



TITLE: **MRI of the Breast for Preoperative Evaluation
in Patients with Localized Breast Cancer**

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MAGNETIC RESONANCE IMAGING OF THE BREAST FOR PREOPERATIVE EVALUATION IN PATIENTS WITH LOCALIZED BREAST CANCER

BACKGROUND

In 2002, there will be an estimated 203,500 new cases of invasive breast cancer in the United States and an estimated 40,000 deaths from this cancer. This represents approximately 31% of all new cancer cases in women and 15% of all cancer deaths in women (ACS 2002). In addition to invasive breast cancer, 54,300 new cases of *in situ* breast cancer are expected to be diagnosed in women in 2002. Cancer of the breast is the most common form of cancer in women. Every American woman is estimated to have a 1 in 8 chance of developing breast cancer at some time during her life.

Most patients with breast cancer present with the complaint of a breast mass or an abnormal screening mammogram. A fine-needle aspiration, core needle biopsy, or open surgical biopsy can be used to obtain a definitive tissue diagnosis of breast cancer.

Once breast cancer has been diagnosed, staging depends on assessment of both the tumor size and regional lymph node involvement. A patient's prognosis is directly related to the initial stage of her breast cancer. Prior to the initial surgical management of breast cancer and after making a tissue diagnosis of breast cancer, the patient undergoes a clinical staging evaluation. This includes bilateral mammography (to evaluate for synchronous cancer), a complete physical examination, chest radiography, and liver function tests. Further testing is done only if abnormalities are found during this evaluation.

Based on this presurgical evaluation the patient is assigned a clinical stage for her breast cancer using the TNM staging system (1997) of the American Joint Committee on Cancer (Table 1).

BACKGROUND, continued

This classification describes tumor size (T), node involvement (N), and evidence of metastasis (M). Initial treatment options are then determined using the presurgical tumor stage. Patients with early stage invasive cancers (defined as stage II or I) usually undergo some form of local surgical excision to completely remove the tumor.

Table 1: TNM Staging for Breast Cancer

Tumor:	Tis	Carcinoma in situ
	T0	No evidence of primary tumor
	T1	Tumor ≤ 2 cm
	T2	Tumor > 2 cm but ≤ 5 cm
	T3	Tumor > 5 cm
	T4	Tumor with direct extension to chest wall or skin
Nodes:	N0	No regional node metastases
	N1	Metastases to ipsilateral axillary nodes, mobile
	N2	Metastases to ipsilateral axillary nodes, fixed
	N3	Metastases to ipsilateral internal mammary nodes
Metastases:	M0	No distant metastases
	M1	Metastases present
	M1	
Stage:	0	Tis, N0, M0
	I	T1, N0, M0
	IIA	T0 or T1, N1, M0 or T2, N0, M0
	IIB	T2, N1, M0 or T3, N0, M0
	IIIA	T0 or T1 or T2, N2, M0 or T3, N1 or N2, M0
	IIIB	Any T, N3 M0 or T4, Any N, M0
	IIIC	Any T, any N, M0
	IV	Any T, any N, M1

BACKGROUND, continued

Options for surgical management of the primary tumor include breast-conserving therapy with radiation therapy, mastectomy plus reconstruction, and mastectomy alone. Surgical staging of the axilla is usually performed. Survival is equivalent with any of these options as documented in randomized prospective trials and meta-analyses of the trials (Sarrazin *et al.* 1989; Veronesi *et al.* 1990; Blichert-Toft *et al.* 1992; van Dongen *et al.* 1992; Fisher *et al.* 1995; Jacobson *et al.* 1995; Veronesi *et al.* 1995; van Dongen *et al.* 2000). Selection of a local therapeutic approach depends on the location and size of the lesion, analysis of the mammogram, breast size, and the patient's attitude toward preserving the breast. The presence of multi-focal disease in the breast or a history of collagen vascular disease are relative contraindications to breast-conserving therapy (Abrams *et al.* 1995).

The most widely used surgical technique to treat breast cancer is the modified radical mastectomy. This procedure combines removal of axillary lymph nodes in continuity with the mastectomy. Unlike the extended radical mastectomy, the modified radical mastectomy leaves the pectoralis major and shoulder musculature intact, allowing for further prosthetic reconstruction.

