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Frequency and Clinical Significance of Extramammary Findings on Breast Magnetic Resonance Imaging

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Abstract

The use of breast magnetic resonance imaging has increased, and with that, questions regarding incidental extramammary findings (EMFs). We analyzed 1305 breast magnetic resonance images and found EMFs reported in 10.7% of studies ($n = 140$). Upstaging was rare and occurred in 0.6% of studies in this series ($n = 8$). EMFs did not lead to significant delay in surgical or systemic treatment for breast cancer.

Background: Use of breast magnetic resonance imaging (MRI) for screening and local staging of breast cancer has increased. With this, questions have emerged regarding the management and effect of extramammary findings (EMFs) reported on breast MRI.

Patients and Methods: Breast MRI studies performed between January 1, 2007 and December 31, 2012 at the University of Iowa were analyzed. Data were collected regarding number and location of EMFs, characteristics of the patients who had a breast MRI, and time to first treatment among the patients who had a breast MRI for stage I-III breast cancer.

Results: During the study period, 1305 breast MRIs were obtained in 772 women. An EMF was found in 140 studies (10.7%) and 113 women (14.6%). EMFs were more likely in MRIs of older patients (50 vs. 54 years, $P = .004$) and postmenopausal women ($P = .001$). Anatomically, most EMFs were seen in the liver (89 of 140) or bone (21 of 140). Eight women (0.6%) had an EMF on breast MRI that led to upstaging to stage IV breast cancer. For patients with stage I-III breast cancer, the finding of an EMF on breast MRI did not affect time to initial cancer treatment (13 vs. 14 days; $P = .586$).

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Disclosure

The authors have stated that they have no conflicts of interest.

Conclusion: EMFs on breast MRI are seen with some frequency and occur more commonly in older, postmenopausal women. In our study, most EMFs were benign and did not affect patient outcome with regard to upstaging to stage IV disease or time to cancer treatment. A very small portion of studies revealed subclinical advanced breast cancer.

Keywords

Breast MRI; Breast neoplasm; Incidental finding; Time to initial treatment; Upstaging

Introduction

The use of breast magnetic resonance imaging (MRI) has become more common in recent years. In fact, a study by Stout et al showed that the use of breast MRI in community practice increased approximately 16-fold from 2000 to 2011.¹

For patients with breast cancer, MRI has increasingly been used as a method for regional staging, to more closely evaluate the breast tissue, and to obtain information on local lymph nodes, which might have implications for further testing and treatment planning.^{2–6} Furthermore, breast MRI has been shown to be effective in evaluation of response to neoadjuvant therapy.^{7–10} As more medical therapies are applied in the neoadjuvant setting and we rely more heavily on accurate preoperative clinical staging, the use of pretreatment breast MRI is likely to continue. Although mammography has long been the mainstay of breast cancer screening and is the only screening tool shown to decrease breast cancer mortality,^{11,12} several studies have shown that breast MRI in addition to mammography is more sensitive in detecting invasive cancer than mammography alone, especially for high-risk patients.^{13–16}

Although there has been more research in the past several years regarding location and prevalence of incidental findings seen outside the breast on breast MRI, little is known about the significance and optimal management of these incidental findings. Although many of these findings will be benign, some will be malignant and affect disease staging. In some cases, even if only a small extramammary disease deposit is found on MRI, a woman who in an earlier era would have been treated with curative intent is now considered to have stage IV disease and generally deemed incurable. Importantly, these extramammary findings (EMFs) could delay care as work-up of nonbreast findings is pursued. Previous studies have reported that 10%–18% of breast MRI studies will contain an EMF and that 9%–34% of patients who undergo a breast MRI will have an EMF.^{17–23} However, there are no evidence-based guidelines that specifically address management of EMFs, creating uncertainty for the clinician and possibly anxiety for the patient, especially in cases of breast cancer, where there might be implications for treatment and ability to achieve cure.

Previous studies on EMFs have focused largely on their prevalence, location, and nature (benign or malignant).^{17–23} One recent study analyzed these aspects of EMFs, and costs associated with follow-up radiographic studies to further evaluate the EMFs.¹⁹ We sought to analyze EMFs in a large contemporary series from a clinical perspective and reviewed how EMFs correlated with patient and tumor characteristics, the indication for MRI, and the

frequency of upstaging to stage IV disease. Additionally, we studied whether the reporting of an EMF in women with stage I-III breast cancer affected time to first cancer treatment.

