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Lessons learned from post-COVID-19 vaccination PET/CT studies

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Short Title: PET/CT studies post-COVID-19 vaccination

Abstract

Anti-COVID-19 vaccination has created new challenges. Lymphadenopathy (LA) with increased uptake in patients undergoing PET/CT may mislead to unnecessary further evaluation. We have analyzed routinely performed PET/CT studies following Pfizer-BioNTech vaccination to familiarize with PET/CT appearances with various PET tracers and to prevent consequences of misinterpretation.

Methods: 1281 PET/CT studies performed between January 01 2021 and February 15 2021 were analyzed. Information about dates and site of vaccination was collected. Visual and semi-quantitative analysis of axillary - neck LA and arm uptake was correlated with immunization data.

Results: Increased uptake in unilateral axillary LA was observed in 66% vaccinated patients, in 55% vaccinated once and in 69% vaccinated twice. Intensity of uptake decreased over time.

64/315 patients (20%) had simultaneous increased activity in the posterior arm and ipsilateral axillary LA ("double sign" [DS]). Sensitivity, specificity, PPV and NPV of axillary LA and DS were 55.4%, 83.6%, 86.7%, 49.2% and 38.6%, 100%, 100% and 66.1%, respectively. No DS was observed later than

10 and 21 days after first and the second vaccinations, respectively. None of the non-vaccinated patients had arm uptake or DS.

Conclusion: Anti-COVID-19 vaccination frequently causes non-specific axillary LA with increased PET tracer activity. In one fifth of our study population this was associated with increased uptake at the vaccination site, DS. DS was 100% specific with 100% PPV for p/vaccination LA hence enabling to avoid misinterpretation of PET/CT studies and further unnecessary evaluation.

Keywords: COVID-19, vaccination, PET/CT, lymphadenopathy, pattern.

INTRODUCTION

The COVID-19 pandemic has changed our personal and professional life (*1*). It has affected the workflow in Nuclear Medicine departments (*2*). Imaging findings of COVID-19 in the acute or residual stages of the disease are detected on PET/CT (*3, 4*).

Since December 2020 mass vaccination has started in Israel, who became one of the first countries with a high percent of population vaccinated against COVID-19. Cancer patients, routinely referred to PET/CT studies, comprise a significant subgroup of vaccinated citizens.

Lymph nodes that are housing T, B and antigen presenting cells have an important role in the immune response to vaccination. Once injected into the muscle the vaccine is transported to the regional lymph nodes, and in some cases it may proceed to the next nearest lymphatic chain stations, with further activation of the T and B cells in these lymph nodes (*5*). Incidental LA on physical examination, mammography, breast MRI or PET/CT challenged interpretation of these studies (*6, 7, 8*). Several studies recently published demonstrated increased FDG uptake in post COVID-19 vaccination LA (*9-12*).

The aim of present study was to describe characteristics and distinctive features of the post-COVID vaccination PET/CT studies with routinely used PET tracers in order to improve the confidence of PET/CT readers and to prevent unnecessary diagnostic and interventional procedures.

MATERIALS AND METHODS

Study design and participants

This retrospective study was approved by the institutional Ethics committee. The need for informed consent was waived.

All PET/CT studies performed at our center between 01.01.2021 and 15.02.2021 were included. Data collected from PET/CT studies were compared with vaccination-related information and analyzed.

PET/CT Studies

Studies were acquired on either Discovery MI digital PET/CT or MI-DR PET/CT (GE Healthcare,Milwaukee WI, USA) 67 ± 9 min after injection of 2.96 MBq/kg 18F fluorodeoxyglucose (FDG) (n=973), 68Ga-DOTA-[Tyr3]-Octreotate (DOTA-TATE) (n=14), 68Ga-prostate-specific membrane antigen

(PSMA) (n=26), 18F-PSMA (n=5). Studies were acquired according to standard protocols. All patients received oral contrast. Intravenous contrast was administered prior to diagnostic CT in 359 patients.

Vaccination

Vaccinations were performed as per manufacturer instructions in the deltoid muscle of the non-dominant arm. The second vaccination was administered 21 ± 6 days after the first one. Referrals to PET/CT were according to clinical indications, independent of vaccination status.

