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Axillary adenopathy detected on breast MRI following COVID-19 vaccination: outcomes and follow-up recommendations

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**Title: Axillary Adenopathy Detected on Breast MRI Following COVID-19**

**Vaccination: Outcomes and Follow-up Recommendations**

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## Abstract:

This retrospective study presents 110 patients with suspected COVID-19 vaccine-related axillary adenopathy on breast MRI. Our study aimed to assess the outcomes of axillary adenopathy detected on breast MRI performed within one year after COVID-19 vaccination. The median time between the COVID-19 vaccine and breast MRI was shorter in patients with detected adenopathy compared to patients without detected adenopathy (6 weeks [2-17] versus 15 [7-24] weeks,  $p < 0.001$ ). Unilateral axillary adenopathy detected on breast MRI had a low malignancy rate (3.3%), and no cases of malignant axillary adenopathy were diagnosed without a known breast cancer in the ipsilateral breast. Our findings suggest that unilateral axillary adenopathy identified on breast MRI ipsilateral to a recent COVID-19 vaccination can be considered benign in the absence of a suspicious breast finding or known breast cancer. Regardless of vaccine status and timing, unilateral axillary adenopathy detected on MRI evaluation with a known malignancy or suspicious breast finding should be considered suspicious. This will avoid unnecessary scheduling constraints, patient anxiety, and cost, without delaying diagnosis of metastatic breast cancer.

## Introduction:

The COVID-19 vaccine has been shown to cause unilateral axillary adenopathy [1]. With increasing COVID-19 vaccine availability and recommendations for additional booster vaccinations to combat COVID-19 variants, the medical community will continue to be challenged with management recommendations for axillary adenopathy in the setting of a recent COVID-19 vaccine. In breast imaging, unilateral axillary adenopathy is typically considered suspicious for locally advanced breast cancer [1]. However, studies have shown that axillary adenopathy following a COVID-19 vaccination is a relatively common finding with incidence reported up to 44% on breast imaging examinations [2,3]. Therefore, this can present a diagnostic challenge for breast imaging radiologist to differentiate between reactive lymphadenopathy from metastatic nodal disease, potentially delaying a cancer diagnosis.

Guidelines for the management of COVID-19 vaccine-related adenopathy identified on screening mammography have evolved over time. Initially in March 2020, the Society of Breast Imaging (SBI) recommended not only delaying screening mammography around the COVID-19 vaccination, but also follow-up ultrasound of the axilla 4-12 weeks after the second vaccine dose if unilateral axillary adenopathy was detected on screening mammography [4,5]. More recent literature, however, has demonstrated that COVID-19 vaccine-related axillary adenopathy detected on screening mammography can persist up to 43 weeks [3,5,6]. This prompted the SBI to update their recommendations concluding that screening mammography no longer needs to be delayed after a COVID-19 vaccine and follow-up axillary ultrasound is no longer needed if there is not a suspicious ipsilateral mammographic finding [4].

The patient population undergoing breast MRI examinations is different than the population undergoing screening mammography. Patients having a breast MRI are most commonly either women with over 20% lifetime risk of breast cancer presenting for high-risk screening or women with a recent diagnosis of breast cancer presenting to evaluate for extent of disease [7]. Furthermore, MRI has an increased sensitivity for breast cancer compared to mammography, making it more likely that an index breast cancer would be visible in the setting of locally advanced disease [7]. There is a paucity of literature on COVID-19 vaccine-related adenopathy identified on breast MRI. Determining the significance of COVID-19 vaccine-related axillary adenopathy in this specific patient population is important as to not confound the early diagnosis of malignancy. This study assesses outcomes of axillary adenopathy detected on breast MRI performed within one year of a COVID-19 vaccination with the goal of informing appropriate updated management guidelines.

#### Materials and Methods:

At our institution, the institutional review board reviewed this study and designated it as exempt under the Department of Health and Human Services regulations. This study is Health Insurance Portability and Accountability Act compliant.

This retrospective cohort study reviewed all breast MRI examinations obtained within one year of receiving a COVID-19 vaccine, performed at a single, multisite academic institution between 12/11/2020 and 12/31/2021. Patient follow-up outcomes were recorded through 6/30/22. Patient characteristics (age, race, and personal history of cancer) and vaccine information (vaccine type and date of vaccine) were extracted

from the electronic medical record. Breast MRI indications and axillary lymph node imaging characteristics were obtained from the original radiology breast MRI and axillary US reports. Breast imaging examinations were interpreted by one of 12 breast imaging radiologists (2 to 35 years of post-training experience; 9 with fellowship training in breast imaging). Times between the patient's imaging examination and COVID-19 vaccination are presented as weeks (interquartile range).