Patients and Methods

Breast MRI scans performed between January 1, 2007 and December 31, 2012 at the University of Iowa were included in the study, along with their associated electronic medical records (n = 1322). MRI reports were reviewed and confirmed by physicians (S.P., A.T., L.Y., C.M., C.X.) to identify EMFs. MRI scans were reviewed by a breast-dedicated radiologist (L.Y.) if specific questions arose. MRI scans were excluded if the individual had known stage IV breast cancer at the time of imaging (n = 17). Internal mammary nodes were not considered to be EMFs.

The incidence and anatomic location of EMFs were identified, along with whether the EMF led to a follow-up study or biopsy, and if the EMF led to upstaging to stage IV disease for the patient. For women with stage I-III breast cancer, time from MRI to initial treatment of surgery or systemic therapy was measured in days. Surgery included lumpectomy, unilateral and bilateral mastectomy, and axillary node dissection. Systemic therapy included chemotherapy, neoadjuvant chemotherapy, and neoadjuvant hormone therapy. Patients who were upstaged to stage IV disease because of an EMF on the MRI were not included in this analysis.

Age at the time of MRI was recorded. Data for menopausal status was obtained from the medical oncology clinician's documentation. Women were categorized as premenopausal or postmenopausal, where premenopausal was defined as women who were premenopausal or had not completed menopause. Indication for MRI was divided into 3 categories: breast cancer, high-risk, or clinical significance. Women with known active breast cancer before the MRI were placed in the "breast cancer" category. Patients were placed in the "high-risk" category if they carried a breast cancer susceptibility gene mutation, were designated high-risk based on family history, had a previous diagnosis of breast cancer that was definitively treated, or were deemed high-risk on the basis of breast tissue characteristics or clinical scenario. If a patient was to undergo an MRI scan for evaluation of a breast symptom or breast examination finding she was placed in the "clinical significance" category.

Receptor status was included for patients with stage I-III breast cancer. Hormone receptor (HR) status was categorized as positive (either estrogen receptor- or progesterone receptor-positive) or negative (both estrogen receptor- and progesterone receptor-negative). HER2 status was categorized as positive or negative. Those with missing subtype information were not included in subtype analyses.

The University of Iowa institutional review board approved this study.

Results

Patient Characteristics

During the study period, 1305 breast MRI scans were obtained in 772 women. Characteristics of the patients and tumors (for those with invasive cancer) are shown in Table

1. Most patients ($n = 505$) had a single MRI study and most studies (89.3%, $n = 1165$) did not have an EMF. There were 140 MRI studies in which an EMF was reported, representing 10.7% of studies and associated with 113 patients. Of these, 93 patients had a single EMF. The 1165 MRI studies without an EMF were associated with 692 unique patients. There were 33 patients who had multiple MRI studies, at least 1 MRI scan with an EMF and another MRI scan without an EMF.

Magnetic resonance imaging scans with EMFs were associated with older women. The median age of those with an EMF was 54 years, compared with 50 years for those without an EMF ($P = .004$). Menopausal status was also associated with a higher risk of having an EMF detected. Of the studies completed on premenopausal patients, 8.3% ($n = 62$) had an EMF compared with 14.5% ($n = 74$) of breast MRI scans completed on postmenopausal women ($P = .001$).

Clinical indication for breast MRI also correlated with the likelihood of an EMF. Among patients who had the MRI performed for stage 0-III breast cancer, 22.4% ($n = 81$) of the studies had an EMF. In contrast, for patients who underwent MRI for a clinically significant breast examination finding or high risk status, only 5.4% ($n = 21$) and 6.9% ($n = 38$) of studies reported an EMF, respectively. However, age also correlated with indication for breast MRI. In this cohort, the median age of patients for the MRI studies with an indication of breast cancer was older than the median age of patients for studies in which high risk was the indication (52 vs. 48 years; $P < .001$). In patients with stage I-III breast cancer, neither HR status nor HER2 status were associated with discovery of an EMF on breast MRI.