Breast-conserving therapy refers to removal of the tumor with a rim of grossly normal appearing breast tissue. Removing the primary lesion with a normal tissue margin of approximately 1 cm is recommended, although the importance of clear margins is still debated. A modification of breast-conserving therapy is quadrantectomy, in which 1 to 2 cm of normal tissue and overlying skin is removed. If pathology shows remaining tumor, re-excision or modified radical mastectomy is recommended. In all of the described procedures, an axillary dissection is done through a separate incision. Breast-conserving therapy is part of a multidisciplinary approach, requiring postoperative radiation to the whole breast and an optional radiation boost to the tumor bed. Without tumor bed radiation after breast-conserving therapy, the incidence of local recurrence is approximately 35% as opposed to 10% (Fisher *et al.* 1995).

Indications for Breast-conserving Therapy

Breast-conserving therapy is appropriate for the majority of women with stage I or II infiltrating breast cancer. Important considerations when selecting the appropriate surgical management include cosmetic result, clinical criteria, psychosocial issues, patient preferences, and locoregional control. Women with tumors greater than 4 cm or small breasts are generally not candidates for breast-conserving therapy due to poor cosmetic results. Women with multicentric neoplasms or diffuse microcalcifications on mammography have not generally been offered breast-conserving therapy due to increased risk of local recurrence.

If breast-conserving therapy has similar outcomes with respect to recurrence and mortality compared to more aggressive surgical management, it may be a psychologically preferable treatment. A systematic review of quality of life studies found better body image, better sexual functioning and better marital and social relations among women receiving breast-conserving therapy compared to those receiving modified radical mastectomy (Kiebert *et al.* 1991).

Unfortunately, breast-conserving therapy continues to be underutilized in the United States. In a national sample of 16,643 women with stage I or II breast cancer, only 43% were treated with breast conservation therapy (Morrow *et al.* 2001). A second study of 231 women with breast cancer found that 29% were offered only mastectomy during their initial consultation (Clauson *et al.* 2002).

Concerns with Breast-conserving Therapy

The main concern with breast conservation therapy is the possibility of leaving behind invasive tumor foci, which then may lead to higher local recurrence rates, distant metastasis, or increased mortality. Holland *et al* (1985) studied a group of 282 patients with invasive breast cancer who were eligible for breast conservation therapy but underwent mastectomy instead. A microscopic analysis of the breast specimens was performed. Only 37% of cases were free of tumor foci around the index lesion. The additional tumor foci were within 2 cm of the index lesion in 20% of the cases and beyond 2 cm in 43%.

Magnetic Resonance Imaging of the Breast

Over the past decade, MRI of the breast has been studied in a variety of clinical settings, including both benign and malignant conditions of the breast. Controversy remains regarding the role MRI should play in the evaluation of patients with known or suspected breast cancer.

Breast MRI is performed using commercially available MRI machines; however, technical approaches to MRI of the breast vary. Breast tissues generally have similar signal intensities as tumor tissue on routine MRI sequences. However, malignant breast lesions typically demonstrate significant enhancement following the intravenous administration of gadolinium contrast. Tumor enhancement relates to increased angiogenesis in tumor tissues and increased vascular permeability (Knopp *et al.* 1999). While the majority of malignant breast lesions exhibit contrast enhancement, some malignancies may not (e.g. lobular carcinoma, ductal carcinoma in situ (DCIS)). Furthermore, some benign breast conditions may demonstrate marked contrast enhancement (e.g. fibroadenoma, inflammatory conditions). Normal breast tissues may demonstrate diffuse enhancement that relates to hormonal influences. MRI during the first two weeks of the menstrual cycle has been recommended to reduce this phenomenon (Rieber *et al.* 1999).

The observation that contrast enhancement of a breast lesion is a nonspecific feature has led investigators to explore whether patterns of lesion enhancement on dynamic imaging after contrast bolus might provide a greater degree of specificity in diagnosing malignancy. Typically, malignant lesions reach peak enhancement quickly and then wash out more quickly. Benign lesions that show enhancement generally demonstrate a less rapid initial increase in enhancement and continue to enhance over time; however, there are variability and overlap in these patterns and time-enhanced patterns alone do not provide an accurate diagnosis in all cases (Kuhl *et al.* 1999; Orel *et al.* 1999).

