

**Covid-19 mRNA Vaccination: Age and Immune Status and its Association with
Axillary Lymph Node PET/CT Uptake**

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The authors declare no conflict of interest related to this study.

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ABSTRACT

With hundreds of millions of coronavirus disease 2019 (COVID-19) mRNA-based vaccine doses planned to be delivered worldwide in the upcoming months, it is important to recognize positron emission tomography with computed tomography (PET/CT) findings in recently vaccinated immunocompetent or immunocompromised patients. We aimed to assess PET/CT uptake in the deltoid muscle and axillary lymph nodes of patients that received a COVID-19 mRNA-based vaccine, and to evaluate its association with patients' age and immune status.

Methods: All consecutive adult subjects undergoing PET/CT scans with any radiotracer at our center during the first month of a national COVID-19 vaccination rollout (between 23 December 2020 and January 27, 2021) were included. Data regarding clinical status, laterality and time interval from recent COVID-19 mRNA vaccination was prospectively collected and retrospectively analyzed, and correlated with deltoid muscle and axillary lymph nodes uptake.

Results: Of 426 eligible, recently vaccinated, subjects (median age, 67 ± 12 years; 49% female), 377 (88%) underwent PET/CT with F-18-fluorodeoxyglucose (FDG) and positive axillary lymph node uptake was seen in 45% of them. Multivariate logistic regression analysis revealed a strong inverse association between positive FDG uptake in ipsilateral lymph nodes and patients' age (Odds Ratio [OR]=0.57, 95% CI, 0.45-0.72; $p < .001$), immunosuppressive treatment (OR=0.37, 95% CI, 0.20-0.64; $p = 0.003$) and presence of hematological disease (OR=0.44, 95% CI, 0.24-0.8; $p = 0.021$). No such association was

found for deltoid muscle uptake. The number of days from the last vaccination and the number of vaccination doses were also significantly associated with increased odds of positive lymph nodes uptake.

Conclusion: Following mRNA-based COVID-19 vaccination, a high proportion of patients showed ipsilateral lymph node axillary uptake, which was more common in immunocompetent patients. This information will help recognize PET/CT pitfalls and may hint about the patient's immune response to the vaccine.

Keywords: COVID-19, mRNA vaccine, PET/CT, axillary lymphadenopathy, immunogenicity

INTRODUCTION

The emergence of pneumonia cases caused by the novel SARS-CoV-2 virus in December 2019 (1) and the subsequent coronavirus disease 2019 (COVID-19) pandemic have led to initiatives for developing an effective vaccine from as early as January 2020. To date more than 230 vaccine candidates have been developed (2), many of them employing new and innovative vaccine development technologies, most of them never commercially used in humans before (3).

The first vaccines to be approved by the US Food and Drugs Administration in December 2020 were based on a mRNA sequence encoding segments of the spike protein of the SARS-CoV-2 virus and encapsulated in lipid nanoparticles (4,5).

To date, there are no published data regarding the efficacy of mRNA vaccines in immunocompromised populations, and both the US Centers for Disease Control and Prevention and the US Food and Drugs Administration state that immunocompromised persons receiving mRNA vaccines may have a diminished immune response (4,5,6).

As the global COVID-19 vaccination endeavor is in its early days, there are no published data regarding the prevalence of post-mRNA vaccination positron emission tomography with computed tomography (PET/CT) findings, especially in oncologic patients, both immunocompetent and immunocompromised. The most common findings described in patients who underwent PET/CT after receiving vaccines against influenza or papillomavirus were ipsilateral lymphadenopathy with varying degrees of uptake (7-15).

In this study, we aimed to describe the PET/CT findings in patients post mRNA-based COVID-19 vaccination and to identify patient's characteristics associated with PET/CT uptake.

METHODS

Study Design and Setting

We conducted a retrospective analysis of prospectively collected data. The study has been approved by the institutional ethics committee. The need for patient informed consent was waived.

Patients

All consecutive adult patients (>18 years) referred for a PET/CT scan (with the use of any radiotracer) for any indication between 23 December 2020 (the initiation date of a national COVID-19 vaccination rollout in the general population) and January 27, 2021 were included in the study. Patients were excluded if they had incomplete medical records or a known malignancy involving axillary lymph nodes.

