Time for Resolution of COVID-19 Vaccine–Related Axillary Lymphadenopathy and Associated Factors

Elizabeth G. Lane, BA[1], Carolyn S. Eisen, MD, Michele B. Drotman, MD, Katerina Dodelzon, MD, Eralda Mema, MD, Charlene Thomas, MS, Martin R. Prince, MD, PhD

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Keywords

breast imaging, cortical thickness, COVID-19 vaccine, screening, ultrasound, unilateral axillary lymphadenopathy

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BACKGROUND. The variable clinical course of subclinical lymphadenopathy detected on breast imaging after COVID-19 vaccination creates management challenges and has led to evolving practice recommendations.

OBJECTIVE. The purpose of this study was to assess the duration of axillary lymphadenopathy ipsilateral to COVID-19 vaccination detected by breast imaging and to assess factors associated with the time until resolution.

METHODS. This retrospective single-center study included 111 patients (mean age, 52 ± 12 years) with unilateral axillary lymphadenopathy ipsilateral to mRNA COVID-19 vaccine administration performed within the prior 8 weeks that was detected on breast ultrasound performed between January 1, 2021, and October 1, 2021, and who underwent follow-up ultrasound examinations at 4- to 12-week intervals until resolution of the lymphadenopathy. Patient information was extracted from medical records. Cortical thickness of the largest axillary lymph node on ultrasound was retrospectively measured and was considered enlarged when greater than 3 mm. Multivariable linear regression analysis was used to identify independent predictors of time until resolution.

RESULTS. The mean cortical thickness at the initial ultrasound examination was 4.7 ± 1.2 mm. The lymphadenopathy resolved a mean of 97 ± 44 days after the initial ultrasound examination, 127 ± 43 days after the first vaccine dose, and 2.4 ± 0.6 follow-up ultrasound examinations. A significant independent predictor of shorter time to resolution was Pfizer-BioNTech (rather than Moderna) vaccination (β = –18.0 [95% CI, –34.3 to –1.7]; p = .03]. Significant independent predictors of longer time to resolution were receipt of the second dose after the initial ultrasound examination (β = 19.2 [95% CI, 3.1–35.2]; p = .02) and greater cortical thickness at the initial ultrasound examination (β = 8.0 [95% CI, 1.5–14.5]; p = .02). Patient age, history of breast cancer, and axillary symptoms were not significantly associated with time to resolution (all p > .05).

CONCLUSION. Axillary lymphadenopathy detected with breast ultrasound after COVID-19 mRNA vaccination lasts longer than reported in initial vaccine clinical trials.

CLINICAL IMPACT. The prolonged time to resolution supports not delaying screening mammography because of recent COVID-19 vaccination. It also supports the professional society recommendation of a follow-up interval of at least 12 weeks when vaccine-related lymphadenopathy is suspected.

Axillary swelling, tenderness, and palpable lymphadenopathy are commonly reported side effects of COVID-19 vaccination [1–4]. During clinical trials of the Moderna COVID-19 vaccine (Spikevax) for patients 18–64 years of age, 11.6% of patients reported axillary swelling and tenderness after the first dose, and 16.0% reported them after the second dose, compared with 5.0% and 4.3% of patients in the respective placebo groups for each of the two doses. Among patients 65 years and older, 6.1% reported axillary swelling or tenderness after the first dose and 8.4% after the second dose, compared with 4.1% and 2.5% of patients in the respective placebo groups [5]. During clinical trials of the Pfizer-BioNTech vaccine (Comirnaty), less than 1% of vaccinated patients reported axillary and/or cervical lymphadenopathy, which typically occurred 2–4 days after vaccination and lasted approximately 10 days [6]. These clinical trials reported only the presence of clinically symptomatic axillary swelling or tenderness and palpable axillary lymphadenopathy and did not report subclinical axillary lymphadenopathy. The trials therefore likely underestimated the actual frequency of lymphadenopathy after COVID-19 vaccination [6], as evidenced by imaging studies showing lymphadenopathy after COVID-19 vaccination on 3% of mammograms [4] and 49% of breast ultrasound studies [7].

[1]All authors: Department of Radiology, Weill Cornell Medicine, 525 E 68th St, New York, NY 10065. Address correspondence to M. B. Drotman (Mid2011@med.cornell.edu).

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Unilateral axillary lymphadenopathy has a broad differential diagnosis, including metastatic breast cancer [8]. The observed increased frequency of unilateral axillary lymphadenopathy on breast imaging during the rollout of COVID-19 vaccination thus motivated development of guidelines for handling the finding. The National Comprehensive Cancer Network and Society of Breast Imaging (SBI) proposed delaying screening breast examinations until 4–6 weeks after the second COVID-19 vaccination dose, when possible [9, 10]. The SBI provided further guidelines in 2021 on the management of unilateral axillary lymphadenopathy suspected of being related to COVID-19 vaccination, recommending that short-term imaging follow-up be performed 4–12 weeks after vaccination [10]. These guidelines were issued early in the clinical experience of COVID-19 vaccine–related lymphadenopathy to provide management strategies; decrease overdiagnosis, undertreatment, and overtreatment; and address patient anxiety. The time intervals chosen were based on experience with other vaccines [11–14] and COVID-19 vaccine trial data showing rapid resolution of palpable self-reported axillary lymphadenopathy [5]. Early clinical experience suggests a more variable and potentially prolonged duration of subclinical lymphadenopathy after COVID-19 vaccination [15, 16], creating challenges in considering whether to recommend biopsy or follow-up (BI-RADS category 3) or to make a benign assessment (BI-RADS category 2) [17, 18]. On the basis of clinical experience to date, in March 2022, the SBI revised its guidelines to recommend a longer follow-up interval of 12 or more weeks [19].

The aim of this study was to assess the duration of axillary lymphadenopathy ipsilateral to COVID-19 vaccination detected on breast imaging and to assess factors associated with time until resolution.

