Frequency and Characteristics of Nodal and Deltoid FDG and ^{11}C-Choline Uptake on PET Performed After COVID-19 Vaccination

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BACKGROUND. COVID-19 vaccination may trigger reactive lymphadenopathy, confounding imaging interpretation. There has been limited systematic analysis of PET findings after COVID-19 vaccination.

OBJECTIVE. The purpose of this study was to evaluate the frequency and characteristics of abnormal FDG and ^{11}C-choline uptake on PET performed after COVID-19 vaccination.

METHODS. This retrospective study included 67 patients (43 men and 24 women; mean [± SD] age, 75.6 ± 9.2 years) who underwent PET examination between December 14, 2020, and March 10, 2021, after COVID-19 vaccination and who had undergone prevaccination PET examination without visible axillary node uptake. A total of 52 patients received the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech; hereafter referred to as the Pfizer-BioNTech vaccine), and 15 received the SARS-CoV-2 mRNA-1273 vaccine (Moderna; hereafter referred to as the Moderna vaccine). Sixty-six of the patients underwent PET/CT, and one underwent PET/MRI. Fifty-four PET examinations used FDG, and 13 used ^{11}C-choline. PET was performed a median of 13 and 10 days after vaccination for patients who had received one ($n = 44$) and two ($n = 23$) vaccine doses, respectively. Two nuclear medicine physicians independently reviewed images and were blinded to injection laterality and the number of days since vaccination. Lymph node or deltoid SUV_{max} greater than the blood pool SUV_{max} was considered positive. Interreader agreement was assessed, and the measurements made by the more experienced physician were used for subsequent analysis.

RESULTS. Positive axillary lymph node uptake was observed in 10.4% (7/67) of patients (7.4% [4/54] of FDG examinations and 23.1% [3/13] of ^{11}C-choline examinations); of the patients with positive axillary lymph nodes, four had received the Pfizer vaccine, and three had received the Moderna vaccine. Injection laterality was documented for five of seven patients with positive axillary lymph nodes and was ipsilateral to the positive node in all five patients. PET was performed within 24 days of vaccination for all patients with a positive node. One patient showed extraaxillary lymph node uptake (ipsilateral supraclavicular uptake on FDG PET). Ipsilateral deltoid uptake was present in 14.5% (8/55) of patients with documented injection laterality, including 42.9% (3/7) of patients with positive axillary lymph nodes. Interreader agreement for SUV measurements (expressed as intraclass correlation coefficients) ranged from 0.600 to 0.988.

CONCLUSION. Increased axillary lymph node or ipsilateral deltoid uptake is occasionally observed on FDG or ^{11}C-choline PET performed after COVID-19 vaccination with the Pfizer-BioNTech or Moderna vaccine.

CLINICAL IMPACT. Interpreting physicians should recognize characteristics of abnormal uptake on PET after COVID-19 vaccination to guide optimal follow-up management and reduce unnecessary biopsies.

COVID-19 has resulted in a global pandemic comprising more than 160 million cases and resulting in more than 3.3 million deaths worldwide to date, and these numbers continue to rise [1, 2]. Accordingly, an unprecedented effort to rapidly develop and deploy vaccinations against the causative agent, SARS-CoV-2, has occurred around the world [3]. In the United States, the first two vaccines to receive approval for emergency use were the SARS-CoV-2 mRNA-1273 vaccine (Moderna; hereafter referred to as the Moderna vaccine) and the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech; hereafter referred to as the

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Pfizer-BioNTech vaccine), which showed efficacy rates of 94.1% and 95.0%, respectively [4, 5]. These two products have been used for most COVID-19 vaccinations in the United States to date, and they are also widely used internationally. These vaccinations produce various minor side effects, including lymphadenopathy secondary to the robust immune response. For example, 0.3% of recipients of the Moderna vaccine reported lymphadenopathy, as recorded in an electronic journal, compared with less than 0.1% of a control group [5]. In addition, on the basis of physical examination findings, lymphadenopathy was reported by 64 patients who received the Pfizer-BioNTech vaccine compared with three patients in a control group [6].

PET is widely used to detect malignancies. Various injected radiotracers are used in PET, with FDG the most common. It has historically been recognized that FDG activity on PET may rarely occur after vaccination, as has been described in numerous case reports [7–12] and in larger studies of patients after influenza and human papillomavirus vaccination [13–17]. These changes most commonly include increased FDG uptake in the axillary lymph nodes ipsilateral to the vaccine injection site [15]. More recently, multiple case reports and small series showed an apparently even stronger association between COVID-19 vaccination and axillary lymphadenopathy by use of a range of imaging modalities [18–20]. The management of FDG-avid lymph nodes detected on PET in patients who have received recent COVID-19 vaccination presents a particular clinical challenge given the common application of PET in the setting of oncology [21–23].

Although imaging manifestations of COVID-19 vaccination have been described, there has been limited systematic analysis of COVID-19 vaccination–induced changes on PET [24, 25]. To our knowledge, the impact of COVID-19 vaccination on PET examinations performed with radiotracers other than FDG, including ^{11}C-choline, also has yet to be systematically evaluated. The purpose of the present study was to evaluate the frequency and characteristics of abnormal uptake of FDG and ^{11}C-choline on PET performed after vaccination with the Pfizer-BioNTech vaccine and the Moderna vaccine.

Methods

Patients

This single-institution retrospective study was performed in a HIPAA-compliant fashion under a waiver from the institutional review board at Mayo Clinic. The requirement for written informed consent was waived.

A nuclear radiologist (M.P.T., who had 2 years of experience) initially performed an electronic database search to identify patients 18 years old or older who had undergone PET examination (PET/CT or PET/MRI) between December 14, 2020 (the first day that COVID-19 vaccination was available in the United States), and March 10, 2021. The search yielded 4471 patients. This list of patients was merged with a dataset containing all COVID-19 vaccinations performed at Mayo Clinic during this period, yielding 169 patients who underwent a PET examination after vaccination. Patients were then excluded for the following reasons (Fig. 1): PET performed for research purposes only (n = 23); PET that covered limited anatomy only (n = 16); clinical PET that was performed but for which the patient did not provide authorization for use of the images for re-

HIGHLIGHTS

Key Finding

- *On PET examinations performed after COVID-19 vaccination, axillary lymph node uptake was observed in 10.4% (7/67) of patients (7.4% and 23.1% of FDG and ^{11}C-choline examinations, respectively), ipsilateral deltoid uptake was observed in 14.5% (8/55) of patients with known injection laterality, and ipsilateral nonaxillary lymph node uptake was observed in one patient.*