Some investigators have incorporated additional criteria into the determination of MRI results in an attempt to increase the specificity without compromising sensitivity. Descriptive features of lesion morphology such as those used in X-ray mammography may be helpful in this regard. For example, lesions with irregular or spiculated margins are characteristically malignant while lesions with smooth, regular margins are usually benign (Nunes *et al.* 1997a; Nunes *et al.* 1997b).

Magnetic Resonance Imaging of the Breast. continued

Others have studied the distribution pattern of contrast enhancement within a lesion noting whether there is uniform or heterogeneous enhancement (Sherif *et al.* 1997; Mussurakis *et al.* 1998).

MRI is performed before contrast administration and after contrast administration, but there are several technical methods employed by different investigators. Post-contrast images may be obtained maximizing spatial resolution for better detail using high-resolution MRI sequences or maximizing temporal resolution using dynamic imaging. High-resolution MRI generally requires several minutes to acquire the data and thus only one or two sets of post-contrast images may be obtained during the 5-minute period of enhancement after contrast injection. Dynamic imaging sequences sacrifice some spatial resolution and are each acquired within seconds so that imaging may be rapidly repeated during the enhancement period. High-resolution imaging demonstrates the presence of enhancing lesions but does not provide dynamic information on the variation of enhancement over time.

In preoperative evaluation and staging of a known breast tumor, whole breast imaging would be necessary. In designing the MRI sequence, it might be preferable to maximize sensitivity (i.e. lesion detection) at the expense of specificity. Using this approach, biopsy confirmation of at least one focus of multicentric tumor would be necessary before treatment decisions were altered.

The magnetic field strength of the MRI machine employed varies in the literature. Most studies use a general -purpose high field MRI system (1.0-1.5 Tesla) for imaging, though low-field MRI systems (0.5 Tesla) have been studied as well. Low-fields have inherent limitations in sensitivity for detecting gadolinium enhancement compared to high-field imaging and may require longer data acquisition times. Possible advantages of low-field systems are lower cost and the potential for open-access designs, permitting access to the patient for MRI-guided biopsy.

Magnetic Resonance Imaging of the Breast. continued

MRI of the breast is typically performed with the patient in a prone position with the breasts hanging through a cutout in the table. The use of a dedicated breast coil is generally recommended. Some studies have explored using breast compression. When MRI-guided biopsy of a lesion is planned, the patient may be positioned on her side to permit easier access to the breast for biopsy. Biopsy of breast lesions identified on MRI has been accomplished using MRI-compatible needles and localization equipment (Orel *et al.* 1994; deSouza *et al.* 1995).

MRI of the breast has the potential to identify multicentric tumors that would not be detected by current pre-surgical staging practices. Furthermore, MRI may more accurately measure tumor size than physical exam and mammography alone. The addition of MRI, in theory, could identify more accurately who would not qualify for breast conservation therapy and may benefit from modified radical mastectomy instead.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate governmental regulatory bodies.

MRI of the breast can be performed using commercially available MRI scanners and intravenous contrast agents. Specialized breast coils such as the OBC-300 Breast Array Coil (MRI Devices Corp., Waukesha, WI) and MRI-compatible equipment for performing biopsy have been developed and approved for marketing via the FDA 510(k) approval process as substantially equivalent to predicate devices for use in conjunction with a magnetic resonance scanner to produce diagnostic images of the breast and axillary tissues that can be interpreted by a trained physician.

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The relevant health outcomes for this review are survival, disease-free survival, and locoregional recurrence. Survival can be examined as overall survival or breast cancer-free survival. Given that various treatment options can increase morbidity and mortality, the overall survival is the most important outcome to consider. The second major health outcome to consider is breast cancer recurrence. Recurrence can be local, locoregional, or distant. In the strictest criteria, local recurrence can be defined as ipsilateral breast tumor recurrence. Locoregional recurrence is defined as recurrence within the ipsilateral breast, chest wall, local lymph nodes, or skin at the surgical site.