Anatomic Location and Evaluation of EMFs

The anatomic location of the EMFs and action taken, if any, and the number of patients upstaged to stage IV breast cancer are presented in Table 2. Location of EMFs included liver, bone, lung or parenchyma, pleural or pericardial effusion, vascular, skin, chest wall, peritoneum, and other (kidney, heart, and muscle). Of the 140 MRI studies with EMFs, 89 were in the liver, 21 were in bone, 10 were in the lung parenchyma, 9 were pleural or pericardial effusions, 8 were vascular findings, 4 were in the skin, 4 were in the chest wall, 2 were in the peritoneum, and 3 in other locations. A single MRI study could have EMFs in multiple locations.

There were 50 EMFs that led to follow-up imaging. Four patients underwent a biopsy or tissue sampling of the EMF. One of these biopsies was of a liver lesion that was pathologically confirmed as small lymphocytic lymphoma (SLL) which was consistent with the patient's known diagnosis of SLL. In total, 8 patients (7.0%) of the 113 patients with an EMF were upstaged to stage IV breast cancer because the EMF represented metastatic disease. These 8 corresponded to 0.6% of the full sample of 1305 MRI studies.

Of these 8 metastatic EMFs, 5 were in bone, 2 were in the liver, and 1 was a malignant pleural effusion. All 5 metastatic bone lesions were seen in the sternum on breast MRI. Positron emission tomography-computed tomography confirmed skeletal metastasis in all of these cases. Three of the 5 did not undergo any biopsies to confirm metastatic disease. The remaining 2 patients underwent biopsy of a bone lesion, which confirmed metastatic breast

cancer. Two patients underwent MRI of the abdomen to confirm the suspected metastatic hepatic lesions. Follow-up abdominal MRI studies showed growth of these hepatic lesions, consistent with metastatic disease. One patient underwent a thoracentesis for a pleural effusion, with cytology positive for metastatic breast cancer cells.

Patient characteristics of those with EMFs who were not upstaged compared with those who were upstaged to stage IV disease on the basis of breast MRI are shown in Table 3. Age, menopausal status, indication for MRI, and receptor status did not differ statistically between those who were upstaged and those who were not. However, the sample size of this subanalysis was very small. The proportion of MRI scans that ultimately led to women being upstaged is shown in Figure 1.

Time to Initial Treatment

A total of 185 patients with stage I-III breast cancer were included in the time to initial treatment analysis (Table 4). Overall, women who received neoadjuvant systemic therapy had a shorter time to initial treatment than those who underwent surgery (9 vs. 15 days; $P < .001$). There was no difference in treatment type for those with and without an EMF.

In women with stage I-III breast cancer who did not have an EMF ($n = 138$) the median time to initial treatment was 14 days and for patients with an EMF ($n = 47$) the median time to initial treatment was 13 days ($P = .620$). When categorized according to type of treatment, median time to surgery was 16 days for patients without an EMF versus 13 days for patients with an EMF ($P = .586$). Delivery of systemic therapy began a median of 9 days after MRI in women without an EMF and in 10 days for women with an EMF ($P = .796$). Time to treatment curves according to type of therapy and EMF status are shown in Figure 2.

Discussion

The role of breast MRI in the care of women with breast disease and at high risk for breast disease continues to evolve. Studies have shown that it clearly has a role in the screening of high-risk women and for treatment planning, especially in the setting of neoadjuvant chemotherapy.^{7,8,10,13,14} As such, management of patients with EMFs on breast MRI scans will likely remain a common clinical scenario.

This series shows that EMFs are reported in a minority of breast MRI studies, although the number of patients affected is significant. Most EMFs were not malignant, and only a very small percentage of patients with breast cancer were upstaged because of an EMF reported on breast MRI scan.