Visual interpretation and semi-quantitative analysis

All studies were reviewed by two experienced Nuclear Medicine physicians (one also a radiologist [MO]). After visual interpretation, relevant areas of increased tracer accumulation were evaluated semi-quantitatively by measuring SUV_{max} with emphasis on posterior arm – deltoid muscle, axillary, supraclavicular and cervical lymph nodes. Increased uptake was defined as $SUV_{max}>1$, not compatible with anatomical or physiological accumulation of radiopharmaceutical. The short axis of lymph nodes (LN) in the field of interest was recorded. LN were defined as benign, malignant or

equivocal according to their radiological appearances. Kidney shaped nodes with preserved fat center, size less than 1.0 cm and peripheral contrast enhancement were defined as benign. O-shaped LN's with no central fat, larger than 1.0 cm in short diameter with diffuse enhancement were defined as malignant. All others were defined as equivocal.

Simultaneously increased uptake at the injection site in the arm and in ipsilateral axillary LN was defined as "double sign" (DS). Studies were interpreted blinded to vaccination status but with full clinical background.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for DS and for axillary LA for each of the PET tracers. Studies were considered as true positive (TP) for DS when a vaccinated patient presented with increased uptake in the ipsilateral arm and axillary LN, and as true negative (TN) when there was no vaccination prior to the study and no uptake in the arm and in the axilla. Vaccinated patients that showed no arm and no axillary uptake were considered false negative (FN). Arm and axillary uptake in non-vaccinated patients was considered false positive (FP).

For the axillary LA TP cases were defined as increased uptake in axillary LA in vaccinated patients and TN as lack of axillary uptake in non-vaccinated patients.

Differences between lymph nodes SUV_{max} or size with or without ipsilateral arm uptake were assessed with Mann–Whitney U test. $p < 0.05$ was considered statistically significant.

RESULTS

FDG PET/CT

Between January 01 2021 and February 15 2021, 1281 PET/CT studies were performed in our department, 973 of them were FDG PET/CT studies. Vaccination status information was available for 458 patients (242 female and 216 male, age range of 8-98 years (mean ± SD: 61.3 ± 14.9 years), consisting the study group. There were 452 (99%) patients with known or suspected malignancy and 6 (1%) were referred for the assessment of infection or inflammation. The most common clinical indications included: breast cancer (n=102), lymphoma and myeloma (n=88), lung cancer (n=86)

and gastro-intestinal tumors (n=73). Patients' clinical characteristics are summarized in Table 1.

At the time of PET/CT 274/458 patients (60%) were vaccinated, 168/458 (37%) were not immunized and 16 (3.5%) recovered from COVID - 19. These 184/458 (40%) patients consisted the control group.

LN-based analysis

Axillary LA was present in 268/458 (59%) patients, 156 unilateral and 112 bilateral. Of these 268, 39 were vaccinated once and 141 were vaccinated twice. LN appearances on CT were benign in 75%, malignant in 13% and in 12% equivocal (Table 2). LN size ranged between 0.2 - 5.3 cm (mean 0.9 ± 0.6 cm) and SUV_{max} in axillary LN was 0.6-24.5 (mean 3.5 ± 3.3). Supraclavicular LN, ipsilateral to the axillary LA, with increased FDG activity were visualized in 26 (5.7%) patients. The sensitivity, specificity, PPV and NPV for axillary LA with benign appearances and increased activity (SUV_{max} > 1.0) were 53.7%, 84.8%, 86.5% and 50.3%, respectively (Table 2).

In the control group, 88 non-vaccinated patients had unilateral axillary LA. LN size range was 0.3-5 cm, SUV_{max} range was 0.7-24.5 and the

appearances were benign in 60 patients (68%), malignant in 18 patients (20%) and equivocal in 10 patients 12% (Table 2).

Vaccination-based analysis

Of the 274 vaccinated patients 71 (26%) were vaccinated once and 203 (74%) patients were vaccinated twice. The mean interval between the first vaccination and PET/CT was 9 days (range: 0-34 days). In patients who were vaccinated twice PET/CT was performed after an average of 15 days (range: 0-34 days) following the second vaccination.

