Review

Application of magnetic resonance imaging to early detection of breast cancer

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Abstract

Since its first introduction approximately 10 years ago, there has been extensive progress in the application of magnetic resonance imaging (MRI) to the detection and diagnosis of breast cancer. Contrast-enhanced MRI has been shown to have value in the diagnostic work-up of women who present with mammogram or clinical abnormalities. In addition, it has been demonstrated that MRI can detect mammogram occult multifocal cancer in patients who present with unifocal disease. Advances in risk stratification and limitations in mammography have stimulated interest in the use of MRI to screen high-risk women for cancer. Several studies of MRI high-risk screening are ongoing. Preliminary results are encouraging.

Keywords: breast cancer, contrast-enhanced, high-risk, magnetic resonance imaging

Introduction

It is estimated that approximately one in nine women will develop breast cancer in her lifetime. For example, in the USA it is estimated that 180 000 women develop breast cancer, and approximately 45 000 women die of the disease each year [1]. It has been demonstrated [2] that the smaller the lesion is at the time of detection, the better the prognosis. The ability of mammography screening to reduce breast cancer mortality rates was demonstrated by several studies performed in the US and Europe [3–5]. As much as a 23% reduction in breast cancer mortality for the screened population has been demonstrated. Additional studies, such as the Breast Cancer Demonstration Project sponsored by the US National Cancer Institute and the American Cancer Society in the 1970s [6], also demonstrated reduction in breast cancer mortality in a screened population. It is now generally accepted that careful screening with mammography will reduce the breast cancer mortality rate in a given population.

Despite the success of mammography screening, mammography does have limitations. Perhaps its most significant limitation is the difficulty in detecting masses within radiographically dense breast [7]. In addition, cancers can be missed by mammography. Retrospective studies of breast cancer in which prior mammograms where read as negative [8–10] showed that the cancer was visible in retrospect in approximately one-third of the cases. In addition, the relatively low specificity of mammography leads to many breast biopsies that reveal benign tissue [11].

Over the past 10 years there has been great progress in our understanding of risk factors for breast cancer. The use of genetic testing or risk modeling allows women to be stratified according to risk [12••,13••]. In addition, it has been suggested that the radiographic density of a woman's mammogram may influence her risk for breast cancer [14••]. High-risk patients develop breast cancer when they are young and when the sensitivity of mammo-

MRI = magnetic resonance imaging.

graphy is most limited. Risk stratification, coupled with the limitations of mammography identified above, has driven an effort to develop more robust techniques for the detection of breast cancer.

Breast magnetic resonance imaging

The application of MRI to detect breast cancer was first reported in the 1980s. Use of intrinsic tissue contrast based on T1 and T2 was shown [15–17] not to be helpful for the detection and diagnosis of breast cancer. These early reports did demonstrate that high-quality images could be obtained from the breast using dedicated surface coils. In 1989, Kaiser *et al* [18] and Heywang *et al* [19] independently reported on the use of contrast-enhanced breast MRI to detect breast cancer. The contrast agents used in those studies were freely diffusable gadolinium chelates. These agents are believed to serve as crude markers for tumor angiogenesis. In addition to detecting mammographically visible lesions, an important finding on early studies was that MRI is capable of detecting breast cancers that are not visible by mammography [20•].

Although there has been great controversy over the details of breast MRI technique, there are a number of principles that are uniformly accepted. Breast MRI is best performed on high field (≥1 T) systems. The efficacy of breast MRI on lower field systems (0.2–0.5 T) has not been clearly demonstrated. In addition, it is widely accepted that dedicated breast surface coils are critical to performing successful breast MRI. It is also widely accepted that breast MRI must be performed with the administration of intravenous contrast. In order to detect angiogenesis, imaging must commence immediately after contrast administration. Carcinoma is identified by its enhancement after contrast administration. Unfortunately, many benign lesions, including fibroadenomas, benign proliferative disease, and atypical proliferative disease, will also enhance after contrast administration. Several strategies have been developed for differentiating benign from malignant enhancing lesions on breast MRI. These include use of the architecture of the enhancing lesion, as well as the kinetics of its enhancement (these techniques are reviewed in detail in an accompanying review by Leach).

