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Pre-Operative MRI Exhibits Limited Utility in Axillary Staging for Breast Cancer

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Abstract

Introduction: Magnetic resonance imaging (MRI) is commonly utilized in treatment planning for breast cancer patients. While axillary lymph node findings are routinely reported in these studies, the utility of these findings remains unclear.

Methods: In this retrospective study from 2008-2014, women diagnosed with invasive breast cancer who did not undergo neoadjuvant therapy were reviewed.MRI characteristics of axillary findings were compared to the final pathologic results.

Results: 218 of 338 female patients met inclusion criteria and comprised our patient cohort. MRI was found to have a sensitivity and specificity of 49% and 78%, respectively. The negative predictive value was 80% with an accuracy of 71% and a false negative rate of 13.8%. MRI was more often accurate in younger patients ($p< 0.04$, CI 0.52-1.19) and those whom had a larger number of lymph nodes harvested ($p< 0.0001$, CI -10.8 to -0.2). True positives had significantly larger primary tumors and a larger number of positive lymph nodes on final pathology.

Conclusion: MRI of the axilla is not a reliable tool for axillary staging in women with breast cancer.

Keywords: Invasive breast cancer; Magnetic resonance imaging; Axillary staging; Sentinel lymph node biopsy

Introduction

Breast conservation therapy (BCT) and the use of sentinel lymph node biopsy have become standard of care in the workup and treatment of invasive breast cancer (IBC). Recently, trends have favored minimal surgical management in the treatment and staging of IBC [1]. This is particularly evident in the surgical management of the axilla. The Z0011 trial showed no survival benefit when performing full axillary dissections in patients having axillary lymphaticmetastasis determining that there was no added benefit of axillary dissection for those with micro-metastases (<2 mm in size) [2]. This, among other data, has changed the axillary management for women with IBC. These surgical advances have paralleled increasing quality options for imaging of the breast and axilla. Preoperative magnetic resonance imaging (MRI) of the breast for patients with suspected or known IBC has become a very common modality used in this patient subset. The National Comprehensive Cancer Network (NCCN), among other organizations, has outlined the patient population that should undergo a preoperative MRI. Specifically, MRI is used in biopsy proven IBC when there is concern for multifocal or multi-centric disease, and when findings on mammography or ultrasound fail to fully delineate the extent of disease [3-5]. Still, many institutions more liberally apply the use of preoperative MRI and obtain these studies in all patients diagnosed with IBC on core needle biopsy. As a part of the study, radiologist will routinely comment on the axillary findings of these preoperative studies; however, unlike axillary ultrasound, what constitutes "concerning characteristics" is not well defined. Moreover, the clinical utility of these findings is poorly understood.

Our study sought to better define the role of axillary findings on preoperative MRI for patients with confirmed IBC. Our hypothesis is that MRI has limited utility in identifying patients with axillary metastasis and thus would not be able to aide in clinical decision making.

Methods

After obtaining Institutional Board Review approval, a retrospective chart review was performed on a prospectively collected quality assurance database completed for patients undergoing work up and treatment for invasive breast cancer at Madigan Army Medical Center from 2008-2014. Patients selected for analysis included all female patients 18 years and older with biopsy proven infiltrating

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Table 1: Demographics Characteristics.

Age, mean –yr (SD)	55±18
Tumor size (cm)	1.8±1.5
Procedure	
Breast conservation therapy	140 (64%)
Mastectomy	78 (35.7%)
Diagnosis	
IDC	200 (92.2%)
ILC	17 (8.3%)
IDC and ILC	1 (0.5%)
Hormone Receptors	
ER/PR positive	156 (62.8%)
ER/PR/HER2neu positive	19 (8.7%)
HER2/neu positive	35 (16.1%)
Triple Negative	9 (4.1%)
Lymph Nodes (LN)	
Average number LN sampled	6.9±8.1
Average number positive LN	4.9±8.0
Number with positive axilla	59 (27.1%)

Table 2: True Positive Subgroup Analysis.