Importance

- *Recognition of occasional abnormal axillary lymph node or deltoid uptake on PET examinations performed after COVID-19 vaccination will aid interpreting physicians and reduce unnecessary biopsies.*

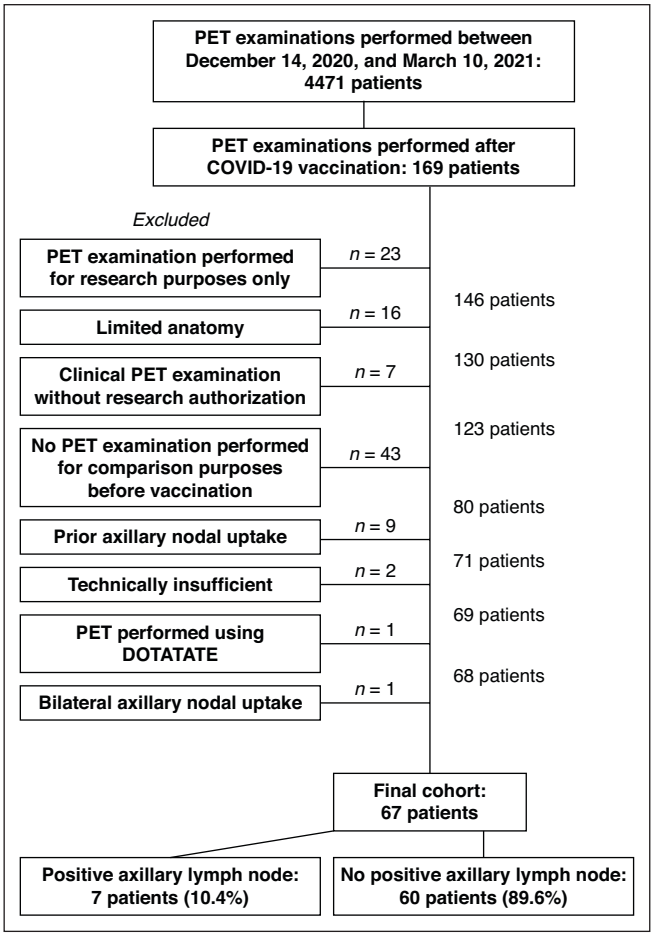

Fig. 1—Flowchart of included and excluded study patients who underwent PET examination after COVID-19 vaccination. Final analysis included 67 PET examinations performed for 67 patients. Before vaccination, all patients had undergone PET that did not show visible axillary nodal uptake. Technically insufficient examinations were related to poor dietary preparation (n = 1) and bilateral shoulder prostheses (n = 1).

search purposes (n = 7); no PET examination performed before COVID-19 vaccination (n = 43); prevaccination PET examination showing visible axillary lymph node uptake on maximum-intensity-projection images that could be attributed to known malignancy or infection in the patients, as assessed retrospectively by the nuclear radiologist (n = 9); examinations that were technically insufficient (n = 2); postvaccination PET performed using DOTATATE (n = 1); and bilateral axillary nodal uptake on the PET examination performed after COVID-19 vaccination (n = 1). These exclusions resulted in a final study sample of 67 patients (mean [± SD] age, 75.6 ± 9.2 years; range, 49–90 years), 64.2% (43/67) of whom were men and 35.8% (24/67) of whom were women, who underwent 67 postvaccination PET examinations (Table 1). The most recent prevaccination PET examination undergone by each patient was selected for comparison of SUV measurements before and after vaccination. The median time between the pre- and postvaccination PET examinations was 6.0 months.

TABLE 1: Clinical and PET Characteristics for the Sample of 67 Patients

Characteristic	Value
Age (y), mean ± SD	75.6 ± 9.2
Sex	
Male	43 (64.2)
Female	24 (35.8)
COVID-19 vaccine	
Pfizer-BioNTech vaccine[a]	52 (77.6)
Moderna vaccine[b]	15 (22.4)
First vaccine dose	
Injection in right deltoid	21 (31.3)
Injection in left deltoid	33 (49.3)
Injection location not recorded	13 (19.4)
No. of days before PET was performed, median (range)	
Among patients who received first dose only	13 (1–42)
Among patients who received second dose	33 (23–54)
Second vaccine dose[c]	
Injection in right deltoid	8 (34.8)
Injection in left deltoid	11 (47.8)
Injection location not recorded	4 (17.4)
No. of days before PET was performed, median (range)	10 (1–31)
Fusion technique	
PET/CT	66 (98.5)
PET/MRI	1 (1.5)
PET agent	
FDG	54 (80.6)
^{11}C-choline	13 (19.4)
Indication for PET	
Hematologic cancer	18 (26.9)
Prostate cancer[d]	13 (19.4)
Lung cancer or nodule	11 (16.4)
Melanoma	8 (11.9)
Breast cancer	6 (9.0)
Gastrointestinal cancer	5 (7.5)
Head and neck cancer	4 (6.0)
Urothelial and thyroid cancer	2 (3.0)
Receiving immunotherapy at time of postvaccination PET	4 (6.0)

Note—Except where otherwise indicated, data are the number (percentage) of patients.
[a]BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech).
[b]SARS-CoV-2 mRNA-1273 vaccine (Moderna).
[c]Among 23 patients.
[d]All PET examinations conducted for the evaluation of prostate cancer were performed using ^{11}C-choline.

PET Acquisition

The following information was extracted from the electronic medical record for each patient: age, sex, COVID-19 vaccine type (Pfizer-BioNTech vaccine or Moderna vaccine), vaccination date(s), vaccine injection site (right or left deltoid), indication for PET examination, radiotracer type (FDG or ^{11}C-choline), injected radiotracer activity, uptake time, infusion site, and presence of any significant radiotracer extravasation based on the note recorded by the technologist at the time of the examination. Additional data recorded for patients who underwent FDG PET included the patients' reported fasting time and blood glucose level immediately before the examination was performed.

A standard clinical oncologic PET acquisition technique was used. Patients were scanned while in a supine position with their arms raised when possible. Examinations were performed using a PET/CT system (Discovery 690, Discovery 710, or Discovery MI [all by GE Healthcare] or Biograph Vision 600 PET/CT [Siemens Healthineers]) or a PET/MRI system (Signa, GE Healthcare). All PET examinations were performed using lutetium yttrium orthosilicate detectors (matrix, 128 × 128; FOV, 70 × 70 cm) with an acquisition time of 3–5 minutes per PET bed based on body mass index. PET/CT was performed using a low-dose 16- or 128-MDCT technique and the following parameters: tube current, approximately 90 mA; rotation time, 0.5 second (tube current–exposure time product, approximately 45 mAs); tube voltage, 120 kVp; and slice thickness, 3.75–5.0 mm. PET/MRI was performed using a 3-T magnet with a bore diameter of 60 cm and anatomic measurements obtained from the chemical shift–based Dixon sequence.

