COVID-19 Vaccination-Related Uptake on FDG PET/CT: An Emerging Dilemma and Suggestions for Management

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As mass COVID-19 vaccination is underway, radiologists are encountering transient FDG uptake in normal or enlarged axillary, supraclavicular, and cervical lymph nodes after ipsilateral deltoid vaccination. This phenomenon may confound interpretation in patients with cancer undergoing FDG PET/CT. In this article, we present our institutional approach for management of COVID-19 vaccine–related lymphadenopathy on FDG PET/CT according to early experience. We suggest performing PET/CT at least 2 weeks after vaccination in patients with a cancer for which interpretation is anticipated to be potentially impacted by the vaccination but optimally 4–6 weeks after vaccination given increased immunogenicity of mRNA vaccines and potentially longer time for resolution than lymphadenopathy after other vaccines. PET/CT should not be delayed when clinically indicated to be performed sooner. Details regarding vaccination should be collected at the time of PET/CT to facilitate interpretation. Follow-up recommendations for postvaccination lymphadenopathy are provided, considering the lymph node's morphology and likely clinical relevance. Consideration should be given to administering the vaccine in the arm contralateral to a unilateral cancer to avoid confounding FDG uptake on the side of cancer. Our preliminary experience and suggested institutional approach should guide radiologists in management of patients with cancer undergoing PET/CT after COVID-19 vaccination.

The widespread deployment of COVID-19 vaccines has potentially important implications for patients seeking medical care after vaccination. One side effect of the vaccine that has become apparent after its mass distribution is enlargement of axillary, supraclavicular, and cervical lymph nodes on the ipsilateral side of deltoid vaccination [1–3]. The implications of this phenomenon have been described primarily in the context of breast imaging [4]. However, vaccine-induced lymphadenopathy may also create challenges in FDG PET/CT interpretation by confounding disease characterization, staging, and assessment of treatment response. This in turn has implications for the timing of performing FDG PET/CT examinations, as well as radiologists' management recommendations according to PET/CT findings in patients undergoing cancer treatment. Radiologists' awareness of this phenomenon and dissemination of practical recommendations are important to prevent FDG PET/CT misinterpretation.

Background

Transient FDG uptake is recognized to occur in morphologically normal or enlarged axillary, supraclavicular, and cervical lymph nodes after intramuscular vaccination to the ipsilateral deltoid muscle [5–9]. This distribution of lymphadenopathy has been reported with multiple vaccinations, including seasonal influenza; swine-origin influenza A (H1N1); pneumococcal; tetanus, diphtheria, and pertussis (Tdap); human papilloma virus (HPV); bacille Calmette-Guérin; measles; smallpox; anthrax; and, more recently, COVID-19 [5–10].

As of this writing, two COVID-19 vaccines (from Pfizer-BioNTech and Moderna) are FDA approved, both using mRNA biotechnology, and Johnson and Johnson's vaccine using adenovirus biotechnology has applied for emergency use authorization. Data from the CDC on local reactions after the Moderna COVID-19 vaccine show that axillary swelling and tenderness was the second most commonly reported local reaction after pain at the injection site. Among patents 18–64 years old, 11.6% receiving the vaccine reported axillary swelling and tenderness after the first dose compared with 5.0% in the placebo arm,

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and 16.0% after the second dose compared with 4.3% in the placebo arm. This reaction was reported less frequently in patients 65 years old and older, occurring in 8.4% after the second dose in this group compared with 2.5% in the placebo arm [1, 2]. Similarly, lymphadenopathy was reported in 64 patients receiving the Pfizer vaccine compared with six patients in the placebo arm [3]. Both in vitro and clinical data suggest that these two mRNA vaccines are inherently immunostimulatory and therefore more immunogenic compared with other traditional vaccine biotechnologies, potentially accounting for the lymphadenopathy observed on imaging [11]. Further data and clinical information are needed to assess the frequency of lymphadenopathy associated with COVID-19 vaccine biotechnologies.

Imaging Findings

After deltoid vaccination, FDG uptake can be seen in the axillary levels 1, 2, and 3; supraclavicular; and cervical lymph nodes (Fig. 1). The degree of FDG uptake varies with temporal proximity to the vaccination, ranging from intense uptake shortly after administration to barely perceptible after a longer time interval (Figs. 2 and 3). Increased FDG uptake is also observed in the spleen after vaccination, which might aid interpretation if information on recent vaccination is not available to the radiologist [12]. In addition, after vaccination, lymph nodes may show variable morphology on CT but are usually normal or show a mildly thickened cortex with maintained fatty hilum (Fig. 4). However, particularly shortly after vaccine administration, lymph nodes may show abnormal morphology and can appear completely rounded with loss of fatty hila (Fig. 5).

Management

An approach to the performance and interpretation of FDG PET/CT after COVID-19 vaccination should seek to provide accurate interpretations and avoid treatment delays, additional patient anxiety, excessive follow-up imaging studies, and unnecessary biopsies (Table 1). Additional imaging and tissue sampling should be suggested only when necessary.

Considerations

The diagnostic challenge posed by lymphadenopathy after COVID-19 vaccination depends on the PET/CT indication. Particularly prone to interpretive challenges are malignancies and other diseases that predominantly manifest in lymph nodes such as lymphoma or Castleman disease; malignancies that tend to involve axillary, supraclavicular, or cervical lymph nodes such as breast cancer, upper extremity or trunk melanoma or sarcoma, lung cancer (especially upper lobe), and head and neck cancer; and advanced-stage cancers (Fig. 6). Conversely, lymphadenopathy on PET/CT performed for workup of a solitary pulmonary nodule or of localized gastrointestinal, genitourinary, or contralateral malignancy might not require special consideration and be readily attributable to a recent ipsilateral deltoid vaccination (Fig. 7).

