The Detection of Axillary Adenopathy After a COVID-19 Vaccine

BY LINDSEY NOLEN

s more of the population is inoculated with the COVID-19 vaccine, researchers are closely monitoring potential side effects—one of which is axillary adenopathy. According to the Society of Breast Imaging (SBI), a concern is that the vaccine may cause some women to experience swollen lymph nodes, leading to potential misinterpretation as suspected breast cancer.

As such, the SBI issued a series of recommendations, including patient intake form requests and scheduling a mammogram either before or several weeks after receiving the vaccine. However, some breast radiologists believe that, since swollen lymph nodes with no other abnormalities on mammography or clinical examination are uncommonly associated with breast cancer, screening and vaccination can be completed within a short window without issue.

"In the setting of a normal mammographic appearance of a breast, the swollen lymph node by itself is very uncommonly associated with breast cancer, but we typically will do further imaging of it to evaluate it to make sure," noted Clayton Taylor, MD, a breast radiologist at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.



SBI Recommendations

While this may be true in most circumstances, the SBI recommendations shared that higher rates of axillary adenopathy have been reported with administration of both Moderna and Pfizer/BioNTech COVID-19 vaccines. Specifically, the society reported that axillary swelling or tenderness was experienced by 11.6 percent of patients upon the first dose and 16 percent of patients following the second dose of the Moderna COVID-19 vaccine. Lymphadenopathy was only reported as an unsolicited adverse event in 58 more patient cases in the vaccine group than the placebo group for the Pfizer/BioNTech COVID-19 vaccine.

"Lymphadenopathy or swollen axillary lymph nodes is something that can happen with vaccines, but there's a lot of reasons you can see swollen lymph nodes," Taylor explained. "We started collecting information about the patient's having COVID-19 vaccines in early January. Then the SBI recommendations case statement came out, basically suggesting that we collect certain information and give some guidance to mammographers about what to do if they happen to see a swollen lymph node." These recommendations further entailed that providers should obtain COVID-19 vaccination status, and in-

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formation regarding the timing and side (left vs. right arm) of vaccination through patient intake forms. Then, to minimize patient anxiety, the SBI recommended including the following introductory statement: "Vaccines of all types can result in temporary swelling of the lymph nodes, which may be a sign that the body is making antibodies in response as intended."

"We really do want women to get vaccinated, and we really do want them to have their screening mammogram."

-Clayton Taylor, MD, a breast radiologist at the Ohio State University Comprehensive Cancer Center

Other recommendations noted that unilateral axillary adenopathy on screening exams warrants a BI-RADS category 0 assessment to allow for further assessment of the ipsilateral breast and documentation of medical history, including COVID-19 vaccination. Mammographers should also follow an appropriate diagnostic workup for unilateral axillary adenopathy in women who received a COVID-19 vaccination in the ipsilateral upper extremity within the preceding 4 weeks, and consider a short-term follow-up exam in 4-12 weeks (BI-RADS category 3) following the second vaccine dose. Lastly, if axillary adenopathy persists after short-term follow-up, the mammography should consider lymph node sampling to exclude breast and non-breast malignancy.

In terms of scheduling screening exams, the SBI ultimately recommends, if possible and when it does not unduly delay care, that patients and providers consider scheduling screening exams prior to the first dose of a COVID-19 vaccination. They might also consider scheduling a mammogram for 4-6 weeks following the second dose of a COVID-19 vaccination to avoid misinterpretation of axillary adenopathy.

Screening Guidance

"This is all very new so no one knows how often people will have swollen lymph nodes following these vaccines, how long it might last and, of those lymph nodes, how many might be seen on a mammogram. I think what [the SBI] is trying to do is just provide some guidance and some help to have a conversation about this," Taylor said. "I think [the Ohio State University Comprehensive Cancer Center] kind of independently arrived at the same idea that it's important to collect this information."

Taylor added that he believes the SBI's recommendations provided a lot of extremely helpful information. Specifically, he has found the recommendations regarding what information to collect from mammogram patients insightful as his cancer center continues to monitor how vaccine response may impact patient mammogram screenings. "We have two really important things that we want people to do. One is getting a screening mammogram, which we know saves lives by reducing the morbidity and mortality from breast cancer. The other is to receive the COVID-19 vaccine, which we expect is also going to reduce the morbidity and mortality from that," Taylor stressed.