PET Interpretation

PET images were reviewed independently by a board-certified nuclear radiologist with 4 years of posttraining clinical experience (J.R.Y.) and a fellow who had completed 1 year of nuclear radiology training (P.J.N.). The readers viewed the pre- and postvaccination PET examinations concurrently for each patient. The readers were aware of the timing of each examination (i.e., whether the examination was performed before vs after vaccination) but were unaware of the laterality of the vaccine injection as well as of the number of days between the most recent dose and the postvaccination examination. Image evaluation was performed using Visage Imaging software (version 7.1.15, Visage Imaging). The readers recorded SUV measurements using spherical volumes of interest. SUV values were measured from ordered-subset expectation maximization iterative reconstruction PET data, harmonized to comply with European

Association of Nuclear Medicine Research Ltd. (EARL) accreditation specifications [26]. To ensure comparable data across scanner types, SUV values were not recorded from any available time-of-flight reconstructions or other advanced reconstruction algorithm data.

For each examination, the readers recorded the SUV_{max} and the SUV_{mean} of the blood pool (measured using a volume of interest with a 2-cm diameter within the center of the right cardiac atrium); for FDG PET examinations, the readers recorded the SUV_{max} and SUV_{mean} of healthy liver (measured using a volume of interest with a 3-cm diameter in the posterior right hepatic lobe) as well as the SUV_{max} of the spleen (measured using a volume of interest with a 2-cm diameter within the center of the spleen). For all examinations, the readers also recorded the SUV_{max} for the single axillary lymph node that was visually most radiotracer avid on each side and, for postvaccination examinations, the area of the deltoid muscle that was visually most radiotracer avid on each side. Axillary lymph node uptake and deltoid uptake were considered positive when the SUV_{max} was greater than the blood pool SUV_{max}. The blood pool was used to provide an internal reference for determining the presence of positive lymph node uptake and deltoid muscle uptake given the potential interpatient variability in the PET technique. The use of blood pool as a reference standard for differentiating malignant and reactive avid lymph nodes on ^{11}C-choline PET has been previously validated elsewhere [27]. One reader (the nuclear radiologist) used the axial low-dose unenhanced CT images that were obtained for attenuation correction and anatomic localization to perform 2D size measurements corresponding with the axillary lymph node selected for SUV measurement on each side. The readers also assessed postvaccination examinations for the presence of any cervical, supraclavicular, mediastinal, or pulmonary hilar lymph nodes that showed radiotracer uptake that was visually greater than physiologic blood pool on maximum-intensity-projection PET images. Last, the readers visually evaluated images to assess for the presence of radiotracer extravasation at the injection site beyond minimal residual activity at the injection site. After the initial review, the readers performed a qualitative post hoc review of cases showing positive deltoid uptake to assess for the presence of an elongated morphology of the uptake within the deltoid muscle that follows the muscular striations.

Clinical Review of Nonaxillary Lymph Nodes

Two board-certified nuclear radiologists (S.M.B. and D.R.J., who had 5 and 2 years of posttraining clinical experience, respectively) in consensus performed an imaging and medical record review to identify all cases with positive lymph nodes detected outside of the axilla on the postvaccination PET examination, to classify the nonaxillary node as likely due to vaccination or likely malignant. This review occurred 1 week after the previous PET review for abnormal FDG uptake. The lymph nodes were deemed likely malignant when they involved a site likely to represent metastatic disease for the patient's primary malignancy and when described as malignant in both the clinical PET report and in the treating clinician's note; the node was otherwise deemed likely to be reactive to vaccination.

Statistical Analysis

Interrater agreement between the two readers was determined for all SUV measurements by use of intraclass correlation coefficients (ICCs) with a two-way random effects agreement model (R statistical programming language, version 4.0.2, with irr package version 0.84.1, R Foundation). Subsequent analyses based on the SUV measurements were performed using the measurements from the board-certified nuclear radiologist only. Categoric data were reported as the frequency and percentage and as the mean ± SD. Continuous variables were compared using paired and unpaired *t* tests when mean values were compared and Kruskal-Wallis tests when median values were compared. Categoric variables were compared using chi-square tests. Correlation of continuous variables was evaluated using Spearman rank correlation. Analysis was performed using BlueSky Statistics Commercial Desktop Edition software (version 6.30, BlueSky Statistics). Graphs were created using Excel 2008 spreadsheet software (Microsoft). A $p < .05$ was considered statistically significant.

Results

Patients and PET Examinations

A total of 77.6% (52/67) of patients received the Pfizer-BioNTech vaccine, and 22.4% (15/67) received the Moderna vaccine. A total of 34.3% (23/67) of patients received the second vaccine dose, with all doses manufactured by the same company that had manufactured the patient's first dose. The anatomic location where the vaccine was administered was available for 80.6% (54/67) and 82.6% (19/23) of patients for the first and second dose, respectively.

A total of 98.5% (66/67) of patients underwent PET/CT, and 1.5% (1/67) underwent PET/MRI. A total of 80.6% (54/67) of patients underwent PET using FDG, and 19.4% (13/67) underwent PET using ^{11}C-choline. All ^{11}C-choline PET examinations were performed for prostate cancer evaluation. For the 23 patients who received both doses, the PET examination was performed at a median of 33 days (range, 23–54 days) after the first vaccine dose was received and 10 days (range, 1–31 days) after the second vaccine dose was received. Of the 44 patients who received the first dose only, the median time from vaccination was 13 days (range, 1–42 days). No case of significant radiotracer extravasation based on technologist notes or visual assessment of the PET images was identified by either reader.

Interreader Agreement

Table 2 presents interreader agreement between the two readers for the various SUV measurements on the postvaccination PET examinations. Interobserver agreement, expressed as ICCs, was 0.884–0.956 for SUV measurements relating to the liver, 0.600–0.930 for SUV measurements relating to blood pool, 0.988 for SUV measurements relating to the spleen, 0.777–0.911 for SUV measurements relating to axillary lymph nodes, and 0.747–0.873 for SUV measurements relating to the deltoid.