Characteristics	
Age, mean –yr (SD)	51±20*
Tumor size (cm)	2.7±1.9**
Procedure	
Breast conservation therapy	6 (20%)
Mastectomy	23 (80%)
Diagnosis	
IDC	25 (86.7%)
ILC	4 (13.3%)
IDC and ILC	1 (3.3%)
Hormone Receptors	
ER/PR positive	21 (73.3%)
ER/PR/HER2neu positive	5 (16.7%)
HER2/neu positive	6 (20%)
Triple Negative	4 (13.3%)
Lymph Nodes (LN)	
Average number LN sampled	15±10.3**
Average number positive LN	10.6±13.1**

*$p < 0.01$; **$p < 0.0001$.

ductal or lobular breast cancer. All patients had a preoperative MRI completed within one month of their operation. Patients were excluded if they had undergone neoadjuvant chemotherapy, had alternate histology on final pathology, were male or did not receive MRI prior to their index operation.

The operations performed (BCT versus mastectomy) as well as the axillary procedure were decided by the patient in conjunction with perioperative counseling with the operating surgeon. The amount of axillary nodal tissue varied from sentinel lymph node sampling to partial axillary dissections during mastectomy to complete axillary dissection upon either grossly positive disease or positive nodal disease on intraoperative frozen pathology evaluation. All care was completed at our institution.

Radiology reports were reviewed from MRIs completed prior to the surgical intervention. Our institution will obtain MRIs using the guidelines set forth by the NCCN. All breast MRIs are read by one of four fellowship trained breast imaging radiologist. Images are obtained using the following standard protocol: Intravenous contrast enhanced MRI of both breasts is performed on a Siemens TrioTrim 3.0 Tesla Magnet using a 7 channel; *In Vivo* Breast Array MR coil with the following pulse sequences: 3 Plane Localizer, T2 TIRM (STIR) Axial BLADE (FOV 340; Time to Repetition [TR] 11070; Time to Echo [TE] 137; 3 mm @ .8 mm Time=4:49), Axial T1 FL3D (FOV 340; TR 6.7; TE 2.63; 1.5 mm @ 20% Time=1:02), Axial T1 FL3D (Q-fat saturation technique; FOV 340; TR 4.0; TE 1.4; 1.00 mm @ 20% Time=6:31 -1 run without and the remaining 5 runs after contrast administration), and Sagittal T1 (FOV 240; TR 4.35; TE 1.75; 2.0 mm @ 20% Time=2:04). Images are reviewed on a dedicated Dyna Cad workstation (Invivo Corp).

Our radiologists predominantly rely upon the Axial T1 FL3D post-contrast sequences which have a special resolution of 1 mm. This is double checked with the Sagittal T1 – 2 mm. Axillary findings are considered abnormal if there is cortical thickening greater than 4 mm in both axial and sagittal planes and/or loss of the normal central fatty hilum. Post lymph node biopsy changes are identified and not considered as a positive axillary finding on MRI. Operative reports and final pathology was reviewed for all diagnostic preoperative breast biopsies as well as final histology for resected tumor and axillary nodal tissue.

Simple statistical analysis was performed to define the demographics and characteristics of our study group. Positive MRI findings were compared to final lymph node pathology to determine our primary endpoints of sensitivity, specificity, negative and positive predictive values and well as accuracy and false positive rate of axillary MRI. Secondary endpoints utilized comparison analysis of our true positive group and different nodal staging to evaluate for any significant differences from the total cohort for age, primary tumor size, number of positive lymph nodes, and hormonal status. Fishers exact, Student's T-test, and one-way ANOVA tests were performed to evaluate for any significant differences between and within comparison groups. Statistical significance was defined as a p value < 0.05 (CI95%). Data was compiled using Microsoft Excel 2011® (Redmond, WA) and statistical analysis of continuous and categorical data were carried out using SPSS v. 22 (IBM Corp., Chicago, IL). Descriptive statistics calculated for continuous data included mean, standard deviation, and percentage.