Data Collection

Before entering the PET/CT unit all patients were asked to fill a standard clinical intake form, which included: age, gender, indication for PET/CT, clinical and oncological status, current oncologic treatment, recent surgical procedures (including localization of the procedure), date of COVID-19 vaccination and arm in which the vaccine was administered on the first and second doses (if applicable).

Immunosuppressive status was assigned to patients with a known hematological diseases (any type of lymphoma, leukemia or multiple myeloma) or treated with one of the following drugs, considered to result in immunosuppression: current corticosteroid therapy, chemotherapy within the last 3 months, treatment with rituximab or daratumumab in the last 6 months, or bone marrow transplantation within the last 6 months (16).

PET/CT Acquisition and Analysis

All PET/CT scans were performed according to our institute's clinical scanning protocols. Diagnostic CT examination was performed on a 64 detector rows helical CT scanner (Philips Vereos, Philips Medical Systems, Cleveland, OH, USA). Field of view and pixel size of the PET images reconstructed for fusion were 57.6 cm and 4 mm, respectively, with a matrix size of 144 X144. The technical parameters used for CT imaging were: pitch 0.83, gantry rotation speed 0.5 s/rot, 120 kVp, modulated tube current 40–300 mA, and specific breath-holding instructions. After 2-6 hours of fasting, patients received an intravenous injection of 5.18 MBq/kg F-18-fluorodeoxyglucose (FDG) or F-18-fluorodopa (DOPA), 3.7 MBq/kg for F-18- prostate specific membrane antigen (PSMA) or 185-296 MBq for Ga-68- PSMA and Ga-68- DOTATATE. About 60 min after tracer administration, CT images were obtained from the vertex to the mid-thigh or for the whole body. An emission PET scan followed in 3D acquisition mode for the same longitudinal coverage, 1.5 min per bed position. CT images were fused with the PET data and used to generate a map for attenuation correction, eventually generating reconstructed images for review on a computer workstation.

Image analysis was carried out using the picture archive and communication system (Carestream Vue PACS version 12.1.5.1, Rochester, NY, USA). Consensus reading of all PET/CTs was performed by a physician with dual-board certification in radiology and nuclear medicine with 6 years of PET/CT reading experience (YE), 2 board-certified radiologists in nuclear medicine residency with 3-year experience in reading PET/CTs (ME and NC) and a nuclear medicine resident with 1-year experience (YA).

Deltoid and axillary lymph node radiotracer maximal standardized uptake values (SUVmax), normalized for body weight, were measured by placing a region of interest in the site of deltoid muscle injection and draining axillary lymph nodes (defined as ipsilateral side) with the highest uptake, as well as in the contralateral deltoid and axillary lymph nodes, which were used for reference.

As SUVmax values depend on tracer used and on variable technical aspects, positive deltoid and axillary lymph node uptake were defined as having a ratio ≥ 1.5 between SUVmax in the ipsilateral and contralateral reference sites, a method previously used by Thomassen et al (8).

Statistical Analysis

Logistic regression models were fit with the binary dependent variable: positive deltoid or axillary lymph node uptake (yes/no) and with the following independent variables: scaled age, sex, immunosuppressive treatment (yes/no), hematologic disease (yes/no), scaled days since last vaccine dose, whether a second vaccine dose was administered (yes/no), and the interaction between the last two independent variables. The Hosmer–Lemeshow test (17) with 8 groups (representing the number of covariates plus

one) was used for assessing the goodness of fit of each model. Benjamini and Hochberg's false discovery rate (FDR) method (18) was used for multiple testing adjustment, jointly, for the two models, at the level of 0.05. All statistical analyses were conducted in R environment (19). Due to small number of non-FDG scans, only FDG scans were included in the statistical analysis.