Methods

Study Sample

This HIPAA-compliant single-institution retrospective study was approved by the Weill Cornell Medicine institutional review board. The requirement for written informed consent was waived. An institutional radiologic imaging database query for all breast imaging examinations performed in patients age 18–89 years from January 1, 2021, through October 1, 2021, identified 16,706 examinations. Of these, 2645 examinations were assessed BI-RADS category 3 or 4 on breast ultrasound (hereafter described as the initial ultrasound). Review of the reports of these ultrasound examinations for those containing both a term associated with COVID-19 vaccination ("COVID" and ["vaccine," "vaccination," "dose," or "shot"]) and a term associated with lymphadenopathy ("prominent," "reactive," "cortical thickening," or "enlarged") yielded 314 unique patients. Additional exclusions were made for the following reasons: lymphadenopathy not followed to resolution on ultrasound (n = 79), information regarding vaccine type and date or dates of administration unavailable (n = 54), initial ultrasound examination performed more than 8 weeks after the most recent vaccine dose (n = 40), active breast cancer (n = 7), lymphadenopathy present before vaccination (n = 6), lymphadenopathy contralateral to injection site (n = 5), imaging reports attributing the lymphadenopathy to mastitis (n = 2) or recent surgery (n = 1), vaccination with a non–messenger RNA COVID vaccine (Johnson & Johnson Janssen COVID-19 Vaccine; n = 1), patient did not receive COVID-19 vaccination (n = 2), absence of lymphadenopathy (n = 1), and lymph node biopsy performed before resolution of lymphadenopathy (n = 5). These exclusions resulted in a final study sample of 111 patients with unilateral ipsilateral lymphadenopathy detected on breast imaging performed within 8 weeks of the most recent dose of COVID-19 vaccine who received an ultrasound assessment of BI-RADS category 3 or 4 and who underwent follow-up ultrasound until resolution of the lymphadenopathy (Fig. 1).

During the study period, breast ultrasound was routinely ordered for all patients with axillary lymphadenopathy detected with other breast imaging modalities, regardless of node morphology, to measure the cortical thickness of the largest node. In addition, during the study period, patients with unilateral axillary lymphadenopathy on ultrasound that was suspected to be related to COVID-19 vaccination received a recommendation for follow-up ultrasound in 4–12 weeks, consistent with SBI recommendations. In general, after the first follow-up ultrasound examination, additional serial ultrasound examinations at 4- to 12-week intervals were recommended until resolution of the lymphadenopathy was documented.

Data Extraction

The electronic medical records were reviewed by a research coordinator (E.G.L.). The following data were recorded: patient age, sex, breast cancer history, and presence of ipsilateral axillary symptoms at initial imaging (e.g., axillary tenderness, pain, or swelling or palpable axillary lymph nodes); vaccine type, injection site, and administration date or dates; indications and modalities of the initial breast imaging; and the dates of the follow-up ultrasound examinations. Although axillary symptoms were recorded when described, the presence or absence of symptoms was not systematically documented in the electronic medical records.

Ultrasound Acquisition and Analysis

All ultrasound examinations were performed with Logiq E9 ultrasound systems with ML6-15 transducers (GE Healthcare) by technologists with a registered diagnostic medical sonographer credential in breast ultrasound. For each patient, two fellowship-trained breast radiologists (E.M. and C.S.E.; 4 and 25 years of

HIGHLIGHTS

Key Finding

- *Axillary lymphadenopathy ipsilateral to COVID-19 mRNA vaccination resolves a mean of 97 days after detection by breast imaging and 127 days after the first dose. Longer times to resolution are observed with Moderna (rather than Pfizer-BioNTech) vaccination, receipt of a second dose after presentation, and thicker cortical thickness at presentation.*

Importance

- *The prolonged resolution time supports a follow-up interval of at least 12 weeks for suspected vaccine-related lymphadenopathy and avoidance of delaying screening mammography after vaccination.*

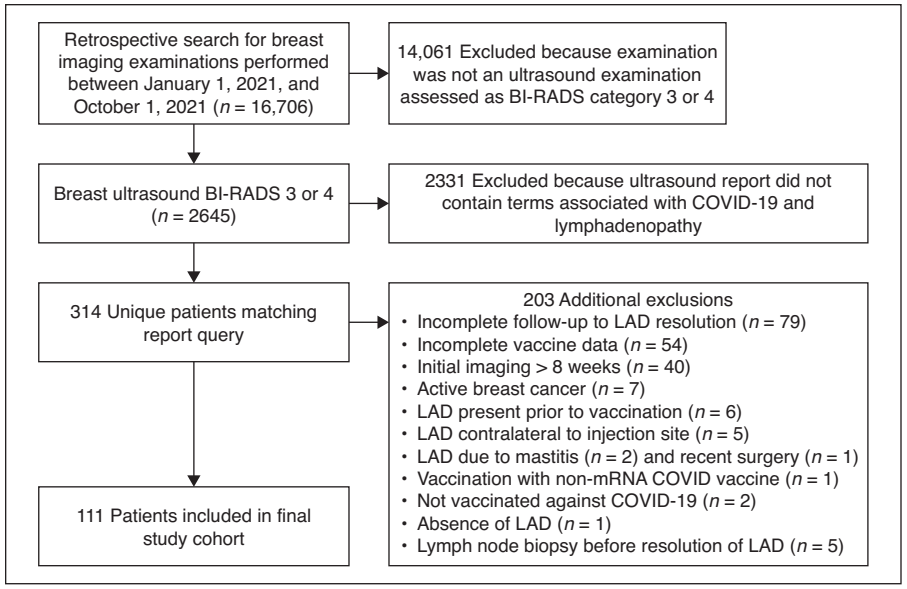

Fig. 1—Chart shows flow of patient selection. LAD = lymphadenopathy, mRNA = messenger RNA.

posttraining experience) independently reviewed the initial ultrasound examination and all follow-up ultrasound examinations until resolution of lymphadenopathy. For each ultrasound examination, the radiologists, using electronic calipers, measured the cortical thickness of the largest lymph node ipsilateral to the site of vaccine administration. Cortical thickness was calculated as the distance from the outer cortex to the inner cortex, measured to the nearest tenth of a millimeter (Fig. 2). The mean value of the two radiologists' measurements was used for analysis. A cortex was considered thickened when it measured more than 3.0 mm. The earliest follow-up ultrasound examination in which the cortical thickness was 3.0 mm or less on the basis of the mean measurement of the two readers was considered the ultrasound examination showing resolution, regardless of the measurement obtained at the time of clinical care. The time to the ultrasound showing resolution was computed for each patient both since the first vaccine dose and since the initial ultrasound. The number of follow-up ultrasound examinations until resolution was also recorded.