Results

A total 338 patients were identified as having undergone work up for IBC. Of these, 120 patients were excluded for reasons outlined in the methods section. Seventy seven out of 120(65%) patients were excluded for not requiring preoperative MRI while 24(20%) received neoadjuvant chemotherapy. Seventeen patients (14%) were excluded due to having alternate histology on final pathology reports with top two alternate types were mammary [6] and papillary [5] and the remaining 6 being split between mucinous, inflammatory, adenoid cystic and metaplastic sarcomatoid carcinoma. Two patients had their index operation completed at an outside hospital leaving 218 patients meeting inclusion criteria for review. The demographic and characteristic makeup of our cohort is summarized in Table 1. The

Table 3: Detection of Lymph Node Metastasis on MRI.

MRI BEFORE DIAGNOSIS					
		SNLB		Sensitivity	50.00%
		Positive	Negative	Specificity	84.40%
MRI	Positive	11	11	PPV	61.10%
	Negative	7	38	NPV	77.60%
				Accuracy	73.10%
MRI AFTER DIAGNOSIS					
		SNLB		Sensitivity	45.20%
		Positive	Negative	Specificity	79.60%
MRI	Positive	19	23	PPV	46.30%
	Negative	22	86	NPV	78.90%
				Accuracy	70.00%
ALL PATIENTS					
		SNLB		Sensitivity	49.10%
		Positive	Negative	Specificity	78.60%
MRI	Positive	30	34	PPV	46.00%
	Negative	29	124	NPV	80.60%
				Accuracy	71.00%

average age at diagnosis was 55 years old. The majority of patients were diagnosed with invasive carcinoma (IDC) at 92.2% and 140 of these patients underwent BCT (64%). Average tumor size was 1.8 cm (+/- 1.5 cm) and the average number of lymph nodes harvested was 6.9 (+/- 8.1). With regards to hormonal status, 62.8% of patients were found to be ER/PR positive with only 9 (4.1%) patients being triple negative (- ER/PR/HER2). Sixty (27.5%) patients demonstrated metastasis to at least one lymph node on final pathology with 8 of those 60(13%) being micrometastasis or isolated tumor cells only. Most patients (n=158, 73%) had N0 nodal staging with 21% (n=46) patients had N1 disease and the remainder (n=14, 6%) had N2 or greater nodal disease Table 2.

Overall, the sensitivity of MRI in detecting axillary metastasis was49% and the specificity was 78%. The negative predictive value (NPV) and positive predictive value (PPV) were 80% and 46%, respectively. The accuracy of MRI for detection of axillary metastasis was 71%. These values were recalculated after excluding patients with micrometastasis or isolated tumor cells only and were not found to be significantly different. Further subgroup analysis was performed comparing patients receiving MRI prior to biopsy versus those receiving MRI after tissue biopsy. There were no statistically significant differences when these groups were compared to each other or in comparison to the overall sensitivity, specificity and accuracy. Specific values can be found in Table 3. Nodal staging determined on final pathology was assessed as well. Forty-three percent of patients with N1 disease had positive axillary findings on preoperative MRI. This increased to 71% with pathological staging of N2 or greater ($p > .001$). False positive (N0) rate was 22%.

We looked specifically at the characteristics of our true positive group and compared those to our total cohort. We found that MRI was more often accurate in younger patients ($p < 0.04$, CI 0.52-1.19) and those whom had a larger number of lymph nodes harvested ($p < 0.0001$, CI -10.8 to -0.2). When comparing final pathology for these two groups we found that patients were more often to have true positive finding if they had more advanced disease. As shown in Figure 1, as you might expect, our true positive group had significantly larger primary tumors and a larger total number of positive lymph nodes on final pathology.

Discussion

A lessinvasive approach in the surgical management of the axilla continues to be the trend for breast cancer. It has been nearly two decades since the replacement of axillary lymph node dissection (ALND) with sentinel lymph node biopsy (SLNB) resulting in significantly less morbidity due to surgery of the axilla. Still, SLNB carries a significant risk of lymphedema, as high as 8%, independent of the inherent of surgery [6,7]. A favorable alternative to surgery would require accurate staging of the axilla with noninvasive imaging. Definitive identification of axillary metastasis could alter the sequence of adjuvant therapies and make surgical intervention of the axilla for staging purposes obsolete.