Early reports of contrast-enhanced breast MRI [18] suggested that lesions in which contrast arrived rapidly (within approximately 2 min) and then washed out over the first 5 min probably represent cancer, whereas those lesions that showed continuous increase in contrast concentration over a prolonged period of time were more likely to be benign. Physiologic models of the kinetic response of the lesion to contrast have been developed in an effort to characterize tumor angiogenesis better. The key parameter provided by fitting the kinetic response of the lesion to a physiologic model is the permeability × surface area product. This was shown [21•] to be an important predictor of lesion histology. Although there has been some work in pharmacokinetic modeling of contrast uptake, it is general clinical practice to consider lesions that demonstrate washout kinetics to be more suspicious than those that exhibit persistent enhancement.

Other early reports on breast MRI [22•] stress the use of the architecture of enhancement to differentiate benign from malignant enhancing lesions. Enhancement in a ductal distribution was considered very suspicious for *in situ* cancer. The borders of focal regions of enhancement were very important determinants of likelihood of malignancy, with the more irregular borders being more suspicious for cancer. Several other architectural features, such as enhancement along the rim (suspicious for cancer) or nonenhancing internal septations (probably representing a benign fibroadenoma), were also described. Nunes *et al* [23] reported a recursive partitioning-based architectural interpretation model for breast MRI, which takes into account many of these architectural features. In a diagnostic population, MRI demonstrated 96% sensitivity and 72% specificity for differentiating benign from malignant enhancing breast lesions. It is now generally accepted that a combination of architectural and kinetic features should be used for differentiating benign from malignant breast lesions. The use of these features in a diagnostic population will have performance similar to that described in the model reported by Nunes *et al* [23].

One of the most exciting uses suggested for breast MRI was in the evaluation of the extent of breast cancer. Harms *et al* [20•] reported that additional foci of cancer could be detected in up to 30% of women who underwent mastectomy for breast cancer. Similar results have been reported by other investigators [24]. These reports are very significant, and they clearly demonstrated the ability of MRI to detect mammographically and clinically occult breast cancer. This fact underscored the need for development of needle guidance systems for MRI, so that MRI-detected lesions could be sampled.

The development of techniques and equipment to perform magnetic resonance-guided breast biopsy was the subject of a meeting of the Federal Multi-Agency Consortium on Imaging Technologies to Improve Women's Health, which was held on May 1, 1997. Two basic approaches have been described for performing magnetic resonance-guided breast interventions. The first involves compressing the breast in a grid similar to the alphanumeric grids that are used for mammographic needle localization procedures [25,26•]. Lesions can be localized in three dimensions relative to this grid by scanning patients in the magnet with the grid applied. Needles can then be placed into the breast outside of the magnet for purposes of localization and biopsy. There are magnetic resonance

compatible, nonmagnetic needles that are available for this purpose. Others have developed interactive breast biopsy techniques using open magnet systems. Higher field, open systems such as the General Electric Magnetic Resonance Intervention system have been shown to be useful in this regard [27]. The proliferation of higher field, open systems will make interactive breast biopsy under magnetic resonance guidance a reality. In addition to needle localization, core biopsy and vacuum-assisted core biopsies are currently being performed under magnetic resonance guidance at centers around the world.

Magnetic resonance imaging in high-risk populations

Perhaps the most exciting applications of breast MRI for the detection of breast cancer involve the screening of high-risk populations. The first attempt at using MRI to detect cancer in a mammographically and clinically normal breast was in the setting of women who present with axillary node disease [28••,29]. Several studies have demonstrated that breast MRI can detect the primary cancer in women who present with malignant axillary adenopathy and unknown primary lesion. In a study reported by Orel *et al* [29], MRI detected the primary lesion in 85% of women who presented with positive axillary nodes, and negative mammography and clinical examinations. Similar results were reported by Morris *et al* [28••].

The next reported application of breast MRI in a screening role was screening of the contralateral breast in women with breast cancer. The published results of several small series [30] suggest a 5–10% cancer yield when screening the contralateral breast at the time of the original presentation. For example, Dunfee *et al* [31] detected nine otherwise occult contralateral cancers with MRI in 92 patients. This is far in excess of the 2–3% incidence of contralateral breast cancer suggested by the National Surgical Adjuvant Breast and Bowel Project B-14 study [32,33]. If these early results were confirmed in larger, more rigorous studies, then this would indicate that MRI can detect lesions before they become mammographically or clinically apparent.

