benefit from this approach. Patients with invasive lobular cancer are often proposed as a subset who would benefit from MRI, yet local recurrence rates in patients with lobular cancer do not differ from those in patients with ductal cancer. We have recently shown in a study of 318 patients with lobular cancer matched to 636 with ductal cancer,[7] that the number of patients failing BCT and the number of operations to achieve negative margins does not vary with histology. The routine application of MRI in any patient subset awaits clinical trials demonstrating a benefit for patients.

Lisa Newman, MD, MPH: No one would question the benefits of having an alternative imaging modality such as

Lisa Newman, MD, MPH

MRI to identify mammographically occult cancers in the breasts of high-risk women. However, in the setting of an established cancer diagnosis, findings from breast MRI indeed have the potential for resulting in more extensive surgery (unilateral or bilateral mastectomy) without clearly-defined outcome benefits. Uncertainty regarding the benefits of these MRI-motivated mastectomies is related to the fact that in the contemporary era of excellent breast preservation outcomes and risk-reducing systemic therapies, we do not understand the biologic significance of microscopic tumor foci that may be identified within the ipsilateral or contralateral breast of a woman presenting with unilateral disease.

Conventional selection criteria for breast preservation candidates yields superb results: the ability to achieve a margin-negative lumpectomy; absence of diffuse suspicious microcalcifications on mammogram; and delivery of adequate breast radiation therapy. Several studies reveal declining local recurrence rates, suggesting improvements in both mammographic breast imaging and radiation therapy techniques. Furthermore, most breast cancers in American women are hormone receptor-positive, and use of adjuvant endocrine therapy contributes to both local and distant control of disease. Local recurrence rates after current breast-conservation approximate 10% to 15% over 20-year follow-up. MRI can identify additional foci of disease in 15% to 30% of the breasts that harbor a known cancer. The obvious risk associated with MRI is that the additional imaging may be detecting foci of disease that would have been eliminated by standard postlumpectomy breast radiation, but documentation of its presence could nonetheless trigger an "unnecessary" conversion to mastectomy.

One compelling potential application of breast MRI is for selection of patients to receive partial breast irradiation, or lumpectomy-alone. In this setting, one could easily rationalize that characterization of a small, prognostically favorable tumor as being unifocal by MRI as well as by mammography could improve the safety of these strategies. The definitive proof, however, would be determined by appropriately designed prospective clinical trials.

Question: Should MRI be used to determine whether contralateral mastectomy should be performed?

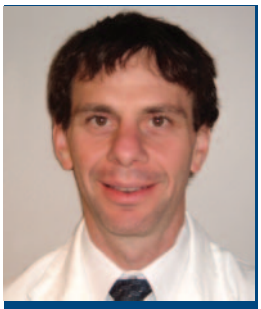
Monica Morrow, MD: Lehman et al,[2] using MRI of the contralateral breast in 969 women with cancer, found that 3.1% had a contralateral cancer 1 year postdiagnosis. This is interesting in light of SEER (Surveillance, Epidemiology and End Results) data in 134,501 breast cancer patients indicating that at 5 years, the incidence of contralateral cancer is only 3.0%.[8] This suggests that either (1) all contralateral cancers are present at the time of diagnosis of the index cancer and all are found by MRI, or (2) some of the cancers identified at the 1-year time point will never become clinically evident. The observation from the Oxford Overview Analysis that the use of adjuvant tamoxifen reduces the risk of contralateral breast cancer by 50%, and the use of adjuvant chemotherapy reduces contralateral cancer by 20%, strongly suggests that not all microscopic foci of tumor found by MRI will become clinically evident. The strategy of routine contralateral MRI runs the risk of overtreatment. Further follow-up is needed to determine whether a long-term reduction in contralateral cancer incidence is observed with this strategy.