PET Examination Findings

Table 3 shows SUV measurements from the pre- and postvaccination PET examinations. The mean ratio of the SUV_{max} of the left axillary lymph node to that of the blood pool was significantly greater ($p = .02$) on postvaccination FDG PET (0.46 ± 0.40) than on prevaccination FDG PET (0.33 ± 0.12). Otherwise, there were no significant differences (all $p > .05$) between the pre- and postvac-

TABLE 2: Interreader Agreement for SUV Measurements

Measurement	Intraclass Correlation Coefficient
Liver SUV_{max} [a]	0.884
Liver SUV_{mean} [a]	0.956
Blood pool SUV_{max}	
FDG	0.797
^{11}C-choline	0.600
Blood pool SUV_{mean}	
FDG	0.930
^{11}C-choline	0.818
Right axillary LN SUV_{max} ratio	
FDG	0.777
^{11}C-choline	0.847
Left axillary LN SUV_{max} ratio	
FDG	0.825
^{11}C-choline	0.911
Right deltoid SUV_{max} ratio	
FDG	0.784
^{11}C-choline	0.747
Left deltoid LN SUV_{max} ratio	
FDG	0.873
^{11}C-choline	0.864
Spleen SUV_{max}	0.988

Note—Fifty-four PET examinations used FDG, and 13 used ^{11}C-choline. LN = lymph node.
[a]Recorded for FDG PET examinations only (n = 54).

cination PET examinations in terms of the liver, blood pool, and axillary lymph node SUV measurements.

A total of 10.4% (7/67; 95% CI, 4.3–20.3) of postvaccination PET examinations showed positive axillary lymph nodes (defined as an axillary lymph node SUV_{max} greater than the blood pool SUV_{max}), including 7.4% (4/54; 95% CI, 2.1–17.9%) of FDG examinations and 23.1% (3/13; 95% CI, 5.0–53.8%) of ^{11}C-choline examinations (Figs. 2 and 3). All four positive axillary lymph nodes observed on FDG PET also had an SUV_{max} greater than the liver SUV_{mean}, although none of the three positive axillary lymph nodes on ^{11}C-choline PET had an SUV_{max} greater than the liver SUV_{mean}. The mean ^{11}C-choline uptake time was significantly lower (p = .03) in patients with positive axillary nodes (3.4 ± 0.8 minutes) than in those without positive axillary nodes (4.8 ± 0.8 minutes) (Table 4). Otherwise, a wide range of PET parameters, including injected radioactivity and FDG uptake time, were not significantly different (p > .05) between patients with and without positive axillary lymph node uptake.

A total of 3.0% (2/67) of the prevaccination PET examinations showed positive axillary lymph node uptake (i.e., nodal SUV_{max} greater than blood pool SUV_{max}, despite no visible axillary lymph node uptake being observed on maximum-intensity-projection images). None of the seven patients with a positive axillary lymph node on postvaccination PET examination also showed a positive axillary lymph node on prevaccination PET, and neither of the two patients with a positive axillary lymph node on prevaccination PET also had a positive axillary lymph node observed on postvaccination PET.

The clinical characteristics of the seven patients with positive axillary lymph nodes on postvaccination PET are summarized in Table 5. Four of the patients had received the Pfizer-BioNTech vaccine, and three had received the Moderna vaccine. For the five patients with positive nodes and a known COVID-19 vaccine injection site, the new increased axillary uptake occurred on the side

TABLE 3: Comparison of SUV Measurements on PET Examinations Performed Before and After COVID-19 Vaccination

Measurement	Prevaccination PET	Postvaccination PET	p
Liver SUV_{max} [a]	3.44 ± 0.57	3.44 ± 0.53	.99
Liver SUV_{mean} [a]	2.75 ± 0.43	2.68 ± 0.39	.40
Blood pool SUV_{max}			
FDG	2.42 ± 0.37	2.55 ± 0.42	.09
^{11}C-choline	1.59 ± 0.46	1.80 ± 1.35	.23
Blood pool SUV_{mean}			
FDG	1.96 ± 0.28	2.06 ± 0.34	.09
^{11}C-choline	1.25 ± 0.33	1.35 ± 0.30	.46
Ratio of right axillary LN SUV_{max} to blood pool SUV_{max} [b]			
FDG	0.32 ± 0.11	0.38 ± 0.22	.08
^{11}C-choline	0.49 ± 0.19	0.68 ± 0.38	.11
Ratio of left axillary LN SUV_{max} to blood pool SUV_{max} [b]			
FDG	0.33 ± 0.12	0.46 ± 0.40	.02
^{11}C-choline	0.63 ± 0.32	0.60 ± 0.29	.85
Positive left axillary LN (relative to blood pool), no. of patients (%)	2 (3.0)	4 (6.0)	.68
Positive right axillary LN (relative to blood pool), no. of patients (%)	0 (0.0)	3 (4.5)	.24

Note—Except where otherwise indicated, data are mean ± SD. Fifty-four PET examinations used FDG, and 13 used ^{11}C-choline. LN = lymph node.
[a]Recorded for FDG PET examinations only (n = 54).
[b]Ratio of LN SUV_{max} to blood pool SUV_{max}.