Increased uptake in axillary LA was observed in 180/274 patients (66%), in 39/71 (55%) after the first vaccination and 141/203 (69%) after the second. LN size ranged between 0.2-5.3 cm (mean: 0.8±0.6 cm) and SUV_{max} ranged from 0.6 to 17.8 (mean: 3.3±2.7). CT appearances and SUV values are summarized in Table 2. There was no significant difference between SUV_{max} values after the first and second vaccinations. SUV_{max} in axillary LA decreased over time. No increased FDG uptake was observed 22 days and 32 days after the first and the second vaccination, respectively. Figure 1(a) shows the frequency of increased LN activity as a function the time after vaccination for patients who received one or two vaccinations. The frequency of increased

activity was higher after the second vaccination and remained stable up to 32 days after vaccination.

Increased uptake at the vaccination site (posterior arm/deltoid muscle) was visualized in 57 patients (12%) (left 41, right 16) with SUV_{max} 1.8 ± 0.7 (range: 0.9-4.4). Nine/57 (16%) patients had focal uptake at the vaccination site after the first vaccination and 48/57 (84%) after the second vaccination. CT showed mild subcutaneous fat stranding in 19 cases and no significant morphological changes in 45 others. There was no increased uptake in the posterior arm/deltoid muscle in the control group.

DS -based analysis

In 54/274 (20%) vaccinated patients and 95% of patients with increased arm uptake, there was simultaneously increased activity in ipsilateral axillary LN, defined as "double sign" (DS) (Figure 2). DS was observed in 9/54 patients (17%) after the first vaccination and in 45 patients (83%) after the second. LN size in short axis was 0.2 - 5.3 cm (mean $\pm$ SD: 0.8 $\pm$ 0.7 cm) and SUV_{max} was 0.9-8.6 (mean $\pm$ SD: 3.1 ± 2.1), respectively. Among these 54 patients, 49 had nodes with benign appearances and in 5 patients the nodes were defined as equivocal. In three of 49 patients there were LNs

with malignant appearances adjacent to benign appearing LN, including a patient with lymphoma, one with ipsilateral breast cancer and a patient with metastatic lung cancer.

The mean interval between the first and second vaccination and DS was 6 and 9 days, respectively, compared to a mean of 9 and 15 days, respectively, for the entire LA group. DS frequency as a function of the time after vaccination in patients who received one and two vaccinations doses is depicted in Figure 1(b).

The highest frequency of DS was observed during the first week after the first or second vaccination (19% and 58%, respectively) with lower frequency on PET/CT studies performed during the second (12% and 25%, respectively) and third weeks (0% and 19%, respectively) after immunization. Arm uptake and DS were seen up to 10 days after the first vaccination and up to 21 days after the 2nd. Sensitivity, specificity, PPV and NPV of DS were 37.2%, 100%, 100% and 66.9%, respectively.

There was no significant correlation between intensity of uptake in the arm and in LN.

There was no significant difference between LN size of the DS group (0.2-5.3 cm) compared to non-DS (0.3-5.0 cm) (P = 0.74). However, SUV_{max} was significantly higher in the DS group (P = 0.001).

Non-FDG PET/CT

There were thirty-one PSMA (26 Ga68-PSMA, 5 F18-PSMA, total 2.4%) and 14 Ga68-DOTA TATE (1.1%) PET/CT studies. A single F18-FDOPA study was excluded. Vaccination data, axillary LA prevalence and characteristics and DS are presented in Table 3 and 4, respectively. LA was present in 26 patients (84%) with PSMA studies, 24 (92%) with benign appearances on CT and was associated with DS in four patients (13%) (Supplemental Figure 1). LA was present in 12 patients (86%) with DOTA TATE studies, all with benign CT appearances and DS was observed in three patients (21%) (Supplemental Figure 2). Sensitivity, specificity, PPV and NPV of DS for PSMA and DOTA TATE were 44.4%, 100%, 100%, 37% and 75%, 100%, 100%, 50%, respectively.

DISCUSSION

The aim of present study was to identify the typical post- COVID- 19 vaccination pattern on PET/CT studies in order to minimize its influence on

routine workflow. We have identified the 'double sign' on PET/CT studies with various radiotracers, showing increased uptake at the vaccination site and ipsilateral axillary lymph nodes. DS occurred in up to a fifth of the vaccinated patients with 100% PPV and specificity. When present, this highly specific imaging pattern first described herewith enables to avoid false disease upstaging or further unnecessary evaluation. Eifer et al. showed increased uptake in deltoid muscle and in axillary LA with slightly different results for FDG and DOTA-TATE (Table 5) and lack of PSMA uptake, probably due to population heterogeneity. Interestingly, a similar pattern has been described on FDG PET/CT studies post-Influenza vaccination with a prevalence of 5.1 - 25 % (*13-16*).