Previous retrospective studies have focused primarily on the prevalence and location of EMFs and the accuracy of radiographic characterization. Some of these studies reported the proportion of patients with an EMF and others reported the proportion of MRI studies with an EMF. In their study, Morakkabati-Spitz et al²⁰ reported a 9% rate of EMFs among their patient cohort, and in the study by Moschetta et al, 17% of patients were found to have an EMF, with 15% of these being malignant.²¹ A very recently published study by Alduk et al showed an EMF rate of 21.4% among their examined patients.²² The study published by

Iodice et al revealed a higher rate of EMFs, in 34% of patients.²³ In the study by Rinaldi et al,¹⁸ approximately 17.6% of MRI studies contained an EMF, with 20.4% of these ultimately deemed malignant, and in the study by Verslegers et al,¹⁷ 10% of MRI studies revealed an EMF, similar to the findings in our study. In one very recent study an EMF rate of 16.8% of MRI studies was reported.¹⁹ This study by Niell et al also analyzed costs associated with follow-up studies of EMFs, and they reported that these costs are relatively low, with abdominal MRI accounting for 55% of costs related to additional imaging.¹⁹

Our results are consistent with previous studies that have shown that the liver is the most common anatomic site of an EMF.^{17–23} Hepatic lesions are not uncommon incidental findings on imaging studies, and contrast-enhanced liver MRI has been shown to be an accurate method of determining whether a liver lesion is benign or malignant.^{24,25} Experienced radiologists can be helpful in describing the hepatic lesion, which is more likely to represent malignancy if there are multiple lesions with indistinct margins and rim enhancement.²⁶

Bone was also a common EMF in previous reports, as was seen in this study. Notably, the metastatic bone lesions found in this cohort were seen exclusively in the sternum. A recently published study analyzed 17 patients with sternal lesions found on breast MRI scans. Results showed that the sternal lesions were malignant in 9 of these 17 patients. In this series, malignant sternal lesions occurred more frequently in association with aggressive breast cancer and had malignant type dynamics on breast MRI scans.²⁷

Overall, we had a relatively low rate of EMFs in our study, with a very low rate of malignant EMFs. The greatest portion of EMFs came from women who underwent MRI for evaluation of known breast cancer, although we did have a single patient who underwent an MRI for high risk status and was found to have metastatic disease based on an EMF found on the screening MRI.

Notably, we found a statistically significant difference in the discovery of EMFs between premenopausal and postmenopausal women. Older age was also associated with a higher likelihood of EMFs. However, the rate of EMFs leading to upstaging was not affected by age or menopausal status. Therefore, we speculate that many of the benign EMFs (such as vascular findings) might be related to chronologic aging.

A clinical concern regarding the use of breast MRI for treatment planning of breast cancer is the potential delay in treatment, because of further evaluation of findings that do not ultimately affect therapy. We found that the use of breast MRI did not delay cancer care in patients with an EMF, which was true for patients who received upfront surgery and primary systemic therapy.

This study has limitations, including its retrospective nature and that it was conducted at a single institution. The patient population was comprised mostly of Caucasian women, which might not be applicable to other centers. As a large academic institution, these cases have the benefit of a multispecialty breast Tumor Board and experienced, dedicated breast MRI radiologists and other oncologic disease specialists. These results, though, are similar to

those seen in other series which suggests that this range of data can be used to inform women who receive contemporary care.

Conclusion

In summary, this series of breast MRI scans showed that although the number of EMFs reported on breast MRI scans is significant, the EMFs are largely benign and do not typically affect patient outcome in terms of upstaging or treatment delays. This provides reassurance that for most patients with stage I-III breast cancer, the curative intent of treatment will not change because of an EMF reported on a breast MRI scan. These results can inform our discussions with female breast cancer patients, who often undergo MRI at a particularly fearful time surrounding diagnosis and early treatment planning.

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Clinical Practice Points

- Although EMFs are reported in a minority of breast MRI studies, the number of MRI scans with EMFs is not insignificant.
- Previous studies have reported that most EMFs are located in the liver.
- There is no standard optimal management of EMFs.
- Additionally, there has been clinical concern that the use of breast MRI has the potential to delay treatment.
- The effect of EMFs on time to cancer treatment has not been previously reported.
- Our findings were similar to earlier studies, with most of the EMFs in our study located in the liver.
- Most EMFs were benign.
- We found that patients who were postmenopausal were more likely to have an EMF.
- Of the 8 EMFs that were metastatic disease, 5 were in bone (sternal lesions), 2 were in the liver, and 1 was a malignant pleural effusion.
- Importantly, we found that for patients with breast cancer there was no significant difference in the time to treatment whether or not a patient had an EMF.
- This is relevant for clinicians who use breast MRI for staging.
- Our findings are reassuring, in that even if an EMF is reported, a small minority of these EMFs represents metastatic cancer, and further, curative therapy is unlikely to be meaningfully delayed.