HIGHLIGHT

- *COVID-19 vaccination can result in FDG-avid lymphadenopathy and increased splenic uptake on PET/CT; findings that can overlap with certain cancers.*

Careful data collection regarding date and site of prior vaccine administration is important to aid the radiologist in readily identifying COVID-19 vaccination as the likely cause of abnormal nodal FDG uptake. At our institution, we have modified intake questionnaires and interviews by the performing technologist to include this information.

Oncologists play an important role in coordination of both imaging and vaccination and can counsel their patients before vaccination to ensure that deltoid administration occurs on a side that will be least likely to interfere with disease status assessment. Inclusion of information regarding a cancer history and any upcoming imaging examinations in the prevaccination forms might also help to avoid injection on a side that might lead to confusing imaging interpretation.

Baseline imaging—mainly CT or ultrasound (US)—performed before FDG PET/CT can be used for comparison but likely will be most helpful in cases of abnormal nodal morphology on FDG PET/CT. FDG uptake in morphologically normal nonenlarged lymph nodes might still present a diagnostic dilemma despite the comparison imaging.

If a patient has a cancer with laterality such as breast cancer, most melanoma, extremity sarcoma, lung cancer (particularly in the upper lobe), or head and neck cancer, the vaccine should be administered in the contralateral arm to avoid potentially confounding FDG uptake in lymph nodes on the side of the cancer. The CDC [13] currently recommends administration by intramuscular injection into the deltoid muscle; further guidance will be

TABLE 1: Considerations for FDG PET/CT in Setting of COVID-19 Vaccination-Related Lymphadenopathy

Consideration	Comment
Indications prone to confounded PET/CT interpretation	Take note of lymph node–predominant diseases including lymphoma and Castleman disease as well as cancers prone to involvement of lymph nodes also involved by COVID-19 vaccination including breast cancer, trunk or upper extremity melanoma or sarcoma, lung cancer (particularly upper lobe), head and neck cancer
FDG PET/CT intake procedures	Collect information on patient questionnaires on-site including date of prior vaccine administration; technologist should confirm questions are completed
Vaccination	
Timing	For cancers prone to confounded interpretation, perform FDG PET/CT before or at least 2 weeks after, but optimally 4–6 weeks after, vaccine administration if possible; do not delay COVID-19 vaccination or FDG PET/CT examination that is clinically warranted earlier
Laterality	Counsel patients to receive vaccine in contralateral arm if disease has laterality

needed before possible consideration of alternate sites of injection (e.g., gluteal muscles) in patients awaiting imaging.

PET/CT Timing

In light of the importance of vaccination in controlling the pandemic, delay in vaccination is not recommended. Other vaccinations that are not considered urgent (e.g., HPV, pneumococcal, shingles, and Tdap vaccines) may be rescheduled without significant clinical risk. If FDG PET/CT is required in an urgent or timely manner (e.g., for disease staging or treatment initiation), then the examination should not be delayed but rather be performed, if possible, before or whenever needed after vaccination as clinically warranted. If the indication for FDG PET/CT is not urgent (e.g., routine surveillance in a low-risk cancer), particularly if likely to result in confounding findings, then delaying or rescheduling the FDG PET/CT may be preferred. According to previous experience with routine vaccinations, vaccine-related nodal FDG uptake typically occurs within 7 days of vaccination and generally subsides by 12–14 days [5, 7, 9] (Fig. 1). However, we have observed vaccine-related lymphadenopathy on PET/CT as long as 4–6 weeks after administration (Fig. 8). In the absence of established practice guidelines, we suggest performing FDG PET/CT at least 2 weeks after COVID-19 vaccination in patients with a cancer that is anticipated to be challenging to interpret after vaccination, recognizing that this will not be practical in all cases and should not drive delays in either vaccination (particularly COVID-19 vaccination) or in oncologic imaging for which there is clinical indication to perform sooner. The mRNA biotechnology vaccines may prove to have more potent and possibly longer manifestations on FDG PET/CT than other vaccines given their previously noted increased immunogenicity, and an even longer time interval might be preferable. In fact, although we suggest PET/CT be performed at least 2 weeks after vaccination, our opinion is that if FDG PET/CT is not urgent and able to be reasonably rescheduled, the ideal spacing of imaging after vaccination is 4–6 weeks to avoid potential confounding findings. More experience and research are needed to establish a concrete timeline, and the timeline will need to be revisited as additional COVID-19 vaccines that use other biotechnologies are distributed.

PET/CT Assessment and Further Management

Figure 9 shows the approach applied at University of Massachusetts Medical School/Memorial Health Care according to experience with routine vaccinations, preliminary experience with COVID-19 vaccination, and initial publications addressing this topic [4, 14, 15]. At this stage in mass vaccination, we have not yet had the opportunity to apply our suggested approach to a large number of patients. Nonetheless, it is important to have an institutional management strategy in place given the anticipated increasing frequency of confounding cases with a growing population of vaccinated patients.