RESULTS

Of 1002 consecutive adult patients scanned during the study period, 44% (443/1002) received at least one vaccine dose before the scan. Of those vaccinated, 23% (103/443) received the second vaccine dose. After excluding patients with incomplete medical records or with a known malignancy involving axillary lymph nodes, the final vaccinated study cohort comprised 426 patients with a mean age of 67 years (standard deviation [SD], 12), each with a single PET/CT scan (Figure 1). Patient demographics are shown in Table 1. Most patients (377/426, 88%) underwent FDG scans. F-18-PSMA and Ga-68-PSMA scans were performed in 37 patients (9%), Ga-68-DOTATATE in 11 patients (2.5%) and an F-18-DOPA scan was performed in one patient (0.5%). Among those that underwent FDG-PET/CT, 20% (76/377) received a second vaccine dose, 62% (232/377) were immunocompetent, and 38% (145/377) were immunocompromised. Among the immunocompromised patients, 52% (75/145) had a hematological malignancy and 56% (82/145) received immunosuppressive therapy. There was an overlap between these two groups, as 12 hematological patients also received immunosuppressive treatment.

The time between the first vaccine dose and the PET/CT scan ranged between 1 and 34 days (median 13 days). The median time between the last vaccination dose and

PET/CT scan was 11 days ($SD \pm 6.4$) for patients that received only one vaccine dose and 4 days ($SD \pm 3.8$) for patients that received a second vaccine dose. Although the overall time frame between vaccination and imaging was large (1-34 days), the distribution was similar between the immunocompromised and the immunocompetent groups (Interquartile range: 6-21, 6-20, respectively).

While positive FDG and DOTATATE axillary lymph node uptake was noted in about half of the patients; F-18-PSMA, Ga-68-PSMA and F-18-DOPA uptake was far less common (Table 2, Figure 2, and Figure 3). Mean FDG SUV max values in patients with positive uptake (ipsilateral uptake ≥ 1.5 of contralateral uptake) were 2 ± 0.8 (range 0.6-4.6) and, 2.7 ± 1.6 (range 0.6-12.4) in the deltoid and axillary lymph nodes, respectively.

A little over half of immunocompetent patients (122/232, 53%) and a third of immunocompromised patients (48/145, 33%) showed FDG axillary lymph node uptake. More specifically, FDG axillary lymph node uptake was observed in 30% (25/82) of patients treated with immunosuppressive treatment and 32% (24/75) of patients with a hematological disease.

The multivariate logistic regression analysis of SUV uptake in the deltoid and the lymph nodes following Covid-19 vaccination is summarized in Tables 3. There was a strong inverse association between positive FDG uptake in ipsilateral lymph nodes and patient age (odds ratio [OR]=0.57, 95% confidence interval [CI], 0.45-0.72; $p < 0.001$), immunosuppressive treatment (OR=0.37, 95% CI, 0.20-0.64; $p = 0.003$) and presence of hematological disease (OR=0.44, 95% CI, 0.24-0.8; $p = 0.021$). In addition, the number of days from the last vaccine dose and the number of vaccine doses were significantly

associated with increased odds of positive lymph node uptake (OR=1.53, 95% CI, 1.18-1.99; p=0.005 and OR=7.53, 95% CI, 2.91-23.50; p=0.001, respectively). No association was found between positive deltoid muscle uptake and patient age (OR=0.86, 95% CI, 0.66-1.12; p=0.32) immunosuppressive treatment (OR=0.63, 95% CI, 0.31-1.23; p=0.277) or hematological disease (OR=0.72, 95% CI, 0.34-1.42; p=0.411). The number of vaccine doses was also associated with increased odds for positive deltoid uptake (OR=2.85, 95%CI, 1.13-6.70; p=0.040), while the interaction between the number of vaccine doses and the number of days from the last vaccination was associated with decreased odds of positive deltoid muscle uptake (OR=0.28, 95%CI, 0.09-0.75; p=0.036).

A single patient presenting for staging of left breast cancer after two doses of vaccination (first dose in left arm and second dose on the right arm) had FDG avid lymphadenopathy in the left axilla, but a further biopsy negated lymph node involvement (Figure 4).