Stand-alone axillary LA can be challenging in cases of lymphoma, breast cancer, melanoma, or other cutaneous malignancies. In present study we have demonstrated FDG avid LA in 59% of patients following vaccination for COVID-19 compared to 45-46 % in recent publications (*9, 10*). The frequency of FDG avid LA was higher after the second vaccination compared to the first, in present study 69% vs 55% respectively, compared to 53.9% and 36.4% (*9*), 43.3% and 14.5% (*12*), respectively, in recent publications. The prevalence of LA with benign CT appearances and low-

grade FDG accumulation was also similar, 77% in present study compared to 80.1% in previous study (*9*). This is significantly higher in comparison to axillary LA post H1V1 influenza A virus vaccination (*15*) which was observed in 29.3 % (*13, 15*) and to post papilloma virus vaccination (*17*), probably due to the high immunogenicity of the COVID-19 vaccine.

The mechanism of FDG uptake has been addressed by Eifer et al. (11). A strong inverse association was demonstrated between axillary lymph node uptake, patient age and immune status, with avid uptake in 53% of immunocompetent patients compared to 33% in immunocompromised patients. Deltoid uptake was associated with the time interval from the vaccine and number of vaccinations. The authors suggest the activity in lymph nodes is associated with immune system activation and deltoid activity is due to inflammatory etiology and to trauma induced by the injection (*11*). The mechanism of PSMA uptake in LA is likely mediated by PSMA expression on immune cells. A non-PSMA related mechanism, similar to the accumulation in salivary glands has also been suggested (*18, 19*). DOTA TATE uptake in LA is based on the expression of somatostatin receptors (SSTR) 1 and 2 on monocytes and

macrophages and its regulatory role in interaction with immune system (20).

The typical response to vaccination is restricted to the regional draining lymph nodes, consistent with axillary nodes when the injection is administered in the proximal arm. Increased tracer accumulation in supraclavicular LA, representing the next lymphatic drainage station, was observed in 5.7% in present study.

In present study increased LA uptake and DS was observed from day one after vaccination up to 22/32 days and 10/21 days after the first and second vaccinations, respectively. Cohen et al. have observed more significant FDG avid LA from day 5 up to 13 after the first vaccination and significantly lower after day 20 after booster vaccine (9). Eshet et al. showed avid axillary LA 7-10 weeks after second vaccination (10). All studies have reported regression in FDG activity in LA and at the injection site. Table 5 summarizes the main PET/CT findings post COVID-19 vaccination in recent publications (*9-12*).

In contrast to a few published case reports showing (*21*) systemic inflammatory response syndrome after COVID-19 vaccination, no systemic

findings were noted in our or in other large cohort. These differences are consistent with the published vaccination-related reaction data (*22, 23*).

Limitations of present study are due to it's retrospective nature. In addition, for obvious reasons none of lymph nodes were biopsied. Positive studies were not repeated for follow up of the LA or the arm uptake. In one case the patient returned for evaluation of treatment response 53 days after the first study, showing complete resolution of all previously visualized findings (Figure 3).

PSMA PET/CT studies with 68Ga and 18F, both routinely used for the assessment of patients with prostate cancer, were analyzed together due to the relative small number of these studies in present cohort. Patients with diseases that have predilection to cause axillary lymphadenopathy, like melanoma, breast cancer and lymphoma were not excluded, reflecting the routine workflow. In these cases the radiological appearances of the LA play a crucial role. In most cases benign and malignant lymph nodes can be separated with only 8% defined as equivocal in present study and 14.8% in another study (*9*).

Familiarity with post-vaccination pattern on PET/CT is important for the interpreting as well as referring physicians. To prevent erroneous interpretation of post-vaccination LA, it has been previously suggested to postpone PET/CT until recovery of post-immunization LA. However, LA may persist for up to 70 days (*11*) after vaccination and such prolonged delays should be avoided, especially in cancer patients. We recommend adding to the routine patient questionnaire dates and location of vaccination and history of COVID-19 infection. It is also advisable to actively look for DS in addition to routine interpretation of LN appearances. Awareness of the different patterns may help prevent FP interpretations of PET/CT studies.