If nodal FDG uptake is seen to be inherently unlikely to represent disease involvement or metastatic disease (see Considerations section), then clinical judgment can be used to attribute the findings to vaccination, and no further follow-up is needed. If nodal FDG uptake is felt to be indeterminate (i.e., could possibly represent malignancy or metastatic disease) or confounding (e.g., vaccine administered on the side of a breast, trunk, or upper extremity cancer or known prior axillary metastases), then management depends on whether the finding is clinically irrelevant or clinically relevant. If clinically irrelevant (i.e., will not change disease stage or drive disease response assessment), then no further imaging is recommended, and attention is given on follow-up. If clinically relevant (i.e., would change disease stage or drive disease response assessment), then management depends on node morphology. If morphologically abnormal, then a US or CT in 2–6 weeks is considered to assess for resolution, and US-guided sampling is suggested if the abnormal nodes persist at that time. This proposed 2–6 week timeline is a result of experience with routine vaccinations for which most abnormal FDG PET/CT findings resolve by 12–14 days [5, 7, 9]. If findings are morphologically normal, then repeat FDG PET/CT in 2–6 weeks is considered to evaluate for resolution, and the timing of potential subsequent vaccine doses is also considered. If the lymph nodes remain abnormal on follow-up PET/CT, then it may be attributed to disease at that time. For clinically relevant morphologically normal lymph nodes, US-guided sampling may also be considered at the time of initial or follow-up PET/CT as clinically indicated. If vaccination is prospectively expected to interfere with FDG PET/CT results and FDG PET/CT cannot be rescheduled or delayed, a baseline unilateral axillary US could be performed before vaccination, as clinically indicated. This baseline axillary US could help serve as a comparison if lymph nodes appear abnormal on the subsequent FDG PET/CT. However, it may not help if lymph nodes show uptake but remain morphologically normal.

Implications

Until recently, FDG-avid vaccine-associated lymphadenopathy and splenic uptake was an occasional observation on PET/CT, usually in the setting of seasonal flu vaccination. However, this phenomenon is becoming increasingly prevalent in the midst of mass COVID-19 vaccination. Radiologists must be aware of this issue and have an organized strategy for its management. We offer our preliminary experience and suggested institutional approach for patients with cancer undergoing FDG PET/CT after COVID-19 vaccination.

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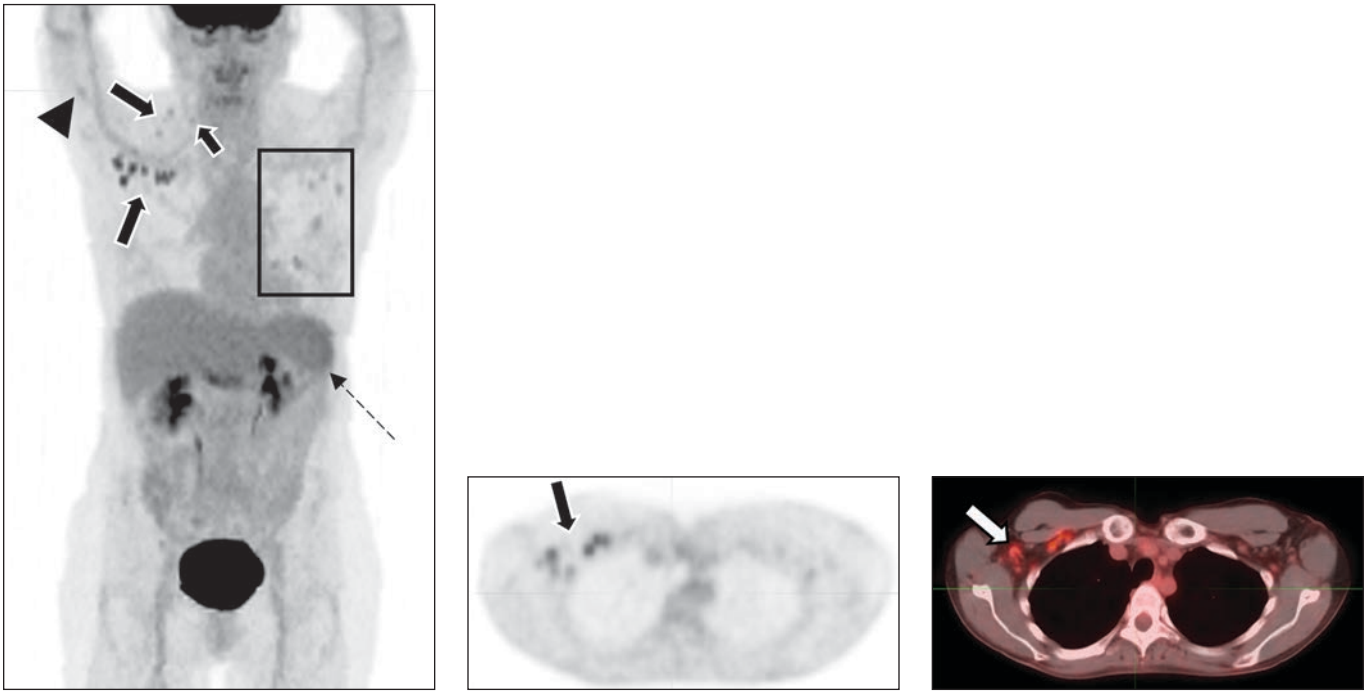
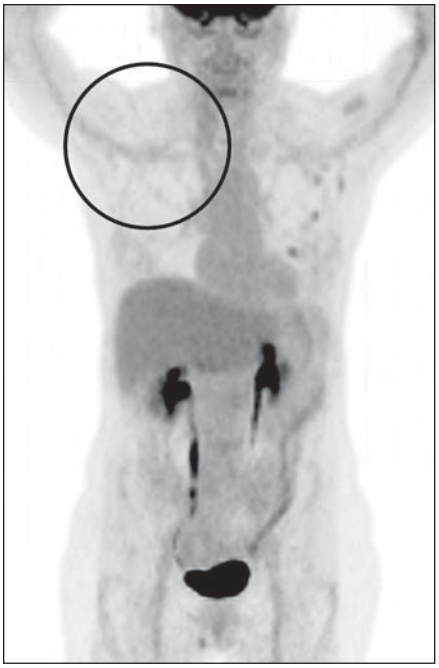