DISCUSSION

With the global vaccination effort against COVID-19 underway, data on the safety and the efficacy of the newly approved vaccines is accumulating (20). In the current study we were able to show that 45% of patients demonstrate avid ipsilateral axillary lymphadenopathy on FDG PET/CT in the weeks following vaccination with the novel mRNA-based COVID-19 vaccine, a finding significantly less common in immunocompromised patients. During Pfizer's phase 3 vaccine approval trial, only 0.3% of vaccinated participants were diagnosed with ipsilateral lymphadenopathy (4), suggesting that the vast majority of lymph node uptake occurs in sub-clinical lymphadenopathy.

In our patient population, we encountered 426 newly mRNA-based COVID-19 vaccinated patients undergoing PET/CT scans over a short time period of 5 weeks (44% of all patients scanned). It soon became apparent that many of those scans showed avid uptake in ipsilateral deltoid muscle and axillary lymph nodes, which were not related to the underlying disease (21).

Previous studies have explored the association between aging and immune status to vaccine-induced protection. Such studies showed impaired primary and secondary antibody responses to vaccination in the elderly (22), low vaccine-induced protection against influenza A (H1N1) in patients receiving anti-CD20 treatment with rituximab (23) as well as weaker antibody response to influenza virus vaccine in patients receiving cancer chemotherapy (24). A previous study failed to show an association between FDG axillary lymph node uptake and chemotherapy treatment in patients vaccinated against influenza virus (8). In our study, we were able to show that in the weeks after injection of the novel mRNA-based vaccination; there was avid ipsilateral axillary lymphadenopathy on FDG PET/CT in 53% of immunocompetent patients, a finding that was less common in immunocompromised patients (33%). Furthermore, we found a strong inverse association between axillary lymph node uptake, patient age and immune status as well as a strong association between the number of administered vaccine doses (the odds of positive lymph node uptake was higher in patients receiving 2 vaccine doses) and time interval from last vaccine (the longer the time interval the higher the odds of positive lymph node uptake). Conversely, no association was found between deltoid uptake and age or immune status. Deltoid uptake was only associated with the time interval from the second vaccine dose and the number of administered vaccine doses (taking into account

that median time between the PET/CT scan and the second vaccine dose was shorter (4 days) than median time from the first vaccine dose (11 days). These associations imply that the high metabolic activity in the lymph nodes might be a marker of vaccine-induced immune system activation, increasing over time and after the second vaccine dose, while metabolic activity in the deltoid muscle is inflammatory in nature, and likely secondary to local trauma by the injection itself. Causal association between axillary lymph node uptake and immunogenicity elicited by vaccination should be further explored.

Our study has a few limitations. First, all patients were vaccinated with the Pfizer-BioNTech COVID-19 vaccine. It is yet unknown whether similar PET/CT findings would be observed following administration of other manufacturer's mRNA vaccines, and whether other vaccine platforms (e.g. viral vectors) would elicit similar uptake on PET/CT. Second, the method used to define patients as immunocompetent versus immunocompromised may have resulted in misclassification of some patients, as we did not account for some conditions requiring immunosuppressive therapy, such as post-transplant or rheumatological diseases; however, we assume their relative proportion in the study cohort was low. Third, as most of the patients underwent FDG PET/CT, the small number of patients undergoing imaging with other tracers (DOTATATE, PSMA and DOPA) were not included in the statistical regression model, and more data is required to assess these tracers. Last, the study was conducted during a short period (37 days), and we did not have a repeat scan of the same patients. Although our data show that FDG uptake may be observed long after the first vaccine dose (up to 34 days), we have no data concerning its trend and change over longer periods of time. This data could be collected in future studies.

Elderly and high-risk patients are more prone to develop malignancies. As many countries choose to vaccinate these populations first, and as hundreds of millions of COVID-19 vaccine doses are planned to be administered by the summer of 2021 (25), the PET/CT findings we describe here will likely be seen more often. Recognition of reactive axillary lymph node uptake as an indication for prior mRNA vaccination will obviate unnecessary oncological patient work-up.