CONCLUSION

COVID-19 vaccine frequently causes axillary radiotracer-avid lymphadenopathy and post-injection arm uptake. DS, observed in present study in 20% of post-vaccinated patients, is highly specific for post-vaccination LA and can reduce misinterpretation of PET/CT and its consequences. Present study included a large patient population, but it is a single center study with only one type of vaccine. Further similar studies with other types of COVID-19 vaccine are needed.

KEY POINTS

COVID-19 vaccine lymphadenopathy challenges interpretation of PET/CT studies.

Post-COVID-19 vaccination PET/CT studies showed post-vaccination stand-alone axillary lymphadenopathy in 68% of patients. A fifth of the patients had simultaneous tracer accumulation at the injection site in the arm and in ipsilateral axillary lymph nodes. This finding was highly specific for post-vaccination lymphadenopathy and awareness can prevent misinterpretation, unnecessary further evaluation and its consequences.

REFERENCES

1. Freudenberg LS, Paez D, Giammarile F, et al. Global impact of COVID-19 on nuclear medicine departments: an international survey in april 2020. *J Nucl Med*. 2020;61:1278-1283.
2. Annunziata S, Albano D, Laudicella R, Bauckneht M; Young Committee of the Italian Association of Nuclear Medicine (AIMN). Surveys on COVID-19 in nuclear medicine: what happened and what we learned. *Clin Transl Imaging*. 2020; 24:1-3.
3. Deng Y, Lei L, Chen Y, Zhang W. The potential added value of FDG PET/CT for COVID-19 pneumonia. *Eur J Nucl Med Mol Imaging*. 2020;47:1634-1635.
4. Qin C, Liu F, Yen TC, Lan X. ^{18}F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases. *Eur J Nucl Med Mol Imaging*. 2020;47:1281-1286.
5. Irvine DJ, Aung A, Silva M. Controlling timing and location in vaccines. *Adv Drug Deliv Rev*. 2020;158:91-115.
6. Xu G, Lu Y. COVID-19 mRNA vaccination-induced lymphadenopathy mimics lymphoma progression on FDG PET/CT. *Clin Nucl Med*. 2021;46:353-354.

7. Ahmed N, Muzaffar S, Binns C, Ilyas MW, Usmani S. COVID-19 vaccination manifesting as incidental lymph nodal uptake on 18F-FDG PET/CT. *Clin Nucl Med*. 2021;46:435-436.
8. Edmonds CE, Zuckerman SP, Conant EF. Management of unilateral axillary lymphadenopathy detected on breast MRI in the era of coronavirus disease (COVID-19) vaccination. *AJR Am J Roentgenol*. 2021;Epub ahead of print.
9. Cohen D, Hazut Krauthammer S, Cohen YC, Perry C, Avivi I, Herishanu Y, Even-Sapir E. Correlation between BNT162b2 mRNA Covid-19 vaccine-associated hypermetabolic lymphadenopathy and humoral immunity in patients with hematologic malignancy. *Eur J Nucl Med Mol Imaging*. 2021;8:1–10.
10. Eshet Y, Tau N, Alhoubani Y, Kanana N, Domachevsky L, Eifer M. Prevalence of increased FDG PET/CT axillary lymph node uptake beyond 6 weeks after mRNA COVID-19 vaccination. *Radiology*. 2021; Epub ahead of print.
11. Eifer M, Tau N, Alhoubani Y, Kanana N, Domachevsky L, Shams J, Keret N, Gorfine M, Eshet Y. Covid-19 mRNA vaccination: age and

immune status and its association with axillary lymph node PET/CT uptake. *J Nucl Med*. 2021;Epub ahead of print.

12. Bernstine H, Priss M, Anati T, Turko O, Gorenberg M, Steinmetz AP, Groshar D. Axillary lymph nodes hypermetabolism after BNT162b2 mRNA COVID-19 vaccination in cancer patients undergoing 18F-FDG PET/CT: A Cohort Study. *Clin Nucl Med*. 2021;46:396-401.
13. Shirone N, Shinkai T, Yamane T, et al. Axillary lymph node accumulation on FDG-PET/CT after influenza vaccination. *Ann Nucl Med*. 2012;26:248-52.
14. Thomassen A, Lerberg Nielsen A, Gerke O, Johansen A, Petersen H. Duration of 18F-FDG avidity in lymph nodes after pandemic H1N1v and seasonal influenza vaccination. *Eur J Nucl Med Mol Imaging*. 2011;38:894-8.
15. Burger IA, Husmann L, Hany TF, Schmid DT, Schaefer NG. Incidence and intensity of F-18 FDG uptake after vaccination with H1N1 vaccine. *Clin Nucl Med*. 2011;36:848-53.