Statistical Analysis

The study sample was summarized descriptively by counts and percentages for categoric factors and mean and SD for continuous factors. The time to resolution of axillary lymphadenopathy in terms of days since the first vaccine dose and since the initial ultrasound examination and the number of follow-up ultrasound examinations were summarized stratified by patient age (above or below the median age in the study sample), type of vaccine (Pfizer-BioNTech or Moderna), whether a second dose was administered after the day of the initial ultrasound examination (in comparison with patients who received the second dose before or on the same day as the initial ultrasound examination or who did not receive the second dose before resolution), presence versus absence of history of breast cancer, presence versus absence of ipsilateral axillary symptoms, and cortical thickness on the initial ultrasound (above or below the median cortical thickness in the study sample).

The mean time to resolution since the initial ultrasound examination was compared among these groups by unpaired *t* test. Univariable and multivariable linear regression analyses were used to identify predictors of the time to resolution from the initial ultrasound examination. The regression analyses included potential predictors of age, history of breast cancer, presence of axillary symptoms, vaccine type, timing of second dose relative to the initial ultrasound, and cortical thickness. Interobserver agreement on

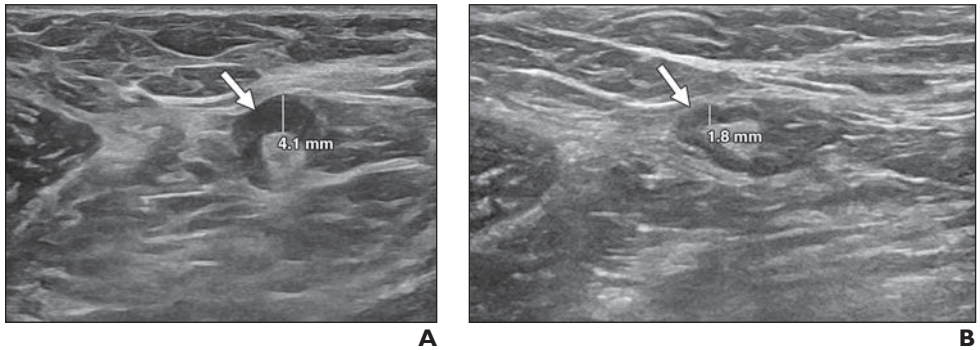

Fig. 2—33-year-old woman undergoing bilateral screening breast ultrasound. Example of retrospective lymph node measurements.
A, Transverse initial breast ultrasound image of left axilla obtained 19 days after first dose of Pfizer-BioNTech COVID-19 vaccine (Comirnaty) to left upper extremity shows increased cortical thickness (*arrow*) measuring 4.1 mm (*line*).
B, Transverse follow-up ultrasound image of left axilla obtained 100 days after first COVID-19 vaccine dose shows cortical thickness (*arrow*) of 1.8 mm (*line*) consistent with resolution of left axillary lymphadenopathy. Patient received second dose 2 days after initial ultrasound examination.

the lymph node thickness measurements was assessed by the intraclass correlation coefficient (ICC) and classified as follows: poor reliability, ICC < 0.50; moderate reliability, 0.50 ≤ ICC < 0.75; good reliability, 0.75 ≤ ICC < 0.90; and excellent reliability, ICC ≥ 0.90 [20]. All *p* values were two-sided with statistical significance evaluated at the .05 alpha level. All analyses were performed with R software.

Results

Patient Characteristics

All 111 patients were women (mean age, 52 ± 12 [SD] years; median, 51 years; range, 26–88 years). Sixty patients (mean age, 50 ± 11 years) received the Pfizer-BioNTech vaccine, and 51 (mean age, 54 ± 13 years) received the Moderna vaccine. Eleven of the 111 patients (10%) had a history of breast cancer. Eleven patients (10%; mean age, 50 ± 15 years) had axillary symptoms (palpable lymph node in four, pain in three, swelling in three, and tenderness in one). Among the 11 patients with axillary symptoms, four received the Moderna vaccine, and seven received the Pfizer-BioNTech vaccine.

Table 1 summarizes the indications for breast imaging with attention to the pathway to ordering the initial ultrasound. Upfront screening mammography and ultrasound were ordered for 64 (58%) patients. In two cases (2%), upfront screening mammography was ordered and led to subsequent ultrasound because lymphadenopathy was identified on mammography. Upfront screening ultrasound only was ordered for five (5%) patients. In six cases (5%), upfront screening breast MRI was ordered and led to subsequent ultrasound because lymphadenopathy was identified. Diagnostic mammography and diagnostic ultrasound were ordered for 26 (23%) patients and upfront diagnostic ultrasound only for eight (7%).

Initial Detection of Axillary Lymphadenopathy

Ipsilateral axillary lymphadenopathy was first detected on concurrently ordered screening or diagnostic mammography in 18 of 111 (16%) patients, on mammography with subsequent targeted ultrasound in 2 of 111 (2%) patients, on breast MRI with subsequent targeted ultrasound in 6 of 111 (5%) patients, and on the initial ultrasound (whether screening or diagnostic and whether or not mammography was concurrently performed) in the other 85 of 111 (77%) patients. The mean interval between the first vaccine dose and the initial ultrasound examination was 30 ± 20 days. The mean cortical thickness at the initial ultrasound examination 4.7 ± 1.2 mm (median, 4.4 mm; range, 3.1–8.8 mm).

Resolution of Lymphadenopathy

Table 2 shows results regarding resolution of lymphadenopathy in terms of patient characteristics. Axillary lymphadenopathy resolved on the basis of the retrospective measurements of cortical thickness in all 111 patients. The lymphadenopathy was resolved at the first follow-up ultrasound examination in 75 of 111 (68%) patients, at the second follow-up ultrasound in 32 of 111 (29%) patients, and at the third follow-up ultrasound examination in 4 of 111 (4%) patients (mean, 2.4 ± 0.6 follow-up ultrasound examinations until resolution). The mean interval since the initial ultrasound examination was 67 ± 47 days for the first, 107 ± 50 days for the second, and 145 ± 39 days for the third follow-up ultrasound examination. Figures 3–5 show examples of lymphadenopathy resolution in three patients.