CONCLUSION

In about half of the patients receiving the novel mRNA-based COVID-19 vaccine, PET/CT showed avid ipsilateral lymphadenopathy, which was significantly less common in immunocompromised and elderly patients. These findings suggest that FDG PET/CT may hint on the patient's immune response to the vaccine. In addition, these findings will help inform nuclear medicine physicians regarding COVID-19 vaccine related PET/CT potential pitfalls, possibly requiring a dedicated intake form, addressing recent COVID-19 vaccinations. Lastly, these findings may help oncologic physicians in deciding the proper workup, such as recommending that breast cancer patients be vaccinated on their healthy side in order to avoid unnecessary biopsies.

DISCLOSURE

Nothing to disclose.

KEY POINTS

Question:

What is the prevalence of PET/CT findings after COVID-19 mRNA vaccination, and are they associated with patient's immune status?

Pertinent findings:

In this cross sectional study of 426 patients after COVID-19 mRNA vaccination, of 377 patients undergoing FDG PET/CT, increased axillary lymph node uptake was found in 45%, and was significantly inversely associated with age and immunosuppressive status.

Implications for patient care:

Axillary lymph node FDG uptake ipsilateral to mRNA COVID 19 injection site may hint to the patient's immune response to the vaccine.

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FIGURE LEGENDS

FIGURE 1. Patient flow chart

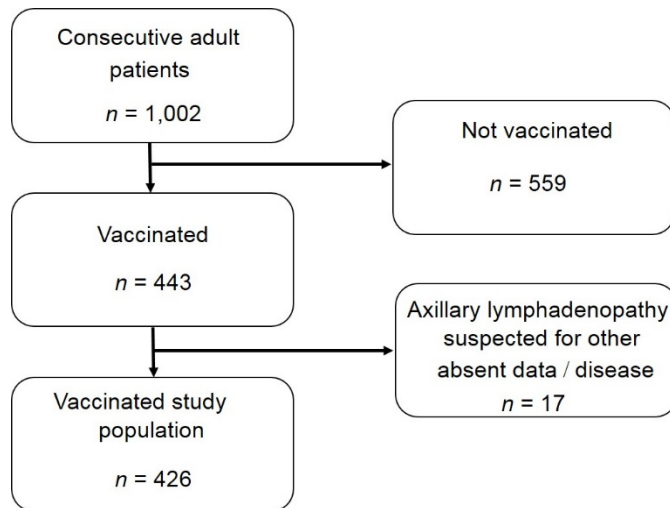


FIGURE 2. FDG PET/CT after COVID-19 vaccination

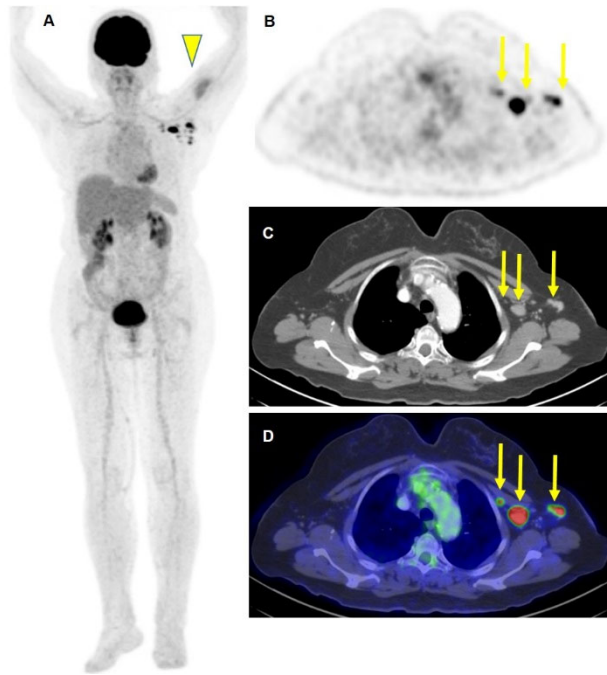


Figure 2: FDG PET/CT scan of a 66-year-old woman with suspected colon cancer and elevated Carcinoembryonic antigen (CEA), with no current immunosuppressive treatment. The scan was performed 25 days after first vaccine dose and 2 days after the second vaccine dose, both in the left arm. (A) Maximal intensity projection (B) Axial MPR (C) Contrast-enhanced CT (D) Fusion. Increased uptake was observed in the left deltoid muscle, corresponding to the injection site (arrowhead), and in the ipsilateral enlarged axillary lymph nodes (arrows). Otherwise, there were no hypermetabolic findings suggestive of malignancy.