Lisa Newman, MD, MPH: The Lehman et al study[2] demonstrated that MRI detects contralateral breast tumors in 3.1% of cases. A personal history of breast cancer is a well-known risk factor for developing a new breast cancer, and in fact data show that contralateral disease is detected in 2% to 3% of patients undergoing bilateral mastectomy for a unilateral breast cancer. However, we do not routinely encourage women to undergo contralateral prophylactic mastectomy because of evidence that survival after bilateral, metachronous breast cancer is determined by the stage of the first cancer detected. Also, widespread use of endocrine therapy can lower the incidence of new primary cancers by 50%. It is therefore not at all clear that newly-diagnosed breast cancer patients will experience any survival benefit from the treatment of an MRI-detected but clinically and mammographically occult contralateral tumor.

MRI may streamline decisions regarding management of the contralateral breast in selected cases. Patients undergoing mastectomy and transrectus abdominis muscle (TRAM) flap reconstruction may be motivated to pursue bilateral mastectomy because of risk-reducing and symmetry benefits, but they may also be ambivalent because of the extensive nature of this surgery. The TRAM flap can only be harvested once, but it can be used for bilateral synchronous reconstruction (if the patient has an adequate volume of abdominal soft tissue). Identification of contralateral disease may facilitate the decision-making process and allow the surgeon to plan appropriate contralateral axillary staging. Similarly, unilateral breast cancer patients with hereditary susceptibility face an elevated risk for developing ipsilateral as well as contralateral new breast primary tumors, and they are therefore often interested in bilateral mastectomies. MRI detection of an occult contralateral breast cancer will alter the surgical approach to the axilla in these cases as well.

Question: Are there sufficient numbers of radiologists specifically trained in breast MRI in order to maximize any possible benefit and minimize harm?

Mitchell Schnall, MD, PhD, and Nealie Hartman: There is a significant learning curve to breast MRI, like any new imaging procedure. Currently, breast MRI is practiced by



Mitchell Schnall, MD, PhD

radiologists with subspecialty expertise in MRI or Breast Imaging. Multicenter trials have demonstrated that breast MRI performance is generalizable across radiologists and sites. Although there are not enough radiologists with expertise in breast MRI to handle the additional procedures that will be generated by the new ACS recommendations, there has been significant progress in training the necessary practitioners. Fundamental to this effort is the development of a lexicon for breast MRI by the American College of Radiology, which serves as a resource for terms and standards. Further, the ACR is currently finalizing a credentialing program for facilities interested in performing breast MRI. There has been extensive support of continuing medical education initiatives related to breast MRI by the major societies and industry.

Question: What is the capacity to institute widespread MRI screening for high-risk women in the US?

Mitchell Schnall, MD, PhD, and Nealie Hartman: It is estimated that approximately 1.4 million American women would be candidates for screening breast MRI based on the recent revisions to the breast cancer screening guidelines from the American Cancer Society. It is estimated that currently approximately 26 million MRI procedures were performed in 2006, with approximately 2% (500,000) representing breast MRI. The number of breast MRI procedures has doubled over the past 3 years and is expected to increase at a higher rate of the next 3 years. Even if an additional breast 1.4 million MRI scans were added each year, breast MRI will still represent only a modest 10% of all MRI procedures and could be accommodated. In addition, there are now commercial supplies of the necessary accessories to perform breast MRI including coils, display and reporting software, biopsy guides, and MRI compatible biopsy needles. I believe there is capacity to accommodate the growth in breast MRI procedures expected from the recent ACS recommendations.

Summary

The experts invited to answer questions raised by the recent ACS guideline and studies offer a range of perspectives. Dr Kramer comments that the ACS guideline does not satisfy some of the most fundamental features of high-quality evidence-based guidelines. In particular, the ACS guideline does not explicitly explain how the evidence considered was assigned to categories of evidence. [Editor's note: Representatives from the ACS were invited to contribute to this article, but we had not received their responses by the time the article went to press]. Dr Kramer notes that none of the recommendations was based on data from a randomized clinical trial which, as many have argued, is the gold standard for demonstrating that a screening test reduces mortality.[9] Current study designs also do not permit an estimate of the degree of overdiagnosis associated with breast MRI, because all women received both MRI and mammography. Relatively short randomized clinical trials using interval clinical cancers as the end point could address this issue.[9]