A total of 109 of 111 (98%) patients received a second vaccine dose before resolution of lymphadenopathy. Of these 109 patients, 60 received the second dose before the initial ultrasound examination; two received the second dose on the same day as the initial ultrasound examination; and 47 received the second dose after the initial ultrasound examination. The mean interval between the second dose and the initial ultrasound examination was 19 ± 17 days in the 60 patients who received the second dose before and 12 ± 7 days in the 47 patients who received the second dose after the initial ultrasound. For all patients who re-

TABLE 1: Indication for Breast Imaging and Pathway to Ultrasound (*n* = 111)

Initial Breast Imaging and Associated Indication	No. of Patients
Screening mammography and screening ultrasound[a]	64 (58)
Dense breasts	55
Referring physician request	8
Diffuse breast pain	1
Screening mammography only[b]	2 (2)
Routine screening	2
Screening ultrasound only[a]	5 (5)
Staggered screening schedule	2
Diffuse breast pain	2
Referring physician request	1
Screening breast MRI[b]	6 (5)
Personal history of breast cancer	3
Family history of breast cancer	3
Diagnostic mammography and diagnostic ultrasound[a]	26 (23)
Palpable lump	9
Short-term follow-up	8
Mass	2
Asymmetry	4
Calcifications	2
Dermatitis	2
Focal breast pain	5
Recent history of breast cancer	2
Diagnostic ultrasound only[a]	8 (7)
Axillary or breast swelling	3
Focal breast pain	2
Inconclusive mammography	1
Short-term follow-up of complicated cyst	1
Recent history of breast cancer	1

Note—Data are numbers of patients. Values in parentheses are percentages.
[a]Ultrasound ordered upfront.
[b]Ultrasound ordered because of lymphadenopathy detected on initial imaging with other modality (mammography or MRI).

TABLE 2: Time to Resolution of Lymphadenopathy

Characteristic	No. of Patients	Time From First Dose to Resolution (d)	Time From Initial Ultrasound to Resolution (d)	No. of Follow-Up Ultrasound Examinations Until Resolution	*p*[a]
All patients	111	127 ± 43	97 ± 44	2.4 ± 0.6	
Age (y)[b]					.55
< 51	53	124 ± 42	94 ± 42	2.3 ± 0.5	
≥ 51	58	129 ± 44	98 ± 46	2.4 ± 0.6	
Vaccine type					.007
Pfizer-BioNTech (Comirnaty)	60	117 ± 38	87 ± 35	2.3 ± 0.5	
Moderna (Spikevax)	51	139 ± 46	108 ± 51	2.4 ± 0.6	
Second vaccine dose after ultrasound					.63
No[c]	64	129 ± 37	87 ± 36	2.4 ± 0.6	
Yes	47	124 ± 50	110 ± 50	2.4 ± 0.6	
History of breast cancer					.61
No	100	128 ± 42	97 ± 43	2.4 ± 0.6	
Yes	11	119 ± 51	91 ± 53	2.1 ± 0.3	
Axillary symptoms					.22
No	100	129 ± 43	98 ± 44	2.4 ± 0.6	
Yes	11	111 ± 42	80 ± 41	2.3 ± 0.5	
Cortical thickness on initial ultrasound (mm)[b]					.23
< 4.4	54	122 ± 35	86 ± 32	2.2 ± 0.5	
≥ 4.4	57	132 ± 49	107 ± 51	2.5 ± 0.6	

Note—Except for number of patients, values are mean ± SD.
[a]Comparison of time since first vaccine dose.
[b]Stratified by median value.
[c]Includes patients who received second dose before or on the same day as the initial ultrasound and patients who did not receive a second dose before resolution.

ceived a second dose, the vaccine type (Pfizer-BioNTech or Moderna) was the same for both doses. No patient received a booster dose before the initial ultrasound examination or during the follow-up period.

The mean time to the ultrasound showing resolution was 127 ± 43 days since the first vaccine dose and 97 ± 44 days since the initial ultrasound. The mean time to resolution since the first dose was 124 ± 42 days in patients younger than 51 years and 129 ± 44 days in patients 51 years and older (p = .55). The mean time to resolution since the first dose was 117 ± 38 days in patients who received the Pfizer-BioNTech vaccine and 139 ± 46 days in patients who received the Moderna vaccine (p = .007). The mean time to resolution since the first dose was 124 ± 50 days in patients who received a second dose after the initial ultrasound examination and 129 ± 37 days in those who did not (p = .63). The mean time to resolution since the first dose was 119 ± 51 days in patients with a history of breast cancer and 128 ± 42 days in patients without a history of breast cancer (p = .61). The mean time to resolution since the first dose was 111 ± 42 days in patients with ipsilateral axillary symptoms and 129 ± 43 days in patients without ipsilateral axillary symptoms (p = .22). The mean time to resolution since the first dose was 122 ± 35 days in patients with cortical thickness less than 4.4 mm and 132 ± 49 days in patients with cortical thickness of 4.4 mm or greater (p = .23).

One patient received a tetanus, diphtheria, and pertussis (TDAP) booster in the same arm as Moderna COVID-19 vaccination. This patient underwent the initial ultrasound examination on the same day as the second COVID-19 vaccine dose; the TDAP booster was administered approximately 2 months after the initial ultrasound examination; and the first follow-up ultrasound was performed after approximately an additional 1 month since the TDAP booster. The lymph node cortical thickness measured 3.9 mm on the initial ultrasound and 3.8 mm on the first follow-up ultrasound. In this patient, the axillary lymphadenopathy resolved 189 days after the first dose of COVID-19 vaccine.

Two patients who received the Pfizer-BioNTech COVID-19 vaccine experienced side effects after the first dose that were documented as severe. One of these two patients declined the second dose. In this patient, the lymphadenopathy was resolved on follow-up ultrasound performed 114 days after the first dose. The second patient received the second dose after resolution of the lymphadenopathy, which was observed on ultrasound performed 106 days after the first dose.

Table 3 shows the results of univariable and multivariable linear regression analyses for predicting the duration of lymphadenopathy from the date of the initial ultrasound until documentation of resolution. In univariable linear regression analysis, the only significant predictor of fewer days until resolution was