FIGURE 3. DOTATATE PET/CT after COVID-19 vaccination

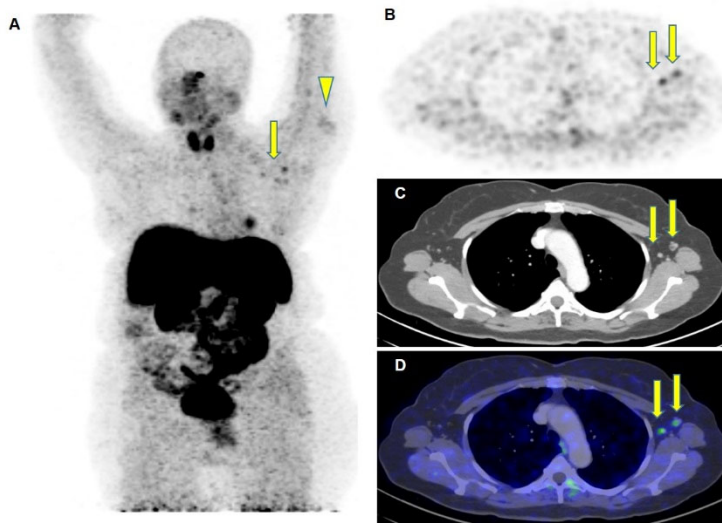


Figure 3: DOTATATE PET/CT scan of a 68 y/o woman with newly diagnosed typical carcinoid (G2), not receiving current immunosuppressive treatment. (A) Maximal intensity projection (B) Axial MPR (C) Contrast-enhanced CT (D) Fusion images 24 days after first vaccine and 3 days after second vaccine both on the left side. There is increased uptake in the left deltoid (arrowhead) corresponding to the vaccine site and increase uptake in left axillary lymph nodes of normal size (arrows).

FIGURE 4: Pathology of reactive, FDG avid, axillary lymph node after COVID-19 vaccination

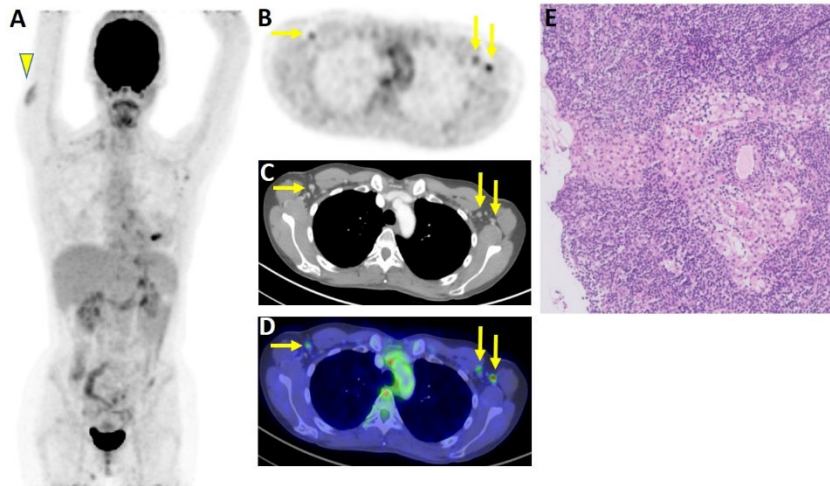


Figure 4: FDG PET/CT scan of a 41 y/o female with newly diagnosed left ER+ PR+ HER2+ breast cancer. First vaccine dose was given prior to diagnosis in the left deltoid muscle 22 days before the scan. Her second vaccine dose was administered after being diagnosed with left breast cancer, and was given in the right deltoid muscle 1 day prior the scan. (A) Maximal intensity projection showing markedly increase FDG uptake in the right deltoid (arrowhead) corresponding to the recent second vaccine dose site, and in several left and right axillary lymph nodes. (B) Axial MPR, (C) Contrast-enhanced CT and (D) Fusion showing markedly increase FDG uptake in bilateral axillary lymph nodes (arrows). The patient underwent US guided core needle biopsy to left suspicious axillary lymph node one day following the PET/CT scan. (E) Hematoxylin and Eosin (H&E) Stained Images of cores of lymph node tissue showing prominently dilated and edematous sinuses that probably reflect reactive changes, the lymphoid tissue is unremarkable, and there is no evidence of malignancy.