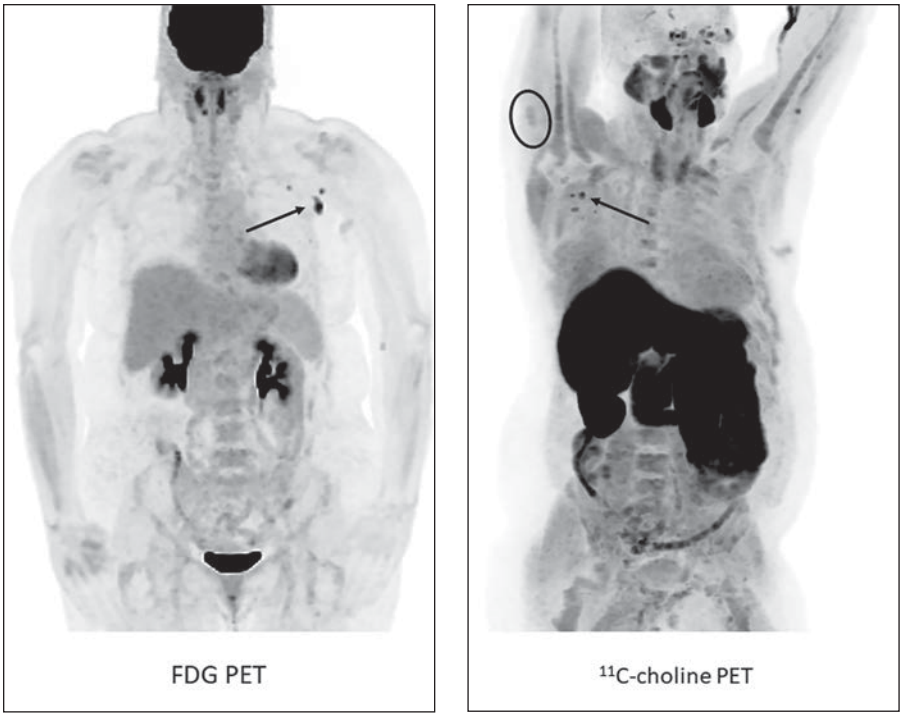

Fig. 2—Maximum-intensity-projection PET images show ipsilateral axillary lymph node uptake using two different radiotracers.
A, 57-year-old woman with melanoma in right upper arm who received first dose of BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech; hereafter referred to as Pfizer-BioNTech vaccine) in left deltoid 15 days before undergoing FDG PET/CT. FDG uptake is observed within left axillary lymph nodes (*arrow*) (SUV_{max} = 9.3).
B, 62-year-old man with metastatic prostate carcinoma who received second dose of Pfizer-BioNTech vaccine in right deltoid 7 days before undergoing ^{11}C-choline PET/CT. Uptake of ^{11}C-choline is observed within right axillary lymph nodes (*arrow*) (SUV_{max} = 3.1) and right deltoid muscle (*oval*) (SUV_{max} = 1.7).

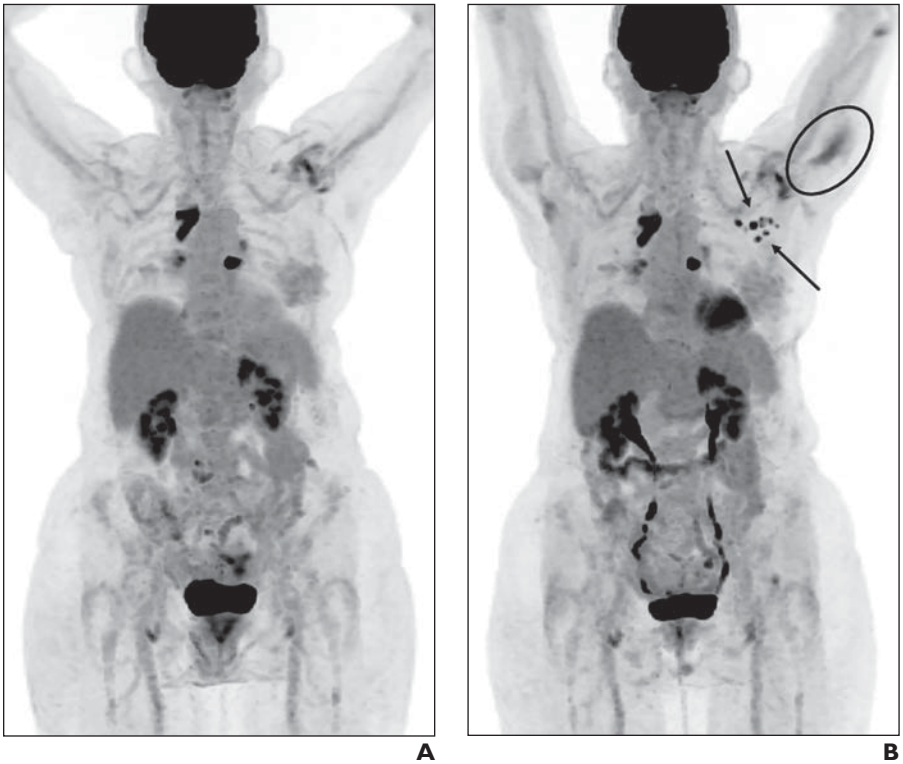

Fig. 3—78-year-old woman with metastatic breast cancer who was receiving hormonal therapy. Patient received second dose of BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) in left deltoid 2 days before undergoing FDG PET/CT.
A, FDG PET/CT image obtained before vaccination shows metastatic uptake in left lung and right hilar region and reactive uptake adjacent to left glenohumeral joint.
B, FDG PET/CT image obtained after vaccination shows new multifocal FDG uptake within left axillary nodes (*arrows*) (SUV_{max} = 4.2) and elongated FDG uptake within left deltoid muscle (*oval*) (SUV_{max} = 3.2) with pattern that follows muscular striations.

ipsilateral to the vaccination. PET examinations of these seven patients were performed a median of 12 days (range, 2–24 days) after the most recent vaccine administration (Fig. 4). The time from the most recent vaccination to PET and the ratio of the SUV_{max} of the axillary lymph node to that of the blood pool were not significantly correlated in these seven patients (r = −0.543, p = .07).

The seven positive axillary lymph nodes showed a mean long-axis diameter of 13 ± 4 mm and a mean short-axis diameter of 8 ± 2 mm; the lymph node was abnormally enlarged (short-axis diameter > 10 mm) in one of these seven patients. The short-axis diameter of the positive axillary nodes was significantly larger (p = .006) than the mean short-axis diameter of the negative ax-

TABLE 4: Comparison of PET Parameters Between Patients With and Without Positive Axillary Lymph Nodes (LNs)

PET Parameter	All Patients	Patients With Positive Axillary LN	Patients Without Positive Axillary LN	*p*
No. of days since last vaccine dose, median (range)	12 (1–42)	12 (2–24)	11.5 (1–42)	.77
Injected radiotracer activity (mCi)[a]				
FDG	11.8 ± 2.4 [436.6 ± 88.8]	11.4 ± 3.0 [421.8 ± 111.0]	11.8 ± 2.4 [436.6 ± 88.8]	.74
^{11}C-choline	15.0 ± 3.0 [555.0 ± 111.0]	12.3 ± 0.4 [455.1 ± 14.8]	15.8 ± 3.0 [584.6 ± 111.0]	.08
Uptake time (min)				
FDG	62.5 ± 3.5	65.6 ± 6.4	62.3 ± 3.1	.06
^{11}C-choline	4.4 ± 1.0	3.4 ± 0.8	4.8 ± 0.8	.03
Blood pool SUV_{max}				
FDG	2.5 ± 0.4	2.4 ± 0.3	2.6 ± 0.4	.55
^{11}C-choline	1.8 ± 0.4	1.5 ± 0.5	1.9 ± 0.3	.19
Blood pool SUV_{mean}				
FDG	2.1 ± 0.3	2.1 ± 0.2	2.0 ± 0.4	.61
^{11}C-choline	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	.25
Liver SUV_{max}[b]	3.4 ± 0.6	3.6 ± 0.5	3.4 ± 0.6	.51
Liver SUV_{mean}[b]	2.7 ± 0.4	2.9 ± 0.3	2.7 ± 0.4	.39
Spleen SUV_{max}[b]	2.7 ± 0.5	2.8 ± 0.2	2.6 ± 0.5	.55
Fasting time (no. of hours since last meal)[b]	10.8 ± 4.2	10.8 ± 4.7	10.8 ± 4.2	.98
Glucose level (mg/dL)[b]	108.0 ± 34.0	91.0 ± 6.1	109.4 ± 35.0	.30

Note—Except where otherwise indicated, data are mean ± SD. Fifty-four patients underwent PET examinations using FDG, and four of those patients had positive axillary LNs. Thirteen patients underwent PET examinations using ^{11}C-choline, and three of those patients had positive axillary LNs.
[a]Values in brackets are millicurie values converted to megabecquerels.
[b]Recorded for FDG PET examinations only (n = 54).

illary lymph nodes (6 ± 2 mm); the long-axis diameter was not significantly different (p = .06) compared with negative axillary lymph nodes (mean, 10 ± 4 mm).