The literature review did not identify any studies evaluating the effect of MRI for breast cancer staging on locoregional recurrence, distant recurrence, or survival. There were multiple publications evaluating the sensitivity and specificity of MRI in identifying multicentric breast tumors and evaluating the primary tumor size (Harms *et al.* 1993a; Boetes *et al.* 1995; Rodenko *et al.* 1996; Orel *et al.* 1997; Rieber *et al.* 1997; Yang *et al.* 1997; Douek *et al.* 1998; Kramer *et al.* 1998; Drew *et al.* 1999). Most of these studies used a pathologic analysis as the gold standard and mammography or clinical exam and ultrasound as a comparison. One retrospective case series (Tillman *et al.* 2002) examined the effect of breast MRI on clinical management of women with early breast cancer.

MRI is clearly more sensitive than standard preoperative evaluation for the detection of multicentric tumors. Numerous studies in the diagnostic setting have estimated that MRI sensitivity rates for detecting invasive breast cancer lie between 95% and 100% (Heywang *et al.* 1989; Kaiser *et al.* 1989; Harms *et al.* 1993b; Boetes *et al.* 1994; Gilles *et al.* 1994; Orel *et al.* 1995; Stomper *et al.* 1995) compared with a sensitivity of approximately 85% for mammography (Homer 1991). The best evidence that MRI offers higher sensitivity in detecting multicentric tumor compared to standard methods is the prospective, blinded study by Drew *et al.* (1999). In 68 patients who underwent surgery for cancer, 35 (51%) had multicentric tumor. MRI correctly identified multicentricity in all cases with 100% sensitivity and 100% specificity.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes (continued).

Standard assessment using a combination of clinical exam, mammography, and needle biopsy only identified 26% of the cases of multicentric tumors. MRI correctly identified 26 patients (38% of 68 total) who were not suspected to have multicentric disease by standard evaluation. This suggests that 38% of patients might have been offered breast-conservation therapy without knowledge of multicentric disease detected only on breast MRI. The unanswered question is whether changes in clinical management based on these MRI findings affect long-term survival or locoregional recurrence.

Tillman *et al* (2002) reported the results of a retrospective review of the records of 207 women with 212 early stage breast cancers who underwent breast MRI during work-up for breast conservation therapy. They report that the MRI findings affected the clinical management in 43 cases (20% of 212 breast cancers). In 19 of the cases, the MRI prompted or hastened mastectomy. Two patients were spared biopsy because the MRI was read as low probability of cancer. In the remaining 22 cases, MRI facilitated biopsy of lesions, 7 of which led to wider local excision. The authors conclude that the changes in clinical management were somewhat or strongly favorable for 24/43 (56%) of the patients in whom MRI prompted change and somewhat or strongly unfavorable for 14/43 (33%). However no long-term clinical outcomes were presented. Of note, 19/207 (9%) women, who otherwise would have been offered breast-conserving therapy, were treated with mastectomy based on the MRI findings.

TA criterion 2 is not met.

Level of Evidence: 5

TA Criterion 3: The technology must improve the net health outcomes.

Given the previously described information, between 9% (Tillman *et al.* 2002) and 38% (Drew *et al.* 1999) of patients who have an MRI as part of their staging workup would have multicentric tumor not found by current preoperative staging. The question remains whether this increased sensitivity translates into benefits with respect to locoregional recurrence, distant recurrence or survival.

To date, there are 8 randomized controlled trials (Atkins *et al.* 1972; Veronesi *et al.* 1981; Sarrazin *et al.* 1989; Blichert-Toft *et al.* 1992; Fisher *et al.* 1995; Jacobson *et al.* 1995; Fisher *et al.* 2002; Veronesi *et al.* 2002) that compare modified radical mastectomy to breast conservation therapy plus radiation (Table 2). In no trial has there been a difference in survival between the two treatment options. Furthermore, in 6 of the 8 trials, there was no difference in locoregional recurrence or disease-free survival. In the Guy's hospital trials I and II (Atkins *et al.* 1972), patients who received a modified radical mastectomy had a lower incidence of locoregional recurrence and better disease-free survival. These two trials were the first studies on modified radical mastectomy versus breast conservation therapy. Overall outcomes, including survival, local recurrence and disease-free survival are considered unacceptable by today's standards. Techniques employed at the time are currently outdated, including failure to microscopically examine surgical margins, lack of axillary node dissection, and too low a radiation dose after breast conservation therapy.