Fig. 1—57-year-old woman with history of breast cancer.
A–C, Maximum intensity projection (MIP) (**A**), axial attenuation correction CT (**B**), and fusion (**C**) images from FDG PET/CT acquired 2 days after influenza vaccination show intense FDG uptake in right axillary 1, 2, and 3; supraclavicular; and lower cervical lymph nodes (*black arrows*, **A** and **B**). Some lymph nodes show minimal cortical thickening (*white arrow*, **C**). Injection site in right deltoid is faintly seen on MIP image (*arrowhead*, **A**). Vaccine-related FDG uptake was much higher than in patient's left-sided breast cancer with local nodal involvement (*rectangle*, **A**). FDG uptake is mildly increased in spleen (*dashed arrow*, **A**), which can be seen after vaccination.

(Fig. 1 continues on next page)



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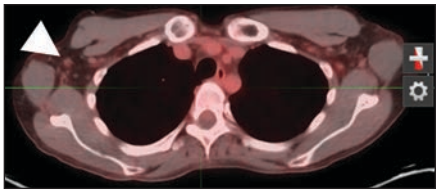
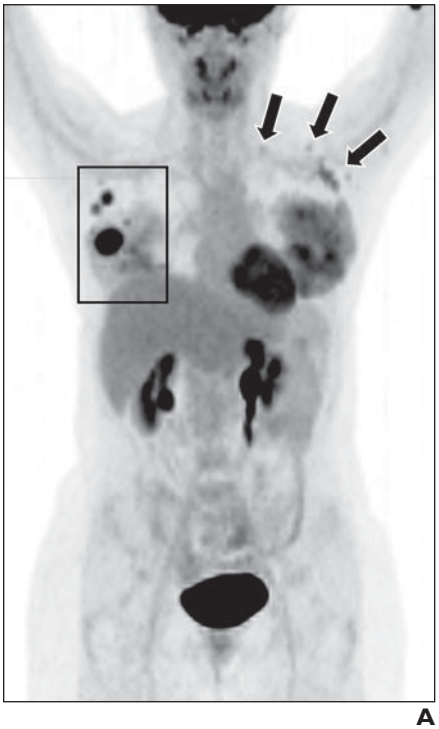


F

Fig. 1 (continued)— 57-year-old woman with history of breast cancer.
D–F, MIP (**D**), axial attenuation correction CT (**E**), and fusion (**F**) images from follow-up FDG PET/CT performed 11 days after first FDG PET/CT show complete resolution of vaccine-related FDG uptake (*circles*, **D** and **E**) and normalization of nodal morphology (*arrowhead*, **F**). Left breast cancer findings are persistent.



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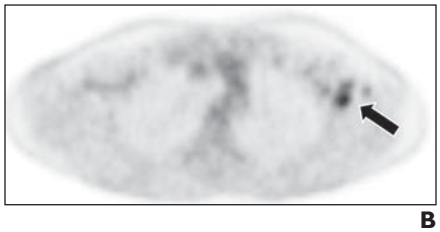

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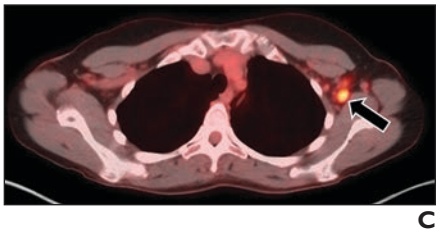
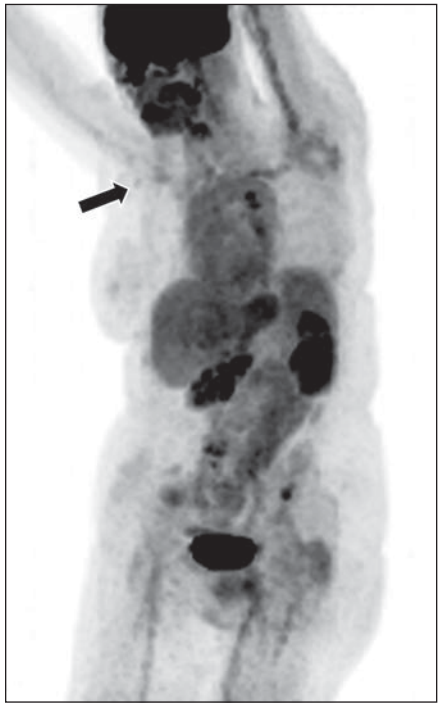


C

Fig. 2—40-year-old woman with right breast cancer 3 days after Moderna COVID-19 vaccination.
A–C, Maximum intensity projection (**A**), axial attenuation correction CT (**B**), and fusion (**C**) images from FDG PET/CT obtained 2 days after left deltoid vaccination show moderately FDG-avid left axillary levels 1, 2, and 3; supraclavicular; and lower cervical lymph nodes (*arrows*). Vaccine-related FDG uptake was lower than in patient's right-sided breast cancer with local nodal involvement (*rectangle*, **A**). In this case, FDG uptake can be attributed to vaccination because of very recent administration and distribution and pattern of uptake on contralateral side. This patient was currently breastfeeding, accounting for uptake in lactating fibroglandular tissues.