TABLE 1. Demographic characteristics of the vaccinated study population

Variables	Study population N=426
Mean age \pmSD, years (range)	67 \pm 12 (20-95)
Female, n (%)	207 (49%)
PET/CT Scan indication, n (%)	
Solid tumor	357 (83%)
Hematologic malignancy	66 (16%)
Inflammation/infection	4 (1%)
Treatment*, n (%)	
No current treatment	235 (55%)
Targeted therapy†	74 (17%)
Chemotherapy	71 (16%)
Immunotherapy	48 (11%)
Steroids	27 (6%)
Other immunosuppressive treatment‡	4 (1%)

PET/CT, positron emission tomography with computed tomography; SD, standard deviation

*Some patients received more than one treatment †Targeted therapies including tyrosine kinase inhibitors, hormonal therapy, proteasome inhibitors ‡Including rituximab, daratumumab, bone marrow transplant

TABLE 2: Prevalence of increased uptake in the ipsilateral deltoid muscle and/or in ipsilateral axillary lymph nodes with different PET/CT tracers

Tracer	Deltoid muscle uptake	Axillary lymph nodes uptake	Both Deltoid and axillary uptake
F-18 FDG	26% (98/377)	45% (170/377)	16% (60/377)
Ga-68 DOTATATE	9% (1/11)	55% (6/11)	9% (1/11)
Ga-68 or F-18 PSMA	0% (0/37)	0.3% (1/37)	0% (0/37)
F-18-DOPA	0% (0/1)	100% (1/1)	0% (0/1)

Fluorodeoxyglucose (FDG), prostate specific membrane antigen (PSMA), fluorodopa (DOPA)

TABLE 3. Multivariate logistic regression analysis of uptake in the deltoid and the lymph nodes following COVID-19 mRNA vaccination

Independent variable	Odds Ratio	95% Confidence Interval	P value	Adjusted P value*
Deltoid†				
Scaled age	0.86	(0.66, 1.12)	0.251	0.320
Sex (Male)	1.09	(0.64, 1.85)	0.744	0.744
Immunosuppressive treatment (yes)	0.63	(0.31, 1.23)	0.192	0.277
Hematologic disease (yes)	0.72	(0.34, 1.42)	0.352	0.411
Scaled number of days from last vaccination	0.74	(0.53, 1.01)	0.066	0.116
Second vaccination (yes)	2.85	(1.13, 6.70)	0.020	0.040*
Scaled number of days from last vaccination : Second vaccination	0.28	(0.09, 0.75)	0.015	0.036*
constant	0.23			
Lymph Nodes†				
Scaled age	0.57	(0.45, 0.72)	0.000	0.000*
Sex (Male)	0.74	(0.47, 1.17)	0.198	0.277
Immunosuppressive treatment (yes)	0.37	(0.20, 0.64)	0.001	0.003*
Hematologic disease (yes)	0.44	(0.24, 0.80)	0.008	0.021*
Scaled number of days from last vaccination	1.53	(1.18, 1.99)	0.001	0.005*
Second vaccination (yes)	7.53	(2.91, 23.50)	0.000	0.001*
Scaled number of days from last vaccination : second vaccination	1.39	(0.50, 4.43)	0.552	0.594
constant	0.93			

* FDR-adjusted P values for multiple testing. Significant results at the level of 0.05 are denoted with an asterisk. † Hosmer–Lemeshow tests showed no indication of poor fit (P=0.919 for the deltoid model, P=0.674 for the lymph nodes model).

Graphical abstract