The primary outcomes were to determine predictors of axillary adenopathy on breast MRI and predictors of resolution of adenopathy on follow-up US. This was compared using Wilcoxon rank sum test for continuous variables and Chi-square test or Fisher's exact test for categorical variables (R Foundation for Statistical Computing, Vienna, Austria). P-value  $\leq 0.05$  was considered statistically significant.

#### Results:

Our study included 1429 patients (mean age 54 years  $\pm$  12) who had a breast MRI performed within one year of a COVID-19 vaccination, of which 7.7% (110/1429) had axillary adenopathy ipsilateral to the vaccination site.

The median time between the COVID-19 vaccine and breast MRI was shorter in patients with detected adenopathy compared to patients without detected adenopathy (6 weeks [2-17] versus 15 [7-24] weeks,  $p < 0.001$ ) (Table 1). There was no association between vaccine type (Pfizer, Moderna, Johnson & Johnson), patient age, race, or personal history of breast cancer and presence of adenopathy on breast MRI ( $p \geq 0.05$ ).

Adherence to recommended axillary US follow-up occurred in 83% (91/110) of patients with axillary adenopathy. At the time of follow-up US, the adenopathy had



resolved in 54/91 (59%) of patients. Patients with resolved adenopathy had longer times between vaccination and US (16 weeks [7-24] versus 10 weeks [4-18],  $p=0,04$ ) and between MRI and US (5 weeks [2-9] versus 2 weeks [1-3],  $p=0.001$ ).

US biopsy was performed in 22% (20/91) of patients who had US, and there were three malignant outcomes (3.3% [3/91]).

Of the 110 patients who were recommended an axillary US on breast MRI, 41.8% (46/110) of patients had a suspicious finding/known cancer in the ipsilateral breast, 10.9% (12/110) of patients had a suspicious finding/known cancer in the contralateral breast, and 47.3% (52/110) of patients had no suspicious finding in either breast. Of the 91 patients who adhered to recommended axillary US follow-up, 40.7% (37/91) of patients had a suspicious finding/known cancer in the ipsilateral breast, 10.9% (12/91) of patients had a suspicious finding/known cancer in the contralateral breast, and 46.2% (42/91) of patients had no suspicious finding in either breast.

The three malignant cases were all detected on breast MRI performed for extent of disease evaluation in patients with recently diagnosed breast cancer (Figure 1). The adenopathy was ipsilateral to the COVID-19 vaccine administration site and the site of known breast malignancy in all three cases. All three cases had abnormally increased cortical thickness measuring at least 6 mm. No case of axillary malignancy was found when there was a suspicious finding in the contralateral breast or when there was no suspicious finding in either breast.

Discussion:

This study evaluates outcomes of COVID-19 vaccine-related axillary adenopathy detected on breast MRI. Unilateral axillary adenopathy was encountered in only a subset of patients (7.7%) who had a COVID-19 vaccine within one year of the breast MRI examination. The time between COVID-19 vaccine and MRI was shorter for patients with axillary adenopathy compared to patients without axillary adenopathy. Similarly, time between COVID-19 vaccine and ultrasound and between MRI and ultrasound were shorter for patients with persistent of adenopathy on ultrasound. These results are similar to prior studies showing that axillary adenopathy resolves with time, although adenopathy can persist for almost one year [2,3].

This is currently the largest study cohort to date for axillary adenopathy detected on breast MRI in the setting of a COVID-19 vaccination [8]. In our study population, axillary adenopathy following a COVID-19 vaccination on breast MRI had a low malignancy rate (3.3%), and no cases of malignant axillary adenopathy were diagnosed without a suspicious finding or known breast cancer in the ipsilateral breast. This is consistent with the findings of Wolfson et al. and Horvat et al. which also demonstrated a low malignancy rate of COVID-19 vaccine-related axillary adenopathy [3,8]. Furthermore, in both studies, all malignant axillary adenopathy were only detected when there were suspicious findings in the ipsilateral breast similar to our findings [3,8]. This emphasizes that unilateral axillary adenopathy when detected in the setting of a suspicious finding in the ipsilateral breast should not be interpreted as likely reactive and should be considered suspicious and undergo further evaluation.