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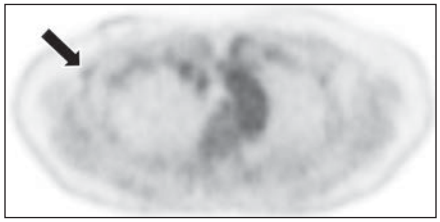

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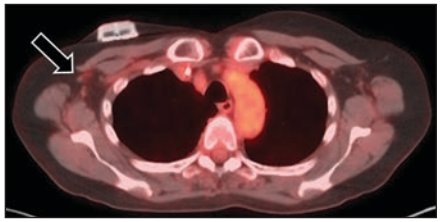
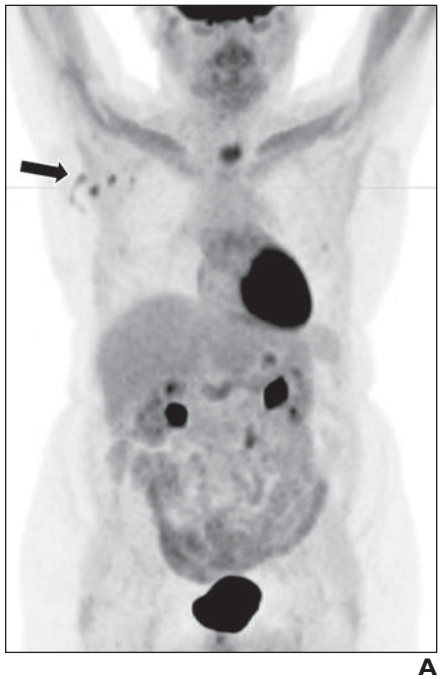


C

Fig. 3—72-year-old woman with breast cancer 11 days after first dose of right deltoid Pfizer-BioNTech COVID-19 vaccination.
A–C, Maximum intensity projection (MIP) (**A**), axial attenuation correction CT (**B**), and fusion (**C**) images on FDG PET/CT show barely perceptible FDG uptake within morphologically normal-appearing right axillary lymph nodes (*arrows*). Careful windowing is necessary to see findings on rotated MIP (**A**). Patient reported transient arm soreness after vaccine that had since resolved.



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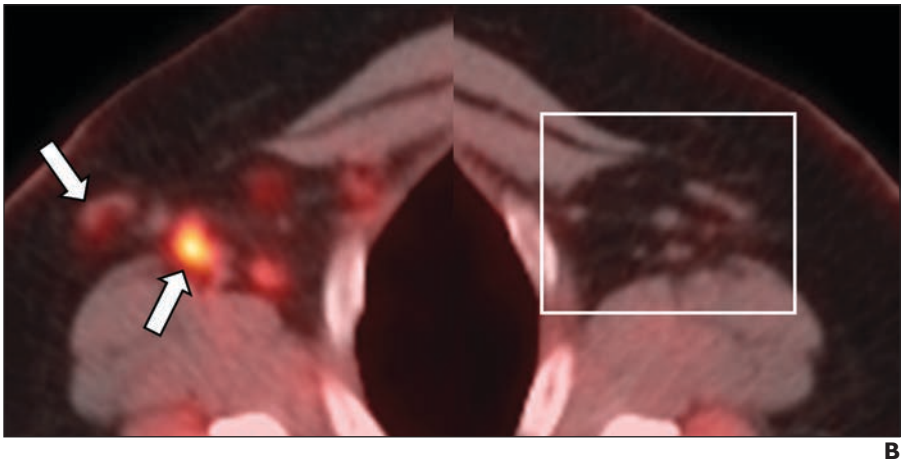

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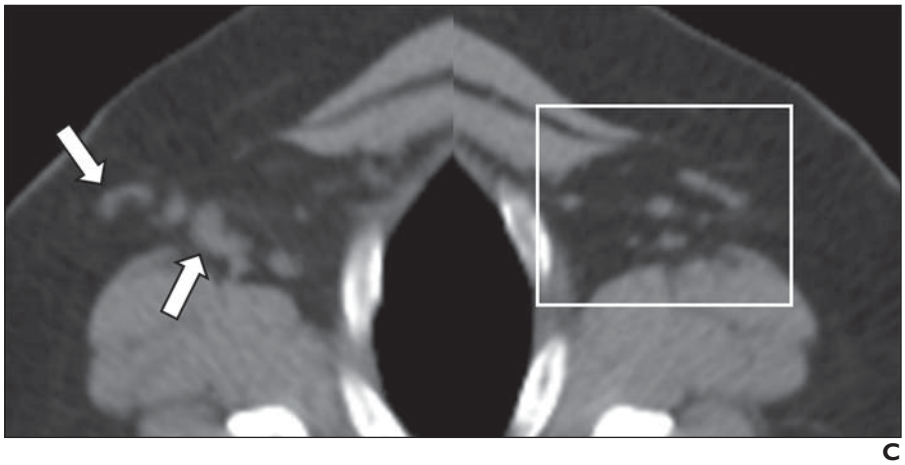

C

Fig. 4—72-year-old woman undergoing workup for solitary pulmonary nodule 4 days after second dose of COVID-19 vaccine (brand not specified).
A–C, Maximum intensity projection (MIP) image (**A**) and magnified fusion (**B**) and CT (**C**) images from FDG PET/CT show moderate-to-intense FDG uptake (*arrow*, **A**) within mildly prominent right axillary levels 1 and 2 lymph nodes that morphologically show mild cortical thickening but maintenance of fatty hila (*arrows*, **B** and **C**) compared with normal left axillary lymph nodes (*rectangles*, **B** and **C**).