The nuclear medicine attending radiologist and fellow both detected uptake within the lymph nodes outside the axilla on the postvaccination PET examination of five patients. However, four of these patients were deemed to have cases that were likely secondary to progressive malignancy on the basis of the consensus clinical review. Thus, only one (1.5%) of 67 patients showed positive lymph node uptake outside of the axilla that was deemed likely to be due to COVID-19 vaccination. This patient was receiving pembrolizumab immunotherapy and showed ipsilateral supraclavicular lymph node uptake on postvaccination FDG PET (Fig. 5). No other lymph node uptake was observed throughout the neck or thorax.

Positive deltoid uptake was seen on postvaccination PET examinations of 14.5% (8/55) of patients with known laterality of the injection. Specifically, the left deltoid showed positive uptake in 14.7% (5/34) of patients with known vaccine injection in the left deltoid, three of whom also had a positive left axillary lymph node. Positive right deltoid uptake was seen in 14.3% (3/21) of patients with known vaccine injection in the right deltoid, but none of these patients also had a positive right axillary lymph node. Overall, 42.9% (3/7) of patients with positive axillary lymph node uptake showed positive ipsilateral deltoid uptake. On post hoc qualitative review, five of eight cases of deltoid uptake showed elongated morphology of the uptake that follows the muscular striations. The time from the most recent vaccination to PET and the ratio of the deltoid SUV_{max} to the blood pool SUV_{max} were not significantly correlated (r = −0.051, p = .28).

Discussion

In the present study, we assessed the frequency of axillary and extraaxillary nodal uptake on PET examinations performed after administration of COVID-19 vaccines manufactured by Pfizer-BioNTech or Moderna among patients in whom there was an absence of axillary lymph node uptake on maximum-intensity-projection images on prevaccination PET. When a sensitive threshold (lymph node SUV_{max} greater than blood pool SUV_{max}) was used, a total of 10.4% of patients had positive axillary lymph nodes after COVID-19 vaccination, all instances of which were observed on PET examinations performed within 24 days of vaccination. The axillary lymph nodes with positive PET uptake had a mean short-axis diameter of only 8 ± 2 mm. Only one patient showed extraaxillary lymph node uptake that was deemed to be likely related to vaccination (specifically, supraclavicular uptake on FDG PET ipsilateral to vaccination). Furthermore, positive deltoid uptake (defined as a deltoid SUV_{max} greater than the blood pool SUV_{max}) was observed in eight of 55 patients in whom the laterality of deltoid injection was documented and in 42.9% of patients

TABLE 5: Characteristics of Patients With Positive Axillary Lymph Node (LN) Uptake on PET Performed After COVID-19 Vaccination

Patient	Age (y)	COVID-19 Vaccine[a]	First-Dose Laterality (No. of Days Before PET)	Second-Dose Laterality (No. of Days Before PET)	PET Agent	Radiotracer Injection Site	Laterality of Positive LN	SUV_{max} Ratio After Vaccination[b]	SUV_{max} Ratio Before Vaccination[b,c]	Size of Positive LN (mm)[d]
A	78	Pfizer-BioNTech vaccine	L (23)	L (2)	FDG	L ACF	L	1.50	0.19	8 × 7
B	57	Pfizer-BioNTech vaccine	L (15)	NA	FDG	L ACF	L	1.65	0.27	17 × 10
C	72	Moderna vaccine	NR (31)	L (4)	FDG	L ACF	L	2.52	0.24	14 × 6
D	65	Moderna vaccine	NR (18)	NA	FDG	R ACF	R	1.59	0.55	19 × 11
E	62	Pfizer-BioNTech vaccine	R (34)	R (7)	^{11}C-choline	L ACF	R	1.63	0.46	13 × 8
F	83	Pfizer-BioNTech vaccine	R (33)	R (12)	^{11}C-choline	L ACF	R	1.06	0.82	11 × 6
G	82	Moderna vaccine	NR (54)	NR (24)	^{11}C-choline	R ACF	L	1.40	0.44	7 × 5

Note—L = left, ACF = antecubital fossa, NA = not administered, NR = not recorded, R = right.

[a]The BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech; hereafter referred to as the Pfizer-BioNTech vaccine) or the SARS-CoV-2 mRNA-1273 vaccine (Moderna; hereafter referred to as the Moderna vaccine).

[b]Ratio of LN SUV_{max} to blood pool SUV_{max}.

[c]LN seen on the prevaccination PET examination was ipsilateral to the positive LN seen on the postvaccination PET examination.

[d]Long axis × short axis.

with positive ipsilateral axillary nodal uptake. The findings indicate the effect of these two COVID-19 vaccinations on axillary and, rarely, extraaxillary lymph node uptake on PET. These alterations in PET findings after COVID-19 vaccination are important confounding pitfalls that could prompt unnecessary biopsies and treatments unless they are appropriately recognized by interpreting physicians.

Axillary nodal uptake was further reported separately for PET examinations performed using FDG and those performed using ^{11}C-choline given the different uptake mechanisms of the two agents. A total of 7.4% versus 23.1% of postvaccination FDG and ^{11}C-choline PET examinations, respectively, showed positive axillary nodes by use of a threshold defined by the blood pool SUV_{max}. The ^{11}C-choline uptake in reactive lymph nodes is hypothesized to be via choline transporter-like protein–1 in immune-activated macrophages, which increases phosphatidylcholine production and induces an inflammatory response [28]. Although all of the axillary nodes on FDG PET detected using blood pool SUV_{max} as the reference would also be deemed positive if liver SUV_{mean} was used instead as the reference, no axillary lymph node on ^{11}C-choline PET would be deemed positive if the liver SUV_{mean} was used as the reference. Further study is needed to assess the impact of different thresholds on positive lymph node detection for the two agents.