The largest primary study of breast conservation therapy versus modified radical mastectomy, the NSABP B-06 trial (Fisher *et al.* 2002), was conducted in the US and enrolled 1851 women. Twenty year follow-up data were recently published with a hazard ratio for death among women receiving breast conservation surgery plus radiation compared with those who underwent mastectomy of 0.97 (95% CI 0.83-1.14, p=0.74) and a hazard ratio for disease-free survival of 0.94 (95% CI 0.82-1.09, p=0.41).

TA Criterion 3: The technology must improve the net health outcomes (continued).

Table 2: Randomized Clinical Trials of Breast-conserving Therapy versus Mastectomy

<i>Trial</i>	<i>Patients (N)</i>	<i>Survival</i>	<i>Locoregional recurrence*</i>
NCI Italy	701	At 5 years	At 5 years
Veronesi (1981, 2002)		- MRM 90%	- MRM 0.9%
		- BCT 90%	- BCT 1.4%
NSABP B-06	1851	At 12 years	At 12 years
Fisher (1995, 2002)		- MRM 62%	- MRM 10%
		- BCT	- BCT
		+XRT 62%	+XRT 10%
		No XRT 60%	No XRT 35%
DBCG-82TM	905	At 6 years	At 6 years
Blichert-Toft (1992)		- MRM 82%	- MRM 3.7%
		- BCT 79%	- BCT 2.5%
EORTC	903	At 8 years	At 8 years
Van Dogen (1992)		- MRM 73%	- MRM 8%
		- BCT 71%	- BCT 13%
NCI USA	247	At 10 years	At 10 years
Jacobson (1995)		- MRM 75%	- MRM 4%
		- BCT 77%	- BCT 4%
IGR	179	At 10 years	At 10 years
Sarrazin (1989)		- MRM 80%	- MRM 12%
		- BCT 79%	- BCT 7%
Guy's Hospital Trial	370	At 5 years	At 5 years
Atkins (1972)		- MRM 72%	- MRM 16%
		- BCT 56%	- BCT 48%

* Locoregional recurrence includes local and regional (chest wall, local lymph nodes, and skin at the surgical site)

BCT Breast-Conservation Therapy
 DBCG Danish Breast Cancer Cooperative Group
 EORTC European Organization for Research and Treatment of Cancer
 IGR Institute Gustave-Roussy
 MRM Modified Radical Mastectomy
 NCI National Cancer Institute
 NSABP National Surgical Adjuvant Breast and Bowel Project
 XRT Radiation therapy

TA Criterion 3: The technology must improve the net health outcomes (continued).

Several meta-analyses have been done in order to increase the power to detect small differences in outcomes. Morris *et al.* (1997) included 6 of the 8 primary trials (excluding the 2 Guy's Hospital trials) and found that survival was insignificantly better for breast-conservation surgery plus radiation (OR = 0.91, 95% CI 0.78-1.05 at 10 years) compared with modified radical mastectomy. The most comprehensive meta-analysis is the Early Breast Cancer Trialists/Collaboration Group (1995). In 9 studies involving 17,273 women, no survival difference was seen between breast conservation therapy with radiation and modified radical mastectomy. Furthermore, in 6 studies involving 3107 women, no differences were seen in the 10-year locoregional recurrence rate (breast conservation therapy = 5.9% and modified radical mastectomy = 6.2%). In a more recent meta-analysis (2000), the Early Breast Cancer Trialists' Collaboration Group showed a marginally significant reduction in the risk of death due to breast cancer after lumpectomy and irradiation ($p=0.04$) compared with mastectomy. This reduction was offset by an increase in the risk of death from causes other than breast cancer ($p=0.05$).