MRI has established itself in the preoperative staging and surgical planning of rectal and endometrial adenocarcinoma. Reliable identification of nodal disease is associated with a NPV of approximately 95% in these populations and is crucial to appropriate planning. Findings on MRI ultimately affect timing of adjuvant therapy as well operative approaches for these malignancies [8,9]. Obviously, these cancers are vastly different from IBC in terms of anatomic location, tumor behavior, and feasibility of surgical nodal sampling. Nonetheless, the utility and impact of MRI for evaluation of metastatic nodal disease in these disease sites is notable.

Current literature regarding the application of pre-operative breast MRI for detecting axillary lymph node metastasis and guiding surgical management is somewhat sparse and conflicting. Axillary ultrasound has established that lymph nodes with absence of fatty hilum, cortical thickening and non-hilar or trans-cortical vascular flow are highly suspicious of metastatic development and often targeted for needle directed biopsies. Absence of the fatty hilum is likely the most specific finding associated with nodal metastasis. Unfortunately this finding is not present often enough to be entirely reliable [7,8]. Cortical thickening of >4 mm is another specific and accurate indication of malignancy, especially in the setting of known breast cancer [9]. Finally although not reproducible on MRI, non-hilar (trans-cortical) vascular flow seen on ultrasound is highly predictive of malignancy if seen with abnormal cortical thickening [7,10]. MRI has been compared to ultrasound to determine which modality is most accurate. These studies have shown no difference in accuracy between modalities with percentages similar to our findings [11]. Interestingly though, if positive findings are concordant between the two modalities the sensitivity and PPV are improved [12]. Our study suggests that the well-described characteristics for suspicious lymphadenopathy on ultrasound cannot be directly applied to findings on preoperative MRI.

In a study evaluating axillary focused MRI short and long axis length, maximal cortical thickness, relative T2 value, loss of fatty hilum ($p < 0.001$ for each), and eccentric cortical thickening ($p < 0.003$) were shown to be statistically significantly different between the metastatic and non-metastatic axillary lymph nodes. Specificity was ~90% when 4 of the previous findings were present [13]. Chung et al. [14] reported similar findings showing that the mean size of nodes is significantly larger in metastatic axillary nodes when compared to benign lymph nodes in the axilla. Perhaps because of limited power, other recent smaller studies have concluded that although breast

MRI has the potential to become a routine method for evaluating the metastatic lymph nodes before submission to ALND, it is not yet a valid alternative to histological analysis. SLNB affords the highest sensitivity (93%) when compared to any current imaging modalities including PET-CT and breast MRI [15,16]. Further studies evaluating dynamic MRI imaging methods of the axilla determined that quantitative MRI features shows little value in identifying axillary metastasis [17].

Our study findings demonstrated that standard preoperative MRI of the breast with inclusion of the axilla has inadequate specificity and accuracy with poor sensitivity for the detection of malignant pathology in the axilla. These findings were not significantly altered when adjusting for and excluding patients having only micro metastasis. Patients demonstrating positive axillary MRI findings with corresponding disease on final pathology tended to be younger women, with larger tumor size, and a higher number of lymph nodes sampled on final pathology. This suggests that patients with more aggressive tumors or those who present at a later stage will more often have accurate MRI findings. This data leads us to conclude that there are currently no specific tumor characteristics or patient populations for which preoperative MRI of the axilla would be able to effectively replace surgical sampling for staging.

The findings of our study are inherently limited as it is a retrospective, single institution analysis therefore exposed to the unavoidable biases associated with its data and analysis. This is exemplified in that our chart review was unable to delineate specific indications for obtaining preoperative MRI and as such we are unable to more specifically characterize our cohort. Finally, the sequence of preoperative work up and definitive treatment was not uniform among our patients and thus makes our findings susceptible to heterogeneity.

Conclusion

Our study finding strongly infers that the role for MRI is limited in the preoperative staging of the axilla in patients with IBC. Staging MRI demonstrated poor sensitivity, specificity, and accuracy in the detection of axillary metastasis in patients with infiltrating ductal and lobular breast cancer. This has the potential to change with the advancement of MRI protocols and modalities and should be further investigated through randomized prospective studies.

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