There are a number of studies being performed around the world that are investigating the potential utility of breast MRI in high-risk populations. In particular, studies are being performed in the UK, The Netherlands, Germany, Canada, and in the USA. The principal investigators of these studies have been organized into a loose consortium under the umbrella of the International Working Group for Breast MRI. The Working Group Technical Report [34] contains information on each of these studies. Patient populations vary from study to study, and the final results are not yet available. Although each of these studies is small, they will collectively accrue approximately 6000 women. Efforts are underway to develop a mechanism for collective analysis of data from across these studies. Some centers have reported interim results.

A high-risk screening study including 1500 women has been initiated in the UK, funded through the Medical Research Council and National Health Service [35••]. Eligible patients are below the age of 50 years and either carry a known breast cancer susceptibility gene or are calculated to have at least a 50% risk of carrying such a gene. The study is being conducted at 19 centers throughout the UK. Women will undergo screening evaluations every year for 4 years that consist of both MRI and mammography. No preliminary results have been reported for the UK study.

A Canadian study is being performed at Sunnybrook and Women's College Health Sciences Center at the University of Toronto [36••]. That pilot study is aimed at accruing 200 high-risk women. Their high-risk criteria include women who have at least three relatives who had breast cancer at age less than 50 years or ovarian cancer at any age. Women also have no previous radiotherapy for breast cancer. The protocol consists of annual mammography, ultrasound, and MRI. Clinical breast examination is performed twice each year. Preliminary results have been reported on 139 women that have been entered into the study [36••]. To date six cancers have been detected. All six were detected by MRI. Two each were detected by clinical breast examination and mammography. Ultrasound detected three cancers. A combination of clinical breast examination and mammography would have detected four cancers. The combination of clinical breast examination, mammography, and ultrasound would also have detected four out of the six cancers. Therefore, two of the six cancers were occult to conventional screening techniques. The largest cancer detected in the study was 1.5 cm, while the smallest was 5 mm.

A study being performed by the National Expert and Training Center for Breast Cancer Screening at the University of Nijmegan in The Netherlands [37••] is considering two populations of women: women who are at personal risk for developing breast cancer on the basis of prior biopsy results; and women in whom familial risk factors for developing breast cancer have been identified. To date, a total of 622 women have been recruited into the screening study, 228 of whom were recruited on the basis of familial risk criteria. To date, a total of 45 cancers have been reported across all individuals enroled in the study.

The National Institutes of Health in the USA is funding a multicenter pilot study that is aimed at screening high-risk women for breast cancer. The study is expected to recruit 400 women who have a 30% lifetime risk of cancer on the basis of the Gail or Clause model, or who have at least a 50% chance of carrying a breast cancer susceptibility

gene as assessed using the Couch model. Women undergo screening examinations every year for 2 years that consist of clinical breast examination, mammography, and MRI. This study is currently recruiting, and no data have yet been released.

The most comprehensive report was that of Kuhl *et al* [38••]. In that study of 192 patients, of whom 105 had adequate follow up to determine disease-free status, a total of nine cancers were discovered through the use of mammography, mammography + ultrasound, and MRI screening. Three cancers were detected by mammography; mammography + ultrasound detected a total of four cancers. MRI detected all nine cancers; this included five cancers that were occult to mammography + ultrasound. These results, although very preliminary, clearly demonstrate great potential for MRI in increasing the yield of screening high-risk women.

Conclusion

Breast MRI is a developing imaging modality that has shown great promise for the early detection of breast cancer. Some of the basic principles of technique and interpretation are beginning to be standardized. Equipment to perform magnetic resonance-guided interventions is beginning to become available. Early results suggest that MRI may dramatically improve the yield of screening certain at-risk populations. However, there has been no large study to validate the efficacy of MRI as a screening modality for any population. Continued work needs to be performed to establish clearly the role for breast MRI in early detection of breast cancer.

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