Figure 1. Proportion of Magnetic Resonance Images (MRIs) With an Extramammary Finding (EMF) and Upstaged to Stage IV Disease (n = 1305)

Figure 2. Time to Initial Treatment in Days for Stage I to III Breast Cancer According to Extramammary Finding (EMF)

Table 1

Patient Characteristics According to EMF

Characteristic	No EMF	EMF	<i>P</i>
MRIs, n (%)	1165 (89.3)	140 (10.7)	-
Median Age, Years	50	54	.004
Menopause Status			
Premenopausal	683 (91.7%) [61.0%]	62 (8.3%) [45.6%]	.001
Postmenopausal	435 (85.5%) [39.0%]	74 (14.5%) [54.4%]	
Indication for MRI			
Breast cancer	281 (77.6%) [24.1%]	81 (22.4%) [57.9%]	<.001
Clinical significance	370 (94.6%) [31.8%]	21 (5.4%) [15.0%]	
High risk	514 (93.1%) [44.1%]	38 (6.9%) [27.1%]	
HR Status^b			
Negative	79 (80.6%) [34.8%]	19 (19.4%) [26.4%]	.185
Positive	148 (73.6%) [65.2%]	53 (26.4%) [73.6%]	
HER2 Status^b			
Negative	179 (75.2%) [80.3%]	59 (24.8%) [83.1%]	.597
Positive	44 (78.6%) [19.7%]	12 (21.4%) [16.9%]	

Row percentages are shown in parentheses and column percentages in brackets. Abbreviations: EMF = extramammary finding; HR = hormone receptor; MRI = magnetic resonance image.

^a Patient characteristics correspond to MRI studies and not unique patients, because individuals might have had multiple MRI studies.

^b MRI studies for women with stage I to III breast cancer with known subtype included in this analysis.

Table 2**Anatomic Location and Management of EMFs**

EMF	^a n	Percentage of Full Sample (n = 1305)	Action		Biopsy	Stage Change to Stage IV
Any EMF	140	10.7%	50	4	8	
Liver	89	6.8%	32	1	2	
Bone	21	1.6%	10	2	5	
Lung, parenchyma	10	0.8%	4	0	0	
Pleural or pericardial effusion	9	0.7%	4	1	1	
Vascular	8	0.6%	0	0	0	
Skin	4	0.3%	0	0	0	
Chest Wall	4	0.3%	2	0	0	
Peritoneum	2	0.2%	1	0	0	
Other (kidney, heart, muscle)	3	0.2%	0	0	0	

Abbreviations: EMF = extramammary finding; MRI = magnetic resonance imaging.

^aIndividuals might have more than 1 EMF for a given MRI study.

Table 3**Characteristics of Patients With an EMF**

Characteristic	Not Upstaged to Stage IV	Upstaged to Stage IV	P
Number of MRIs	132	8	-
Median Age, Years	54	53.5	.968
Menopause Status, %			.796
Premenopausal	93.6	6.5	
Postmenopausal	94.6	5.4	
Indication for MRI, %			.199
Breast cancer	91.4	8.6	
Clinical significance	100.0	0.0	
High risk	97.4	2.6	
HR Status, %^a			.413
Negative	94.7	5.3	
Positive	88.7	11.3	
HER2 Status, %^a			.374
Negative	91.5	8.5	
Positive	83.3	16.7	
Action as a Result of MRI, %			.017
No	97.8	2.2	
Yes	88.0	12.0	
Biopsy as a Result of MRI, %			<.001
No	96.3	3.7	
Yes	25.0	75.0	

Abbreviations: EMF = extramammary finding; HR = hormone receptor; MRI = magnetic resonance imaging.

^a MRI studies for women with stage I to III breast cancer with known subtype included in this analysis.

Table 4

Time to Initial Treatment in Days According to EMF

EMF Status	n	25% Value	Median Value	75% Value
No EMF				
Full sample	138	8	14	21
Surgery	96	12.5	16	22.5
Systemic	42	7	9	15
EMF				
Full sample	47	9	13	20
Surgery	34	10	13	21
Systemic	13	7	10	17

Abbreviation: EMF = extramammary finding.