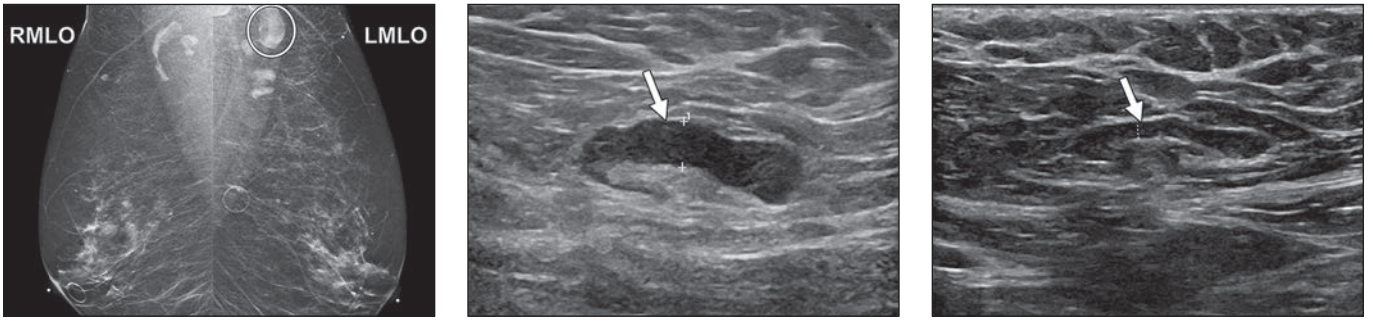

Fig. 3—53-year-old woman undergoing screening mammography and breast ultrasound.
A, Right (RMLO) and left (LMLO) mediolateral oblique screening mammograms obtained 26 days after first dose of Pfizer-BioNTech (Comirnaty) COVID-19 vaccination to left deltoid show left axillary lymphadenopathy (*oval*). No right axillary lymphadenopathy was visualized. Lighter circles in center and lower left of image indicate skin markers.
B, Left axillary screening ultrasound image obtained on same day as **A** shows enlarged lymph node (*arrow, calipers*) with cortical thickness of 5 mm. 1 = first caliper placement.
C, Ultrasound image of left axilla obtained 119 days after first vaccine dose shows cortical thickness (*arrow*) of 2 mm (*line*) consistent with resolution of lymphadenopathy. Patient received second vaccine dose 5 days before initial ultrasound examination.

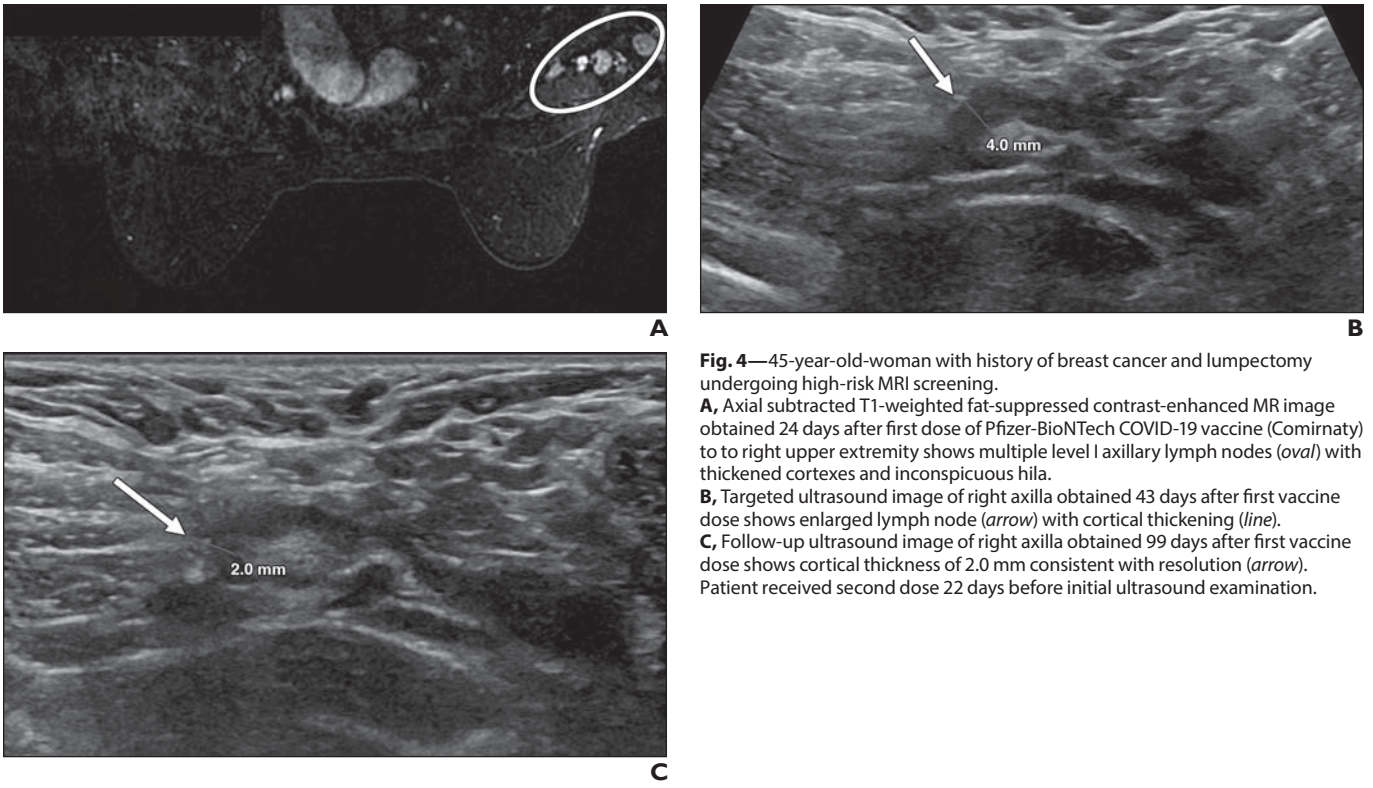

Fig. 4—45-year-old-woman with history of breast cancer and lumpectomy undergoing high-risk MRI screening.
A, Axial subtracted T1-weighted fat-suppressed contrast-enhanced MR image obtained 24 days after first dose of Pfizer-BioNTech COVID-19 vaccine (Comirnaty) to to right upper extremity shows multiple level I axillary lymph nodes (*oval*) with thickened cortexes and inconspicuous hila.
B, Targeted ultrasound image of right axilla obtained 43 days after first vaccine dose shows enlarged lymph node (*arrow*) with cortical thickening (*line*).
C, Follow-up ultrasound image of right axilla obtained 99 days after first vaccine dose shows cortical thickness of 2.0 mm consistent with resolution (*arrow*). Patient received second dose 22 days before initial ultrasound examination.