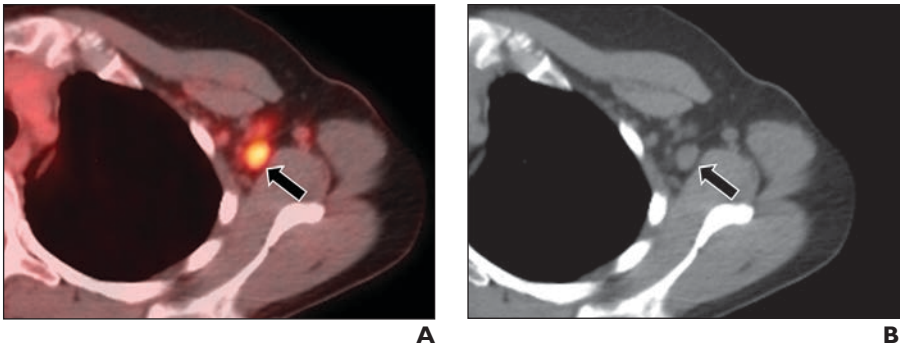

Fig. 5—40-year-old woman 3 days after Moderna COVID-19 vaccination.
A and **B,** Axial attenuation correction CT (**A**) and fusion (**B**) images from FDG PET/CT show rounded morphology with loss of fatty hilum in mildly enlarged FDG-avid left axillary lymph node (*arrows*).

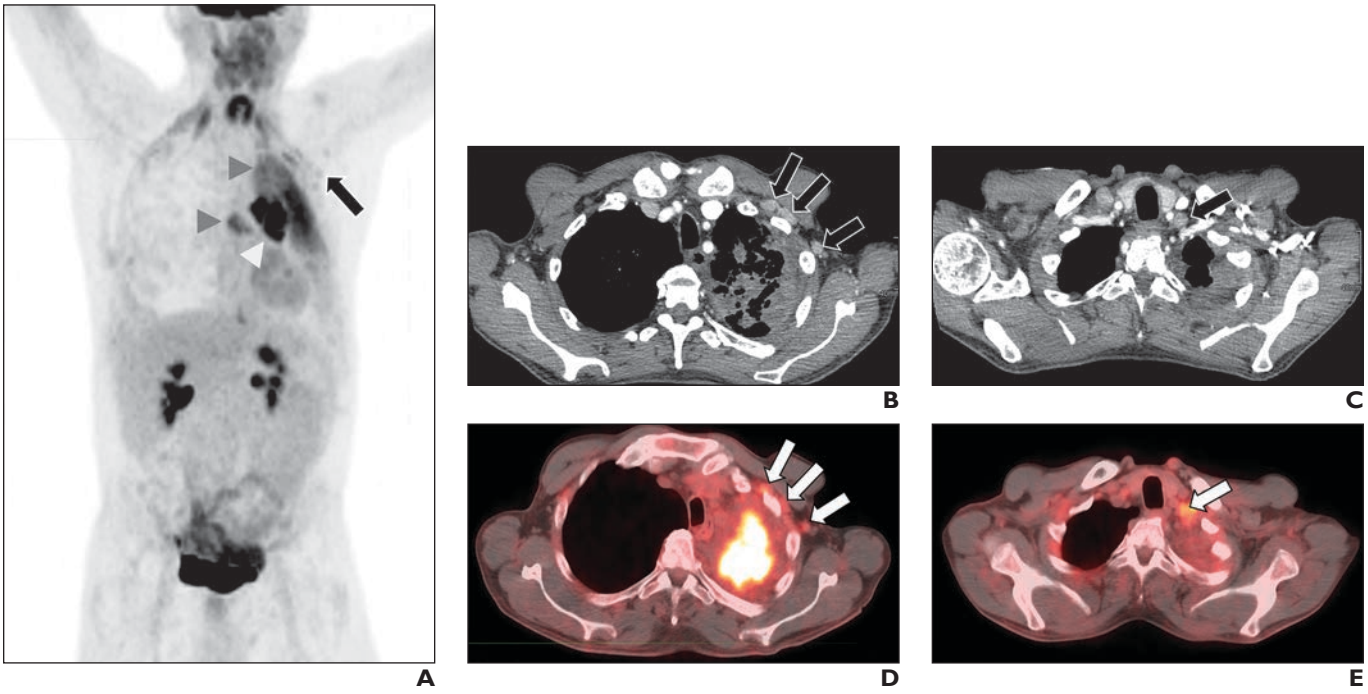

Fig. 6—59-year-old man with newly diagnosed lung cancer 2 weeks after COVID-19 vaccination (brand not specified).
A–E, Maximum intensity projection image (**A**), axial contrast-enhanced CT images of axillary levels 1 and 2 (**B**) and supraclavicular (**C**) lymph nodes, and fusion images of axillary levels 1 and 2 (**D**) and supraclavicular (**E**) lymph nodes from FDG PET/CT show enhancing FDG-avid left axillary levels 1 and 2 (*arrows*, **B** and **D**) and supraclavicular lymphadenopathy (*arrows*, **C** and **E**). Lower cervical levels were also FDG avid (not shown). Although findings in axillary nodes are likely related to vaccination, lower cervical and supraclavicular lymphadenopathies are indeterminate in this patient with left upper lobe squamous cell carcinoma (*white arrowhead*, **A**) and ascending nodal involvement (*gray arrowheads*, **A**).