McIntosh et al. [29] showed FDG-avid lymph nodes outside of the ipsilateral axilla, including the ipsilateral cervical and supraclavicular lymph nodes, after COVID-19 vaccination. In the present study, the single patient with ipsilateral supraclavicular nodal uptake was receiving pembrolizumab immunotherapy. We speculate that receiving immunotherapy during oncologic treatment may lead to a greater immune response to vaccination, contributing to increased lymph node positivity on PET both in and outside of the axilla.

In the study by Mehta et al. [18], two of four cases of COVID-19 vaccination–related axillary lymphadenopathy showed axillary lymph nodes that measured at least 1.0 cm in the short axis. In the present study, the seven positive axillary lymph nodes had a mean short-axis diameter of only 8 mm, and only one was abnormally enlarged (short-axis diameter > 10 mm). This lack of substantial enlargement may provide a helpful indication to the interpreting physician that the increased uptake is reactive to vaccination. Furthermore, nodes of this size may be technically challenging to biopsy using ultrasound or CT guidance. Note that the lymph nodes measured in the present study were those with the greatest PET uptake, which was not necessarily the node with the largest size.

The present study was conducted during a period when only older patients were approved to receive the COVID-19 vaccine, which may have affected the observed incidence of positive axillary lymph nodes. The mean age of the patient sample was 75.6 years old (range, 49–90 years). As such, the findings may not be generalizable to a broader population of patients undergoing PET that includes younger patients. As vaccination has become available for all adults in many regions, future studies may explore the relationship between age and the frequency of COVID-19 vaccination–associated nodal uptake.

A recent study by Cohen et al. [24] evaluated the incidence of axillary lymph node uptake FDG PET after administration of the Pfizer-BioNTech vaccine. The study reported that vaccine-associated axillary lymph node uptake occurred in 36.5% of patients who received the vaccine, which is higher than both our study's overall frequency of 10.4% and the frequency of 7.4% among patients who underwent FDG PET. The higher incidence reported by Cohen and colleagues could potentially reflect the differences in patient samples (including a younger mean age of 69.2 years in the study by Cohen et al. vs a mean age of 75.6 years in the present study) and differences in the criteria for positive axillary lymph node uptake. Nonetheless, Cohen and colleagues reported a similar observation of a decrease in vaccine-associated axillary

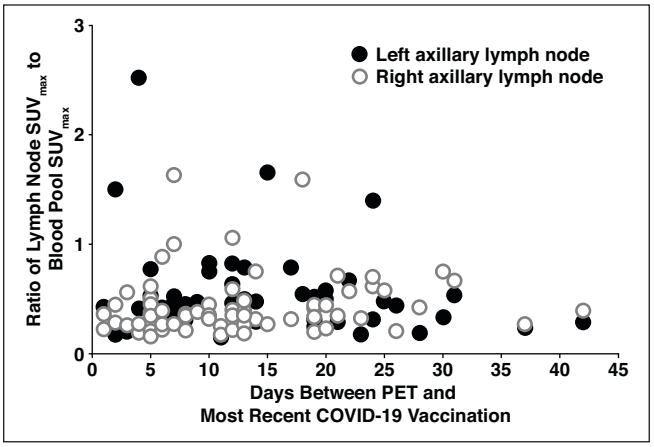

Fig. 4—Scatterplot of ratio of lymph node SUV_{max} to blood pool SUV_{max} according to days since most recent administration of COVID-19 vaccine. One lymph node with highest uptake from left and right axillary nodal chains was measured in each patient. Blood pool was measured from right atrium. Seven patients showed single positive axillary lymph node (ipsilateral to vaccine dose in five of seven patients with known laterality of vaccine injection), represented by patients with ratio of lymph node SUV_{max} to blood pool SUV_{max} that was greater than 1.

nodal uptake at approximately 3 weeks after vaccine administration (specifically, high FDG uptake in 7% of patients after 20 days).

A local inflammatory reaction at the site of injection is a common effect of COVID-19 vaccination, but it is usually mild and transient [30]. Eifer and Eshet [22] reported a case of ipsilateral axillary nodal and deltoid uptake after COVID-19 vaccination. Burger et al. [14] observed deltoid uptake in 15 of 17 patients with axillary nodal uptake after influenza A virus (H1N1) vaccination. We observed positive deltoid uptake (deltoid SUV_{max} greater than blood pool SUV_{max}) in 14.5% of patients on PET performed after vaccination. The deltoid uptake showed a characteristic pattern, which appeared as elongated uptake within the deltoid muscle that follows the muscular striations. Although observed in only 42.9% of patients with positive axillary lymph nodes, the deltoid activity at the site of injection may serve as an additional indication that the ipsilateral axillary lymph node uptake is reactive and potentially caused by recent COVID-19 vaccination.

Recommendations have been provided for performing and interpreting FDG PET/CT after COVID-19 vaccination. For example, McIntosh et al. [29] recommended that FDG PET/CT ideally be deferred 4–6 weeks after COVID-19 vaccination but for at least 2 weeks after vaccination for oncology patients. Becker et al. [31] recommended that nonurgent imaging be postponed for at least 6 weeks after completion of recommended vaccinations. Multiple groups have also recommended collecting details of COVID-19 vaccination at the time of FDG PET/CT to facilitate image interpretation [29, 30]. At our institution, we have a newly initiated process whereby technologists verbally screen patients before PET examination because vaccination history is not always readily available in the patient's chart. The screening questions asked by the technologists include questions about the history of COVID-19 vaccination, date of vaccination (or estimated date of vaccination, if uncertain), whether the patient received a first or second vaccine dose, the laterality of each dose, the vaccine manufacturer (if known), and the severity of vaccine-related symptoms (e.g., body aches or fever) on a scale from 1 to 10. These screening data are entered into the patient's chart and are made available to the interpreting physician. In the present study, we included only those patients with COVID-19 vaccination documented in the medical records at our institution; a greater number of patients potentially