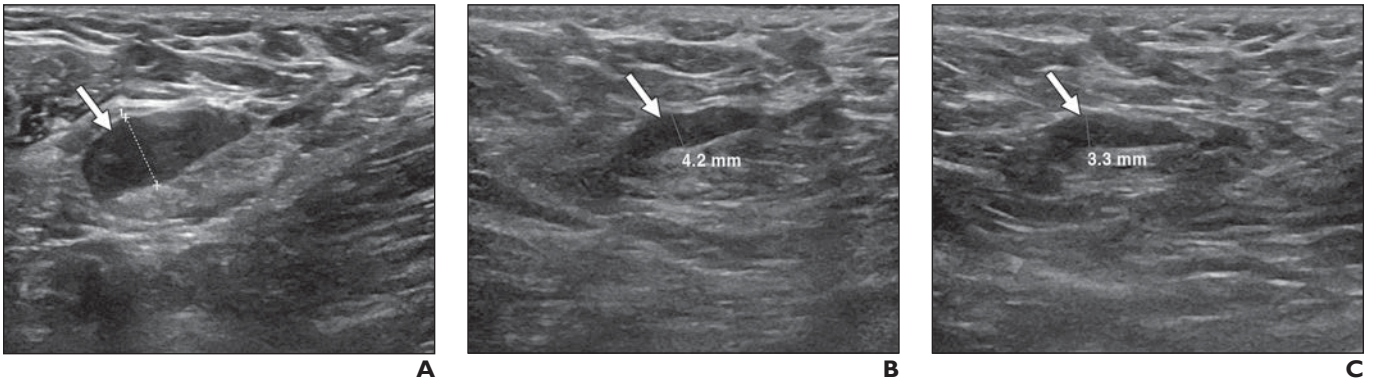

Fig. 5—49-year-old woman undergoing screening breast ultrasound.
A, Initial ultrasound image obtained 16 days after first dose of Pfizer-BioNTech COVID-19 vaccine (Comirnaty) to left upper extremity shows enlarged lymph node (*arrow*) with cortical thickness of 9 mm (*calipers, line*). 1 = first caliper placement.
B, Follow-up ultrasound image obtained 114 days after first vaccine dose shows persistent enlarged lymph node (*arrow*) with cortical thickness of 4.2 mm (*line*).
C, Additional follow-up ultrasound obtained 196 days after first vaccine dose shows cortical thickness (*arrow*) of 3.3 mm (*line*) consistent with resolution of lymphadenopathy. Patient received second dose 5 days after initial ultrasound examination.

TABLE 3: Univariable and Multivariable Linear Regression Models for Predicting Time to Resolution in Days

Characteristic	Univariable			Multivariable		
	β	95% CI	*p*	β	95% CI	*p*
Age (y)	0.5	−0.2 to 1.2	.16	0.3	−0.4 to 1.0	.31
Pfizer-BioNTech (Comirnaty) (reference, Moderna [Spikevax])	−20.7	−36.9 to −4.4	.01	−18.0	−34.3 to −1.7	.03
Second dose after initial ultrasound (reference, no second dose after initial ultrasound[a])	23.6	7.4–39.9	.005	19.2	3.1–35.2	.02
History of breast cancer (reference, no history)	−6.7	−34.6 to 21.2	.64	−7.5	−34.5 to 19.4	.58
Cortical thickness (mm) on initial ultrasound	6.8	0.05–13.5	.048	8.0	1.5–14.5	.02
Presence of axillary symptoms (reference, no symptoms)	−18.2	−45.9 to 9.6	.20	−19.0	−45.1 to 7.1	.15

[a]Includes patients who received second dose before or on the same day as the initial ultrasound examination and patients who did not receive a second dose before resolution.

Pfizer-BioNTech vaccination (β = –20.7 [95% CI, –36.9 to –4.4]; *p* = .01). Significant predictors of more days until resolution were receipt of a second dose after the initial ultrasound (β = 23.6 [95% CI, 7.4–39.9]; *p* = .005) and thicker lymph node cortex on the initial ultrasound (β = 6.8 [95% CI, 0.05–13.5]; *p* = .048). In multivariable analysis, significant independent predictors of number of days for resolution were Pfizer-BioNTech vaccination (β = –18.0 [95% CI, –34.3 to –1.7]; *p* = .03) (i.e., predicted resolution approximately 18 days faster in patients who received Pfizer-BioNTech rather than Moderna vaccination), receipt of a second dose after the initial ultrasound examination (β = 19.2 [95% CI, 3.1–35.2]; *p* = .02) (i.e., predicted resolution approximately 19 days longer in patients who received a second dose after the initial ultrasound), and cortical thickness on the initial ultrasound (β = 8.0 [95% CI, 1.5–14.5]; *p* = .02) (i.e., predicted resolution approximately 8 days longer for each 1-mm increase in cortical thickness). Patient age, history of breast cancer, and ipsilateral axillary symptoms were not significant predictors of time to resolution in univariable or multivariable analysis (all *p* > .05).

Interobserver Agreement

Interobserver agreement on measurement of cortical thickness on the initial ultrasound was good (ICC, 0.83 [95% CI, 0.72–0.89]), on the first follow-up ultrasound was excellent (ICC, 0.94 [95% CI, 0.91–0.96]), and on the second follow-up ultrasound was good (ICC, 0.85 [95% CI, 0.70–0.92]).

Discussion

This study of patients who underwent ultrasound follow-up for unilateral ipsilateral axillary lymphadenopathy suspected to be related to COVID-19 vaccination showed a mean time to lymphadenopathy resolution of 97 days from the initial ultrasound showing lymphadenopathy and 127 days from first vaccine dose. This is longer than the time to resolution reported in vaccine trials [5, 6]. The finding further supports the most recent proposed SBI recommendations for a follow-up interval of at least 12 weeks for suspected vaccine-related lymphadenopathy [17] and recommendations not to delay screening mammography because of recent vaccination, as was previously recommended [9, 10]. In addition, only 10% of patients had associated axillary symptoms, suggesting that axillary lymphadenopathy after COVID-19 vaccination is more prevalent than reported in clinical trials that documented only symptomatic lymphadenopathy. The presence of subclinical lymphadenopathy and the long resolution time of lymphadenopathy, as observed in this study, should reassure radiologists and patients when lymph nodes suspected to be vaccine-related persist over multiple visits.