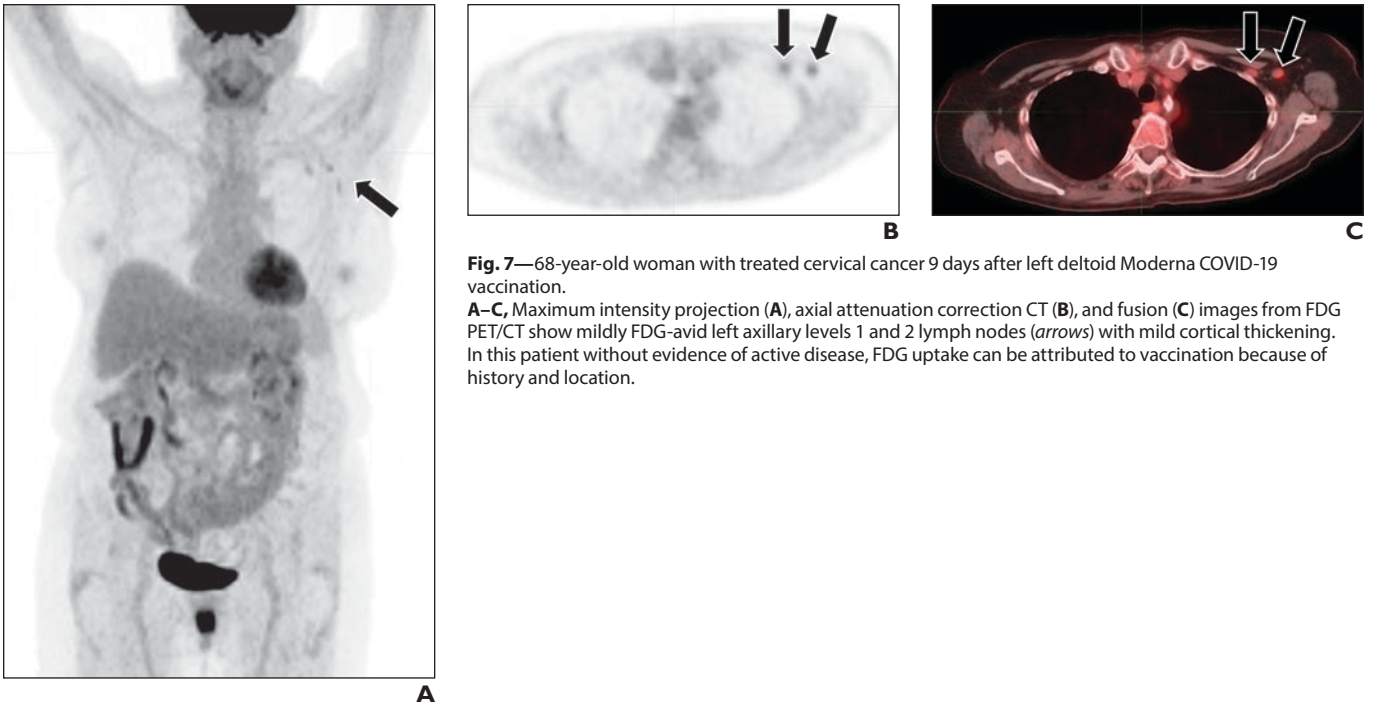

Fig. 7—68-year-old woman with treated cervical cancer 9 days after left deltoid Moderna COVID-19 vaccination.
A–C, Maximum intensity projection (**A**), axial attenuation correction CT (**B**), and fusion (**C**) images from FDG PET/CT show mildly FDG-avid left axillary levels 1 and 2 lymph nodes (*arrows*) with mild cortical thickening. In this patient without evidence of active disease, FDG uptake can be attributed to vaccination because of history and location.