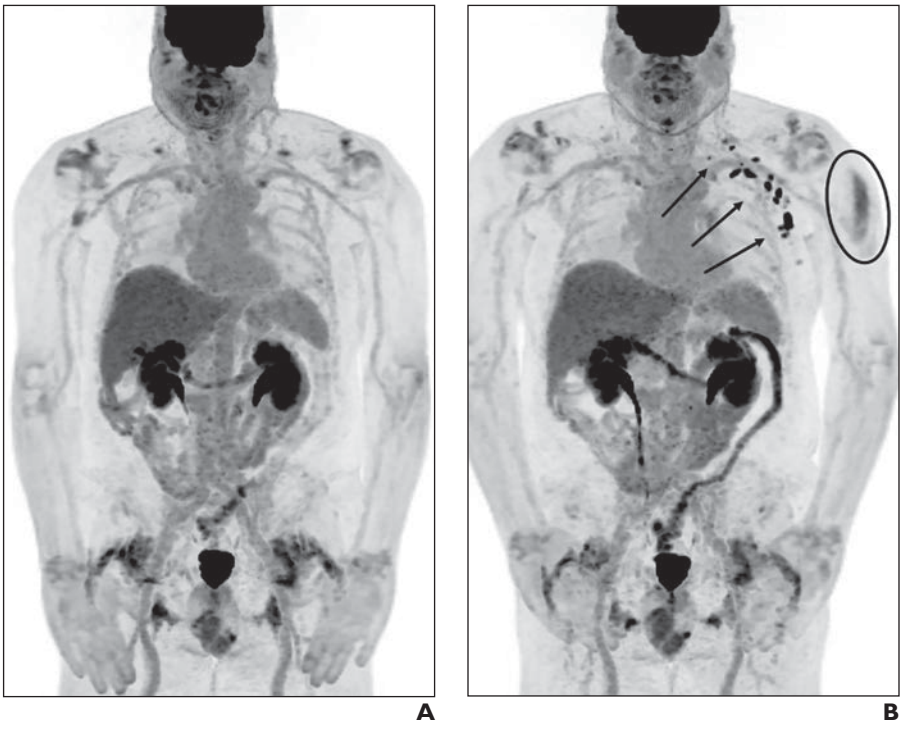

Fig. 5—72-year-old man with metastatic colon cancer who was receiving pembrolizumab immunotherapy. Patient received second dose of SARS-CoV-2 mRNA-1273 vaccine (Moderna) in left deltoid 4 days before undergoing FDG PET/CT.
A, FDG PET/CT image obtained before vaccination shows no hypermetabolic metastatic disease.
B, FDG PET/CT image obtained after vaccination shows multifocal FDG uptake within left axillary and supraclavicular lymph nodes (*arrows*) (SUV_{max} = 9.6) and elongated FDG uptake within lateral head of left deltoid muscle (*oval*) (SUV_{max} = 2.9) with pattern that follows muscular striations.

could have been included had we also included patients who underwent verbal screening for this information.

The decision to proceed with PET after recent COVID-19 vaccination should take into account the evolving knowledge of the confounding pitfalls that such vaccinations can cause on PET, including those described in the present study, as well as patient-specific factors such as cancer type, cancer stage, and the urgency of the clinical decisions to be made on the basis of the PET findings. Given that the frequency of axillary lymph node PET avidity after COVID-19 vaccination was only 10.4% in the present study, PET examinations in our practice are, in general, continuing to proceed as originally scheduled regardless of vaccination status or timeline. Nonetheless, we did not observe any PET-positive axillary lymph nodes at more than 24 days after vaccination. Thus, waiting 3–4 weeks after vaccination before undergoing PET examination for initial oncologic evaluation may also be reasonable, particularly for patients at greater risk of axillary nodal disease.

The primary limitation of the present study is the lack of biopsy results or follow-up PET data for positive lymph nodes to confirm that the observed activity was not malignant and to assess the time needed for resolution of the lymph node uptake. In addition, we included only those patients who received vaccines manufactured by Pfizer-BioNTech and Moderna Therapeutics. Also, our definition of positive lymph nodes (those for which the lymph node SUV_{max} was greater than the blood pool SUV_{max}) is subject to debate; nonetheless, the criterion is reproducible and applicable in clinical practice. Activity in axillary nodes that is mildly greater than that in blood pool is occasionally encountered in patients without recent vaccination and is typically attributed as reactive. Furthermore, our inclusion criterion that required that a PET examination be performed before vaccination and not show visible axillary lymph node uptake could have introduced selection bias, although the criterion was incorporated to support identification of positive nodes that likely were due to vaccination. Finally, the small sample size and small number of positive lymph nodes limit the robustness of some of the study's comparisons among patient subsets.

In conclusion, we observed positive axillary lymph nodes in 7.4% of FDG and 23.1% of ^{11}C-choline PET examinations (10.4% of all PET examinations) performed after COVID-19 vaccination of patients without visible axillary nodal uptake on PET performed before vaccination. One patient showed extraaxillary lymph node uptake (ipsilateral supraclavicular uptake on FDG PET). All examinations that showed positive axillary lymph nodes were performed within 24 days of vaccination. Ipsilateral deltoid uptake with a characteristic appearance was observed in 14.5% of examinations. Recognition of these findings by interpreting physicians, when encountered on PET examinations after COVID-19 examination, may help guide optimal follow-up management and reduce unnecessary biopsies.

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Editorial Comment: Nodal and Deltoid Uptake on FDG and ^{11}C-Choline PET/CT

The authors provide a timely assessment of the frequency of COVID-19 vaccination–related nodal and deltoid muscle uptake on PET/CT. In recent months, increases in the size and FDG activity of axillary, supraclavicular, and cervical lymph nodes on PET/CT have been more frequently reported [1]. These findings may heighten patient anxiety and cause unnecessary workup and potential biopsy for oncologic patients. This study highlights findings that can increase the confidence of the interpreting physician in determining that axillary nodal uptake is likely a postvaccination effect rather than neoplastic. Examples of helpful observations that support a postvaccination effect include the presence of ipsilateral deltoid muscle uptake and a lack of pathologic enlargement of the axillary lymph node. In addition, through inclusion of patients imaged using ^{11}C-choline in this series, the study shows that postvaccination axillary nodal uptake is not purely a phenomenon associated with FDG administration but can be seen with other PET agents.

The single case of ipsilateral supraclavicular nodal uptake that was observed in this series involved a patient who was receiving immunotherapy. This is a tantalizing piece of information. The authors speculate that the heightened immune response of patients who were receiving immunotherapy may contribute to lymphadenopathy. Indeed, the impact of immunotherapy on the effects of vaccination merits future research.

A problematic issue for patients and physicians relates to the optimal timing for conducting PET/CT examination of a recently vaccinated patient. This decision needs to balance clinical needs with minimization of potential false-positive results. Expert recommendations on this topic vary, but delaying PET/CT for 2 to 6 weeks after vaccination has been suggested [1, 2]. Because no significant abnormal axillary nodal uptake was observed in patients beyond 24 days after vaccination, the authors suggest that a time window of 4 weeks is likely adequate. Nonetheless, observation of positive axillary nodal uptake up to 10 weeks after vaccination has been reported [3].

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