In summary, MRI is more sensitive for multicentric disease in the staging of early breast cancer. Between 9% and 38% of women will be found to have multi-centric disease and may be offered mastectomy as opposed to breast-conserving therapy with radiation therapy. However, there are no comparative studies demonstrating improved outcomes in women staged with MRI. Furthermore, the long-term results of the primary clinical trials using the standard staging evaluation show no trend towards worse outcomes in women randomized to breast-conserving treatment as opposed to mastectomy. It is unlikely that the addition of MRI to staging will improve disease-free or overall survival and it may result in an increase in the number of women undergoing mastectomy.

TA Criterion 3 is not met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The scientific evidence is insufficient to permit conclusion concerning the benefits of the addition of MRI to the standard staging workup of suspected early stage invasive breast cancer; therefore, it is not possible to determine whether the procedure is as beneficial as alternatives. Indeed there would likely be a decrease in the number of women offered breast-conserving therapy. Current evidence supports that breast-conserving therapy and mastectomy produce equivalent long-term rates of locoregional recurrence and survival. Thus fewer women would be offered breast-conserving therapy for no gain in clinical outcomes; clearly an undesirable effect.

TA criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside the investigational setting.

Whether the addition of MRI to the standard staging work-up of suspected early stage invasive breast cancer improves health outcomes has not been established in the investigational setting.

TA criterion 5 is not met.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association

In December 2000, a Blue Cross Blue Shield Association Medical Advisory Panel concluded that MRI of the breast as a technique to evaluate the presence of multicentric disease in patients with clinically localized breast cancer is considered investigational.

Centers for Medicare and Medicaid Services (CMS)

This technology has not been specifically addressed by CMS on either a national or local basis.



RECOMMENDATIONS OF OTHERS, continued

California Radiological Society (CRS)

The Society has been asked to provide a position statement and representation at the meeting.

Association of Northern California Oncologists (ANCO)

The Association has been asked to provide a position statement and representation at the meeting.

Medical Oncology Association of Southern California (MOASC)

The Association has been asked to provide a position statement and representation at the meeting.

American Society of Breast Surgeons

The Society has been asked to provide a position statement and representation at the meeting.

CONCLUSION

It has been suggested that MRI should be part of the preoperative evaluation of early breast cancer. These recommendations are based on the identification of unsuspected foci of carcinoma in 9% to 38% of women (Drew *et al.* 1999; Tilman *et al.* 2002) who undergo MRI. The possibility that small foci of carcinoma can be present in apparently normal breast tissue has been recognized since the 1970s. Pathological studies of breast tissue specimens from women with localized tumors have shown occult carcinoma in similar proportions of women (Rosen *et al.* 1975; Holland *et al.* 1985). These pathological studies formed the cornerstone of the argument that breast-conserving therapy was inappropriate. The NSABP B-06 trial conducted by Fisher *et al.* (2002) demonstrated that these foci of tumor are clinically significant. Among patients treated with lumpectomy alone, the incidence of a recurrence in the ipsilateral breast was 39.2%, whereas it was 14.3% when the treatment was lumpectomy plus irradiation of the breast.

CONCLUSION, continued

However, in the same study, there were no differences in locoregional recurrence or long-term survival between women treated with lumpectomy plus irradiation of the breast and those treated with mastectomy (Fisher *et al.* 2002). This is a consistent finding in clinical trials of breast conserving therapy versus mastectomy (Early Breast Cancer Trialists' Collaborative Group 1995). As Dr. Morrow writes in her editorial accompanying the publication of the 20 year NSABP B-06 results and NCI Italy results: "Subjecting women to mastectomy because we now have an imaging technique that is sensitive enough to detect microscopic foci of tumor is not a step forward" (Morrow 2002). The preponderance of the evidence is that breast-conserving therapy is underutilized in the treatment of early breast cancer. The use of magnetic resonance imaging during preoperative evaluation would tend to decrease the number of women offered breast-conserving therapy with no evidence to support improved health outcomes.

RECOMMENDATION

It is recommended that magnetic imaging of the breast for preoperative evaluation in patients with localized breast cancer does not meet California Technology Assessment Forum criteria.

The California Technology Assessment Forum voted to accept the recommendation as written.

February 12, 2003

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