16. Panagiotidis E, Exarhos D, Housianakou I, Bournazos A, Datseris I. FDG uptake in axillary lymph nodes after vaccination against pandemic (H1N1). *Eur Radiol*. 2010;20:1251-3.

17. Coates EE, Costner PJ, Nason MC, et al. Lymph node activation by PET/CT following vaccination with licensed vaccines for human papillomaviruses. *Clin Nucl Med*. 2017;42:329-334.

18. de Galiza Barbosa F, Queiroz MA, Nunes RF, Costa LB, Zaniboni EC, Marin JFG, Cerri GG, Buchpiguel CA. Nonprostatic diseases on PSMA PET imaging: a spectrum of benign and malignant findings. *Cancer Imaging*. 2020;14;20:23.

19. Rupp NJ, Umbricht CA, Pizzuto DA, Lenggenhager D, Töpfer A, Müller J, Muehlematter UJ, Ferraro DA, Messerli M, Morand GB, Huber GF, Eberli D, Schibli R, Müller C, Burger IA. First clinicopathologic evidence of a non-psma-related uptake mechanism for 68Ga-PSMA-11 in salivary glands. *J Nucl Med.* 2019;60:1270-1276.

20. Armani C, Catalani E, Balbarini A, Bagnoli P, Cervia D. Expression, pharmacology, and functional role of somatostatin receptor

subtypes 1 and 2 in human macrophages. *J Leukoc Biol*. 2007;81:845-55.

21. Steinberg J, Thomas A, Iravani A. ^{18}Fluorodeoxyglucose PET/CT findings in a systemic inflammatory response syndrome after COVID-19 vaccine. *Lancet*. 2021;8;397.

22. Mulligan MJ, Lyke KE, Kitchin N, et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature*. 2020;586:589-593.

23. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-416.

Table 1. Patient characteristics (n=458)

Characteristics	Values
Age	61 ± 15 years
Gender	
Male	216
Female	242
Indications for PET/CT	
○ breast cancer	102
○ lymphoma and myeloma	88
○ lung cancer	86
○ gastro-intestinal tumor	73
○ urological and gynecological cancer	40
○ skin cancer	22
○ head & neck oncology	19
○ tumor of unknown origin	6
○ fever of unknown origin, bacteremia	6
and infection –inflammation	2
○ sarcoma	14

Table 2. Results summary – FDG PET/CT

Patient number			Total 458	Control group 184	Vaccinated 274		DS 54		Sensitivity Specificity PPV NPV (%)
					Once 71	Twice 203	Once 9	Twice 45	
Vaccination to PET/CT Interval (days)			N/A	N/A	9 (0-34)	15 (0-34)	6 (1-10)	9 (1-21)	N/A
LA	(number of patients and %)		268 (59%)	88 (48%)	39 (14%)	141 (51%)	9(17%)	45 (83%)	S* = 53.7 Sp* = 84.8 PPV* = 86.5 NPV* = 50.3
	LN appearance	B	200(75%)	60 (68%)	30 (77%)	110 (78%)	49 (91%)		
		M	36 (13%)	18 (20%)	4 (10%)	14 (10%)	0		
		E	32 (12%)	10 (12%)	5 (13%)	17 (12%)	5 (9%)		
	Size (cm) in short axis		0.2-5.3	0.3-5.0	0.2-5.3		0.2-5.3		
	SUV max		0.6-24.5	0.7-24.5	0.6-17.8		0.9-8.6		
number of patients and %)			57 (12%)	0	57 (21%)		54 (100%)		N/A
					9 (16%)	48 (84%)	9 (17%)	45 (83%)	
DS (number of patients and %)			54 (12%)	0	54 (20%)		--		S = 37.2 Sp = 100 PPV = 100 NPV = 66.9
					9 (17%)	45 (83%)	--		

* for unilateral axillary LA only with increased uptake (SUVmax > 1.0) and benign appearance. LN= lymph nodes, DS= double sign, LA= lymphadenopathy, PPV=positive predictive value, NPV=negative predictive value, S= sensitivity, Sp=specificity, B= benign, M=malignant, E=equivocal.