Multivariable regression analysis showed that Pfizer-BioNTech vaccination was associated with resolution approximately 18 days faster than was Moderna vaccination when other factors were controlled for. This difference may be secondary to the higher dose used for the Moderna vaccine (0.5 mL) than for the Pfizer-BioNTech vaccine (0.3 mL), there being reports of more side effects after vaccination with the Moderna COVID-19 vaccine [21–23]. Receipt of the second vaccine dose after the initial ultrasound examination was associated with an approximately 19-day increase in time to resolution when other factors were controlled for. Time to resolution of lymphadenopathy was also independently related to cortical thickness at presentation; each 1-mm increase in cortical thickness was associated with an additional approximately 8 days until resolution, according to the regression analysis. These findings may allow tailoring of the interval for short-term follow-up ultrasound examinations, potentially including recommendations for longer intervals for patients who receive Moderna vaccination and for patients with greater cortical thickness at presentation. The findings also provide objective data for counseling patients about the expected time to resolution, thus more appropriately managing expectations and potentially decreasing patient anxiety.

Our study expands on recent work by Park et al. [24] and Horvat et al. [25] that showed lymphadenopathy persisting for more than 8 weeks after vaccination. During the study period, our clinical practice closely followed the 2021 SBI recommendations for follow-up of suspected COVID-19 lymphadenopathy [10]. Thus, patients with unilateral lymphadenopathy suspected of being related to COVID-19 vaccination underwent routine imaging follow-up until resolution of lymphadenopathy. This surveillance enabled evaluation of the natural history and duration of COVID-19 vaccine–related lymphadenopathy. Our findings, consistent with those of Wolfson et al. [26], reveal that a prolonged duration until resolution of lymphadenopathy is ultimately documented. These data support a pragmatic approach to the management of COVID-19 vaccine–related lymphadenopathy, including consideration of potential BI-RADS category 2 assessment in the absence of axillary symptoms and history of breast can-

cer and otherwise negative breast imaging, as has been recommended by other groups [17, 18, 27].

Limitations of this study include the retrospective single-center design with potential selection bias. For example, some patients were excluded because of an unavailable or incomplete vaccine history. Also, because patients without resolution were excluded, outcomes in those patients were not assessed. In addition, variability in the number of days between follow-up ultrasound examinations and the 4- to 12-week follow-up intervals reduce the precision of the determination of the time to resolution and are expected to be slight overestimates of the true time until resolution. Moreover, the number of patients with axillary symptoms may have been underestimated given that information regarding symptoms was not systematically collected. Conversely, the extent of axillary symptoms may have been underestimated because breast symptoms not explicitly described as involving the axilla were not considered to represent axillary symptoms and because axillary symptoms after vaccination that resolved before the initial imaging would also not have been captured. Finally, our findings cannot be generalized to patients with concurrent breast cancer, who were excluded from the analysis. Unilateral lymphadenopathy should be assessed with greater care in these patients, and tissue diagnosis may remain appropriate depending on the clinical context.

In conclusion, we observed a prolonged duration to resolution of unilateral ipsilateral axillary lymphadenopathy suspected to be related to COVID-19 vaccination. Administration of Moderna vaccine, receipt of a second vaccine dose after the initial lymphadenopathy presentation, and greater cortical thickness at initial presentation were independently associated with a longer time to resolution after presentation. The findings support a follow-up interval of at least 12 weeks for suspected vaccination-related lymphadenopathy and not delaying screening mammography because of recent vaccination.

References

1. Mehta N, Sales RM, Babagbemi K, et al. Unilateral axillary adenopathy in the setting of COVID-19 vaccine. *Clin Imaging* 2021; 75:12–15
2. Mortazavi S. COVID-19 vaccination–associated axillary adenopathy: imaging findings and follow-up recommendations in 23 women. *AJR* 2021; 217:857–858
3. Raj S, Ogola G, Han J. COVID-19 vaccine–associated subclinical axillary lymphadenopathy on screening mammogram. *Acad Radiol* 2022; 29:501–507
4. Robinson KA, Maimone S, Gococo-Benore DA, Li Z, Advani PP, Chumsri S. Incidence of axillary adenopathy in breast imaging after COVID-19 vaccination. *JAMA Oncol* 2021; 7:1395–1397
5. Centers for Disease Control and Prevention website. The Moderna COVID-19 vaccine's local reactions, systemic reactions, adverse events, and serious adverse events. www.cdc.gov/vaccines/covid-19/info-by-product/moderna/reactogenicity.html. Last reviewed August 9, 2021. Accessed March 1, 2022
6. Centers for Disease Control and Prevention website. Pfizer-BioNTech COVID-19 vaccine reactions & adverse events. www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/reactogenicity.html. Last reviewed November 5, 2021. Accessed March 1, 2022
7. Park JY, Lee JY, Yi SY. Axillary lymphadenopathy on ultrasound after COVID-19 vaccination and its influencing factors: a single-center study. *J Clin Med*. 2022;11:238
8. Dialani V, James DF, Slanetz PJ. A practical approach to imaging the axilla. *Insights Imaging* 2015; 6:217–229
9. National Comprehensive Cancer Network website. Recommendations of the National Comprehensive Cancer Network (NCCN) Advisory Committee on COVID-19 vaccination and pre-exposure prophylaxis. www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v3-0.pdf? Published April 27, 2022. Accessed June 15, 2021
10. Grimm L, Destounis S, Dogan B, et al. SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging website. www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf. Updated March 9, 2021. Accessed March 1, 2022
11. Newfield L, Naschitz JE, Yeshurun D. BCG-induced axillary lymph-adenitis in the adult [in Hebrew]. *Harefuah* 1990; 119:199–200
12. Studdiford J, Lamb K, Horvath K, Altshuler M, Stonehouse A. Development of unilateral cervical and supraclavicular lymphadenopathy after human papilloma virus vaccination. *Pharmacotherapy* 2008; 28:1194–1197
13. Shirone N, Shinkai T, Yamane T, et al. Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination. *Ann Nucl Med* 2012; 26:248–252
14. Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG. Incidence and intensity of F-18 FDG uptake after vaccination with H1N1 vaccine. *Clin Nucl Med* 2011; 36:848–853
15. Hanneman K, Iwanochko RM, Thavendiranathan P. Evolution of lymphadenopathy at PET/MRI after COVID-19 vaccination. *Radiology* 2021; 300:E338
16. Raj S, Ogola G, Han J. COVID-19 vaccine–associated subclinical axillary lymphadenopathy on screening mammogram. *Acad Radiol*. 2022; 29:501–507
17. Lehman CD, Lamb LR, D'Alessandro HA. Mitigating the impact of coronavirus disease (COVID-19) vaccinations on patients undergoing breast imaging examinations: a pragmatic approach. *AJR* 2021; 217:584–586
18. Schiaffino S, Pinker K, Magni V, et al. Axillary lymphadenopathy at the time of COVID-19 vaccination: ten recommendations from the European Society of Breast Imaging (EUSOBI). *Insights Imaging* 2021; 12:119
19. Grimm L, Srini A, Dontchos B, et al. Revised SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging website. www.sbi-online.org/Portals/0/Position%20Statements/2022/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination_updatedFeb2022.pdf. Updated February 2022. Accessed January 23, 2022
20. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016; 15:155–163 [Erratum in *J Chiropr Med* 2017; 16:346]
21. Centers for Disease Control and Prevention website. Pfizer-BioNTech COVID-19 vaccine (purple cap) age 12 and over. www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/bioNTech-purple-cap-12-and-over.html. Accessed March 9, 2022
22. Centers for Disease Control and Prevention website. Moderna COVID-19 vaccine. www.cdc.gov/vaccines/covid-19/info-by-product/moderna/index.html. Accessed March 9, 2022
23. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna vaccines. *Eur Rev Med Pharmacol Sci* 2021; 25:1663–1669
24. Park JY, Lee JY, Yi SY. Axillary lymphadenopathy on ultrasound after COVID-19 vaccination and its influencing factors: a single-center study. *J Clin Med* 2022; 11:238
25. Horvat JV, Sevilimedu V, Becker AS, Perez-Johnston R, Yeh R, Feigin KN. Frequency and outcomes of MRI-detected axillary adenopathy following COVID-19 vaccination. *Eur Radiol* 2022 Mar 5 [published online]
26. Wolfson S, Kim E, Plaunova A, et al. Axillary adenopathy after COVID-19 vaccine: no reason to delay screening mammogram. *Radiology* 2022; 303:297–299
27. Becker AS, Perez-Johnston R, Chikarmane SA, et al. Multidisciplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: *Radiology* scientific expert panel. *Radiology* 2021; 300:E323–E327