With the increasing number of COVID-19 variants requiring additional vaccinations for protection, we will continue to identify axillary adenopathy on imaging. It

is critical that we standardize recommendations in order to limit unnecessary exams and biopsies without compromising our goal of early detection of breast cancer. The Society of Breast Imaging currently recommends that unilateral COVID-19 vaccine-related axillary adenopathy detected on screening mammography can be classified as benign if there are no suspicious mammographic findings [4]. Although we did not identify any cases of metastatic adenopathy without a known breast cancer, we would recommend extending the current Society of Breast Imaging recommendations for screening mammography to the patient population obtaining breast MRI.

Limitations of our study include the single, academic institution design, small sample size (despite being largest study cohort to date), and the nature of being a retrospective cohort study.

In conclusion, our findings suggest that axillary adenopathy identified on an MRI performed following a recent COVID-19 can be considered benign if there are no suspicious findings or a known breast cancer in the ipsilateral breast. In addition, it is not necessary to delay MRI exams following a COVID-19 vaccine. Regardless of vaccination status and timing, axillary adenopathy detected on breast MRI evaluation with a known breast malignancy or suspicious breast finding should be considered suspicious and recommended for further evaluation. This new recommendation could avoid unnecessary scheduling constraints, patient anxiety, and healthcare costs, without delaying the diagnosis of locally advanced breast cancer.

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Table 1. Study cohort and characteristics

Characteristic	No adenopathy, N = 1,319 <sup>1</sup>	Adenopathy, N = 110 <sup>1</sup>	p-value <sup>2</sup>
Age	54 (45, 64)	50 (42, 61)	0.050
Race			0.20
White or Caucasian	966/1,308 (74%)	75/109 (69%)	
Black or African American	177/1,308 (14%)	23/109 (21%)	
Asian	110/1,308 (8.4%)	8/109 (7.3%)	
Other	55/1,308 (4.2%)	3/109 (2.8%)	
Unknown	11	1	
Indication for MRI			<0.001
High-risk screening	822/1,319 (62%)	52/110 (47%)	
Extent of disease	250/1,319 (19%)	39/110 (35%)	
B3 or MRI biopsy follow-up	175/1,319 (13%)	13/110 (12%)	
Other	77/1,319 (5.8%)	6/110 (5.5%)	
Personal history of breast cancer			0.13
Yes	387/1,074 (36%)	19/71 (27%)	
No	687/1,074 (64%)	52/71 (73%)	
Not applicable (current cancer)	245	39	
Vaccine type			0.29
Pfizer	720/1,256 (57%)	53/105 (50%)	
Moderna	487/1,256 (39%)	46/105 (44%)	
Johnson & Johnson	49/1,256 (3.9%)	6/105 (5.7%)	
Unknown	63	5	
Weeks between Covid vaccine and MRI	15 (7, 24)	6 (2, 17)	<0.001

<sup>1</sup> Median (IQR); n/N (%)

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<b>Characteristic</b>	<b>No adenopathy, N =</b> 1,319 <sup>1</sup>	<b>Adenopathy, N =</b> 110 <sup>1</sup>	<b>p-value</b> <sup>2</sup>
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<sup>2</sup>Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

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Figure 1. In a 48-year-old female with newly diagnosed left breast invasive ductal carcinoma (IDC), a breast MRI was performed for extent of disease evaluation 24 weeks following her second COVID-19 vaccination in the left arm (Pfizer). (A) Axial and sagittal (B) T1-weighted fat-saturated dynamic postcontrast image demonstrate known-biopsy proven left breast IDC (white arrow) with left axillary adenopathy (yellow arrow). Ultrasound-guided biopsy of the left axillary lymph node was recommended based on MRI imaging findings. Patient presented for US-guided biopsy 3 days later with ultrasound findings of an abnormal lymph node with complete loss of central fatty hilum measuring 3.9 x 1.8 x 3.3 cm (C) and pathologic analysis demonstrated poorly differentiated IDC involving lymphoid tissue (D).





## Highlights:

1. The median time between the COVID-19 vaccine and breast MRI was shorter in patients with detected adenopathy compared to patients without detected adenopathy (6 weeks [2-17] versus 15 [7-24] weeks,  $p < 0.001$ ).
2. Axillary adenopathy detected on breast MRI following COVID-19 vaccination had a low malignancy rate (3.3% [3/91]). No cases of malignant axillary adenopathy were diagnosed without a known breast cancer in the ipsilateral breast.
3. Unilateral axillary adenopathy identified on breast MRI ipsilateral to a recent COVID-19 vaccination could be considered benign in the absence of a suspicious breast finding or known breast cancer.