Table 3. Results summary – PSMA PET/CT

Patient number			Total 31	Control group 3	Vaccinated 28 Once 3	Vaccinated 28 Twice 25	DS 4 Once 0	DS 4 Twice 4	Sensitivity Specificity PPV NPV (%)
Vaccination to PET/CT Interval (days)			N/A	N/A	10 (6-18)	14 (0-24)	N/A	1-19 (mean 12)	N/A
LA	(number of patients and %)		26 (84%)	3 (10%)	3 (11%)	20 (71%)	0	4 (100%)	S* = 61.5 Sp* = 0 PPV* = 80 NPV* = 0
	LN appearance	B	24 (92%)	3 (100%)	3 (100%)	18 (90%)	3 (75%)		
		M	0	0	0	0	0		
		E	2 (8%)	0	0	2 (10%)	1 (25%)		
	Size (cm) in short axis		0.3-1.6	0.3-0.6	0.4-1.6		0.7-1.5		
	SUV max		1.1-3.1	1.1-2	1.3-3.1		1.4-3.1		
Arm (number of patients and %)			4 (13%)	0	4 (14%)		4 (100%)		N/A
					0 (0%)	4 (100%)	0 (0%)	4 (100%)	
DS (number of patients and %)			4 (13%)	0	4 (14%)		--		S = 44.4 Sp = 100 PPV = 100
					0	4 (100%)	--		

						NPV = 37.5

* for unilateral axillary LA only with increased uptake (SUVmax > 1.0) and benign appearance. LN= lymph nodes, DS= double sign, LA= lymphadenopathy, PPV=positive predictive value, NPV=negative predictive value, S= sensitivity, Sp=specificity, B= benign, M=malignant, E=equivocal.

Table 4. Results summary – ^{68}Ga DOTATATE

Patient number			Total 14	Control group 1	Vaccinated 13		DS 3		Sensitivity Specificity PPV NPV (%)
					Once 2	Twice 11	Once 1	Twice 2	
Vaccination to PET/CT Interval (days)			N/A	N/A	6 (3-8)	14 (2-21)	3	4 (2-5)	N/A
LA	(number of patients and %)		12 (86%)	0	2 (15%)	10 (77%)	1 (33%)	2 (67%)	S* = 87.5 Sp* = 100 PPV* = 100 NPV* = 50 ! Control group only 1 patient!
	LN appearance	B	12 (100%)	N/A	2 (100%)	10 100%()	3 (100%)		
		M	0	N/A	0	0	0		
		E	0	N/A	0	0	0		
	Size (cm) in short axis		0.5-1.1	N/A	0.5-1.1		0.5-0.9		
	SUV max		1-3.5	N/A	1-3.5		1.6-3.5		
Arm (number of patients and %)			3 (21%)	0	3 (23%)		3 (100%)		N/A
					1 (33%)	2 (67%)	1 (33%)	2 (67%)	
DS (number of patients and %)			3 (21%)	0	3 (23%)		--		S = 75 Sp = 100

			1 (33%)	2 (67%)	--	PPV = 100 NPV = 50

* for unilateral axillary LA only with increased uptake (SUVmax > 1.0) and benign appearance. LN= lymph nodes, DS= double sign, LA= lymphadenopathy, PPV=positive predictive value, NPV=negative predictive value, S= sensitivity, Sp=specificity, B= benign, M=malignant, E=equivocal.

Table 5. Comparison of PET/CT post-vaccination studies

	Vaccine (total patient number)/ Tracer	Number of vaccinated patients	Duration of increased uptake in lymphadenopathy (days)			Increased uptake in deltoid muscle
			after 1st / single	after 2nd	after 3d	
			vaccination administration			
Orevi M., et al	COVID19 FDG DOTA TATE PSMA	503	up to 22	up to 32		FDG 20% DOTA TATE 21% PSMA 13%
Cohen D., et al (9)	COVID19 FDG	728	~13	~20		NA
Eshet Y., et al. (10)	COVID19 FDG	169	NA	Up to 70		NA
Eifer M., et al. (11)	COVID19 FDG DOTA TATE PSMA	426	NA	NA		FDG 26% DOTA TATE 9% PSMA 0%
Bernstine H., et al. (12)	COVID19 FDG	650	22	22		NA

Figure 1.