(Editorial Comment starts on next page)

Editorial Comment: Prolonged Resolution of COVID-19 Vaccine–Related Axillary Lymphadenopathy Necessitates a Long Imaging Follow-Up Interval

Ipsilateral axillary lymphadenopathy is a well-known side effect of the COVID-19 messenger RNA (mRNA) vaccines (Comirnaty, Pfizer-BioNTech; Spikevax, Moderna) and has been a widely observed phenomenon in breast imaging since these vaccines became available under emergency use authorization in the United States in late 2020. This postvaccination lymphadenopathy can occur days to weeks after vaccination, is typically subclinical, and often presents on imaging as diffuse or focal cortical thickening [1]. Initially, in an effort to reduce false-positive findings associated with COVID-19 vaccine–related axillary lymphadenopathy, professional organizations, such as the Society of Breast Imaging, recommended that women at average risk delay screening mammography for 4–6 weeks after COVID-19 vaccinations [2]. The SBI recommendation has since been eliminated owing to the updated understanding that COVID-19 vaccine–related lymphadenopathy can persist well beyond 6 weeks after vaccination and to emphasize that delaying either breast imaging care or COVID-19 vaccination can have deleterious health effects [3].

The revision of the SBI recommendation is further supported by the retrospective data presented by the authors of this article: COVID-19 vaccine–related unilateral axillary lymphadenopathy took a mean of 97 ± 44 days from initial imaging to resolve, and the time to resolution varied significantly depending on the type of mRNA vaccine administered. Therefore, in patients without concurrent breast cancer or other abnormal imaging findings, if breast imaging radiologists recommend short-interval follow-up imaging for presumed COVID-19 vaccine–related axillary lymphadenopathy, the length of time between initial and follow-up imaging should be appropriately long, at least 12 weeks, to allow resolution of imaging findings [3].

Hannah Perry, MD, MS
University of Vermont Medical Center
Larner College of Medicine at the University of Vermont
Burlington, VT
Hannah.Perry@UVMHealth.org

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References

1. Keshavarz P, Yazdanpanah F, Rafiee F, Mizandari M. Lymphadenopathy following COVID-19 vaccination: imaging findings review. *Acad Radiol* 2021; 28:1058–1071
2. Grimm L, Destounis S, Dogan B, et al. SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging website. www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf. Updated March 9, 2021. Accessed June 24, 2022
3. Grimm L, Srini A, Dontchos B, et al. Revised SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging website. www.sbi-online.org/Portals/0/Position%20Statements/2022/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination_updatedFeb2022.pdf. Updated February 2022. Accessed June 24, 2022

STUDY GUIDE

Time for Resolution of COVID-19 Vaccine–Related Axillary Lymphadenopathy and Associated Factors

Joseph J. Budovec, MD[1], Alan Mautz, MD[2]

[1]Medical College of Wisconsin, Milwaukee, WI.

[2]Northern Light AR Gould Hospital, Presque Isle, ME.

*jbudovec@mcw.edu, amautz@emhs.org**

Introduction

1. What are common indications for breast ultrasound?
2. What are the most common causes of ipsilateral axillary lymphadenopathy?
3. What questions did the investigators intend to address? What was the rationale for the study? Does the study address a gap in the literature?

Methods

4. What study design was used? What were the inclusion criteria? What were the exclusion criteria?
5. How were data gathered for this study? How was the cortical thickness of the lymph node measured?
6. What types of data analysis were conducted?

Results

7. What was the mean cortical thickness on the initial ultrasound? What was the mean time to resolution?
8. What characteristics were significant predictors of the time to resolution?
9. What percentage of patients had associated axillary symptoms after COVID-19 vaccination?

Discussion

10. What were the limitations of this study? Are they adequately discussed?
11. What BI-RADS category do the authors suggest assigning to patients with COVID-19 vaccine-related lymphadenopathy?
12. What recommendations does your institution or practice make for patients with suspected COVID-19 vaccine lymphadenopathy?
13. How might you design a follow-up study?

Suggested Reading

1. Grimm L, Srini A, Dontchos B, et al. Revised SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Society of Breast Imaging website. www.sbi-online.org/Portals/0/Position%20Statements/2022/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination_updatedFeb2022.pdf. Updated February 2022. Accessed June 24, 2022
2. Lehman CD, Lamb LR, D'Alessandro HA. Mitigating the impact of coronavirus disease (COVID-19) vaccinations on patients undergoing breast imaging examinations: a pragmatic approach. *AJR* 2021; 217:584–586

*Please note that the authors of the Study Guide are distinct from those of the companion article.