To date, Taylor emphasizes that his center has not seen frequent issues regarding lymphadenopathy and COVID-19 vaccination. Yet, the key to monitoring these implications moving forward, as the SBI suggested, is knowing all relevant information pertaining to a patient's vaccine status while reading the mammogram, helping his team to make the right determination at that time.

"We have told our patients that we don't feel like they need to reschedule their screening mammograms, but if they're very concerned about that small false-positive risk, to reschedule it 4-6 weeks after their second dose, just like the SBI recommendation," Taylor shared. "I think the risk of delaying [a mammogram] 4-6 weeks is very, very low. I think the risk would be if the person delays significantly longer than that, or waits a year or doesn't resume their screening."

Ultimately, as it is very early in the vaccination process, there is limited data on the profound implications of COVID-19 vaccination on mammogram screening. As more women receive the vaccination and continue their regular mammogram screenings, breast radiologists and mammographers, such as Taylor, will have a much better idea of how the two processes impact one another.

"Overall, I think the SBI guidelines are very helpful and that they provided a lot of information where there was none," Taylor said. "Hopefully we'll know a lot more very soon as more and more people undergo COVID-19 vaccination."

In the meantime, Taylor and the Ohio State University Comprehensive Cancer Center remain dedicated to providing patients with all information pertaining to the possible side effects of scheduling a mammogram right before or soon after a COVID-19 vaccine. He explains that, in a worst-case scenario, if an axillary adenopathy were to be misinterpreted as suspected breast cancer, this would only result in the patient needing to come back for additional imaging.

"We really do want women to get vaccinated, and we really do want them to have their screening mammogram," Taylor said. "Currently, we're not asking people to reschedule their mammograms, but we're assessing it all the time. If we need to make a change, we will."

Lindsey Nolen is a contributing writer.

ALL MONITORING

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Oncology Times: What would be some of the factors which pose challenges in implementing this novel methodology into the clinic?

Doan: "Clinical deployment would require a careful collection of data across sites and operators to train a robust deep learning model for each type of instrument and sample preparation protocol. Updating the machine models to control overfitting should be a continuous process to ensure reliable accuracy of the prediction on new patient data or new disease monitoring applications—and this poses a regulatory challenge.

"Although eliminating the use of laser-based instruments and staining protocols should reduce patient-to-patient and facility-to-facility variations, the quality of the label-free images inherently depends on the imaging instrumentations and the imagers. Our analysis technique itself is a 'software' solution, which must synchronize well with other modernized imaging modalities (the 'hardware') to collectively deliver reliable outputs.

"Altogether, these are challenging issues in data science, where new batches of (big) clinical data are streaming and evolving every minute. The data generation, data management, and data analysis system will all need constant monitoring and maintenance, and in turn, demanding well-trained experts to ensure good quality performance over time."

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Identify the incidence of axillary lymphadenopathy from the Moderna and Pfizer-BioNTech COVID-19 vaccines.

2. Explain recommendations from the Society of Breast Imaging (SBI) related to axillary lymphadenopathy detected on mammography.

Disclosure: The author(s), faculty, staff, and planners, including spouse/partners (if any), in any position in any position to control the content of this activity, have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

Oncology Times: What types of morphological features were included in the label-free channels that were sufficient to achieve clear discrimination of ALL cell phenotypes, even when they are a very small percentage of the total white cells? **Doan:** "We tested both hand-crafted pre-engineered features (conventional morphology features such as size, shape, intensity, texture, granularity...of the cells) and feature embeddings from representation learning methods such as deep learning. From both approaches, the feature space was sufficient to identify the unique cellular fingerprints to identify ALL cell phenotypes. We did not deeply examine the interpretability of the features uniquely diagnostic for ALL phenotype; this is a challenge for machine learning methods, particularly those involving deep learning."

Oncology Times: Why was it important to provide open-source scripts for this study?

Doan: "We provided our code open-source to facilitate reproducibility of the study, as well as to enable the ever-expanding use of the technique to new clinical and basic biology problems. We hope to encourage a wider research community to battle-test such kind of AI/ ML applications to ensure the continuous advancement of the field.

"We certainly look forward to seeing more similar studies to advocate the practical implementation of state-of-the-art machine learning and computer vision in clinical settings to ultimately benefit the patients." OT

Dibash Kumar Das is a contributing writer.