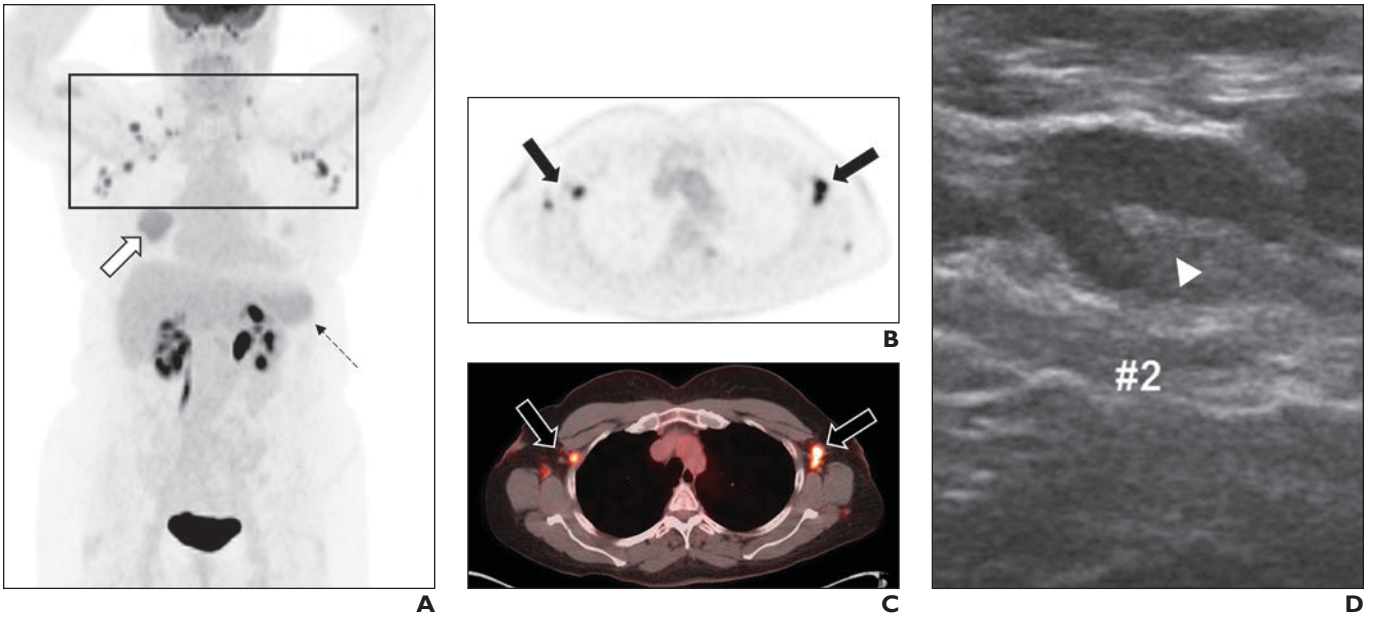

Fig. 8—61-year-old woman with history of breast cancer 4 weeks after right pneumococcal and left influenza deltoid vaccinations.
A–C, Maximum intensity projection (**A**), axial attenuation correction CT (**B**), and fusion (**C**) images from FDG PET/CT show intense FDG uptake in bilateral axillary levels 1, 2, and 3 supraclavicular and lower and mid cervical lymph nodes (*rectangle*, **A**, and *arrows*, **B** and **C**). Mildly increased FDG uptake is seen in spleen (*dashed arrow*, **A**), which can be seen after vaccination. Left-sided findings were attributable to prior vaccination, although significant FDG uptake is atypical beyond 12–14 day interval. Right-sided findings are difficult to interpret in setting of newly diagnosed right breast cancer (*solid arrow*, **A**), and their positivity would change disease staging and treatment.
D, Ultrasound of right axillary lymph node shows mild cortical thickening and preserved fatty hilum (*arrowhead*). This lymph node underwent ultrasound-guided fine-needle aspiration and was negative for malignancy. At surgery, two sentinel lymph nodes were both negative for carcinoma. #2 indicates second lymph node identified on ultrasound.

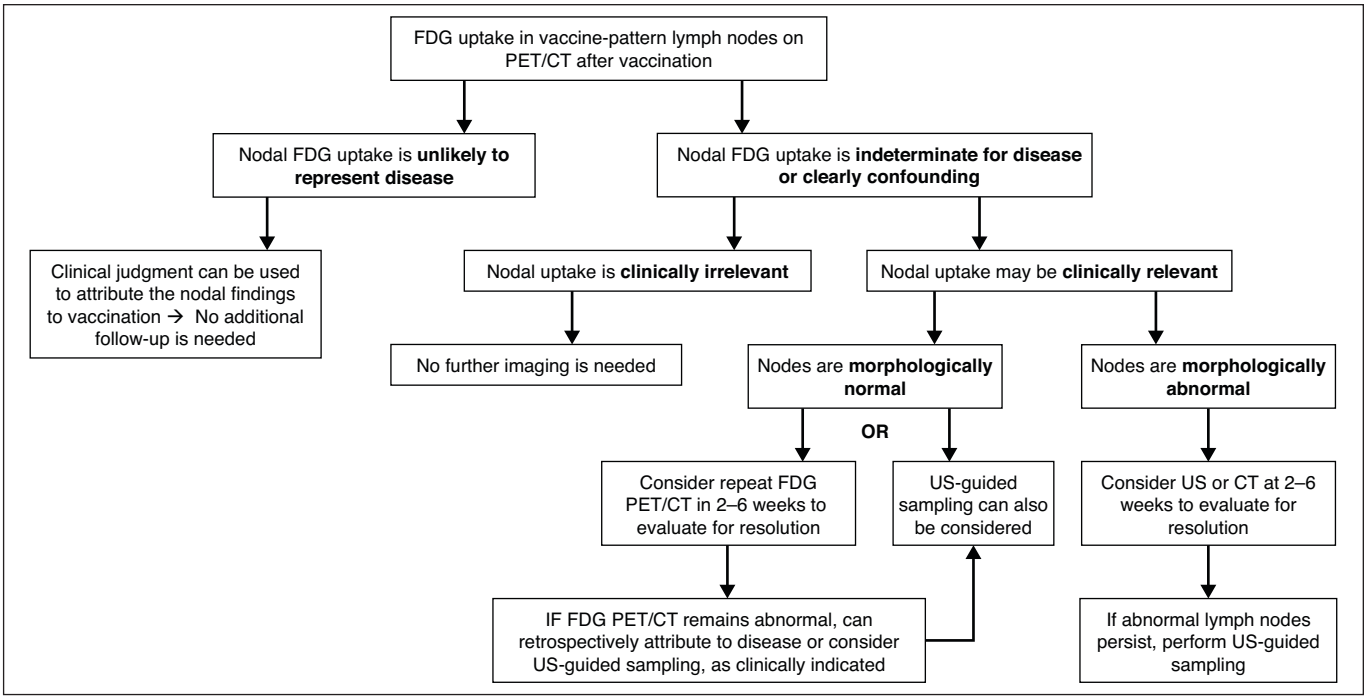

Fig. 9—Flow chart of institutional management strategy. US = ultrasound.

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