Both Drs Hortobagyi and Kramer underscore that overdiagnosis is a real possibility with MRI screening in the population addressed by the ACS guideline. Dr Hortobagyi ultimately supports use of MRI in high-risk women with the proviso that these women be made aware of the risk of false-positive findings and the consequences of those findings. In a recent systematic review of the literature, Lord et al[10] stressed the need for the development of comprehensive risk prediction models to aid in the identification of women at high risk of breast cancer who would benefit the most from MRI screening. Dr Burstein echoes this call for careful attention to the benefits and risks of MRI screening, including the increased risk of biopsy for benign breast disease. He further encourages patients and clinicians to ensure that the MRI facility has sufficient experience with the technique before permitting a facility to perform this test.

In evaluating patients with newly diagnosed breast cancer both Drs Morrow and Newman believe that routine MRI use is inappropriate and leads to unnecessary mastectomies. Although MRI detects cancer that is not evident clinically or by mammogram in 10% to 20% of patients, much of the disease found on MRI is controlled by standard postlumpectomy breast radiation. Even in patients with invasive lobular cancer, a subset often proposed to benefit from MRI, no different local recurrence rate is shown compared to patients with ductal cancer.

Although contralateral disease is detected in 2% to 3% of patients undergoing bilateral mastectomy for a unilateral breast cancer, both Drs Morrow and Newman agree that MRI should not be used to determine whether contralateral mastectomy should be performed. It is not clear that newly diagnosed breast cancer patients will derive any survival benefit from treating a contralateral tumor detected by MRI but not evident clinically or mammographically. Dr Newman notes, however, that MRI may assist in management decision-making in selected cases, such as when mastectomy and TRAM flap reconstruction is planned (the TRAM flap can only be harvested once but can be used for bilateral reconstruction if done synchronously), or in a patient at increased hereditary risk for cancer.

With respect to the number of adequately trained specialists required to accommodate changes in MRI screening practices

that may result from the ACS recommendations, Dr Schall and Ms Hartman admit that there are currently not enough radiologists with expertise in breast MRI to handle the potential increase in MRI procedures. They believe, however, that there is sufficient capacity in the system to accommodate the expected increase in breast MRI procedures and they note that there has been progress in training practitioners.

DOI: 10.1200/JOP.0813501

References

1. Saslow D, Boetes C, Burke W, et al: American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 57:75-89, 2007

2. Lehman CD, Gastonis C, Kuhl CK, et al: MRI evaluation of the contralateral breast in women with recently diagnosed breast cancer. N Engl J Med 356:1295-1303, 2007

3. Smith RA: The evolving role of MRI in the detection and evaluation of breast cancer. N Engl J Med 356:1362-1364, 2007

4. Kuhl CK, Schrading S, Bieling HB, et al: MRI for diagnosis of pure ductal carcinoma in situ: A prospective observational study. Lancet 370:485-492, 2007

5. Garrido-Laguna I, Hidalgo OF, Foncillas JG: MRI evaluation of breast cancer. N Engl J Med 357:191, 2007

6. Sweeney KJ, Sacchini V: MRI evaluation of breast cancer. N Engl J Med 357:192, 2007

7. Morrow M, Keeney K, Scholtens D, et al: Selecting patients for breast-conserving therapy: The importance of lobular histology. Cancer 106:2563-2568, 2006

8. Gao X, Fisher SG, Emani B: Risk of second primary cancer in the contralateral breast in women treated for early-stage breast cancer: A population-based study. Int J Radiat Oncol Biol Phys 56:1038-1045, 2003

9. Irwig L, Houssami N, Armstrong B, et al: Evaluating new screening tests for breast cancer may require randomized controlled trials to assess overdetection. BMJ 332:678-679, 2006

10. Lord SJ, Lei W, Craft P: A systematic review of the effectiveness of magnetic resonance imaging (MRI) as an addition to mammography and ultrasound in screening young women at high risk of breast cancer. Eur J Cancer 43:1905-1917, 2007