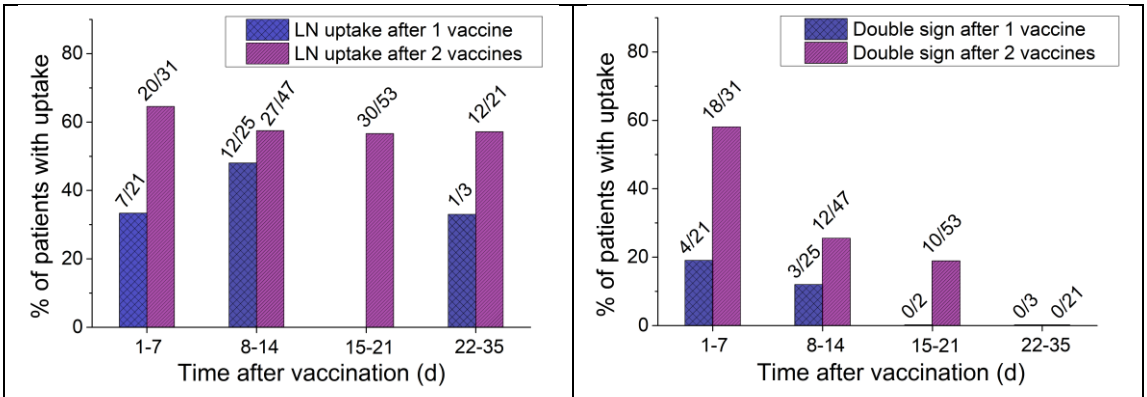


Figure 1: (A) Axillary LA and (B) DS appearance frequency as a function time after vaccination in patients vaccinated once (blue bars) or twice (purple bars). The ratio above the bars represents the proportion of patients with LN or DS among vaccinated patients who underwent PET/CT at the same time. LA= lymphadenopathy, DS= double sign, LN= lymph nodes.

Figure 2.

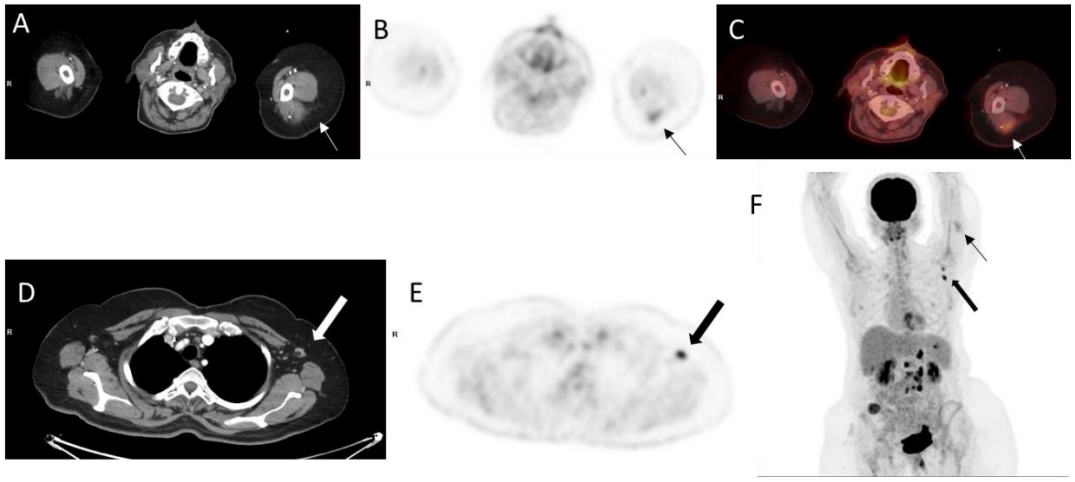


Figure 2: 52-year-old female with gastro-intestinal tumor was referred for routine F18 FDG PET/CT follow up study. The study was performed two days after the second COVID19 vaccination. Selected transaxial CT (A, D), and PET (B, E) slices at the level of posterior arm uptake and axillary lymph nodes , fused image (C) at the level of posterior arm uptake and MIP (F) demonstrate moderate intensity uptake in the left posterior arm, SUV max 3.6 (thin black and white arrows) and high grade activity in left axillary nodes measuring 1.0 cm in short axis with benign appearances (thick white and black arrows), SUV max 7.1. The MIP also shows high grade FDG activity in retroperitoneal nodes and multiple implants.
MIP=Maximum intensity projection

Figure 3.

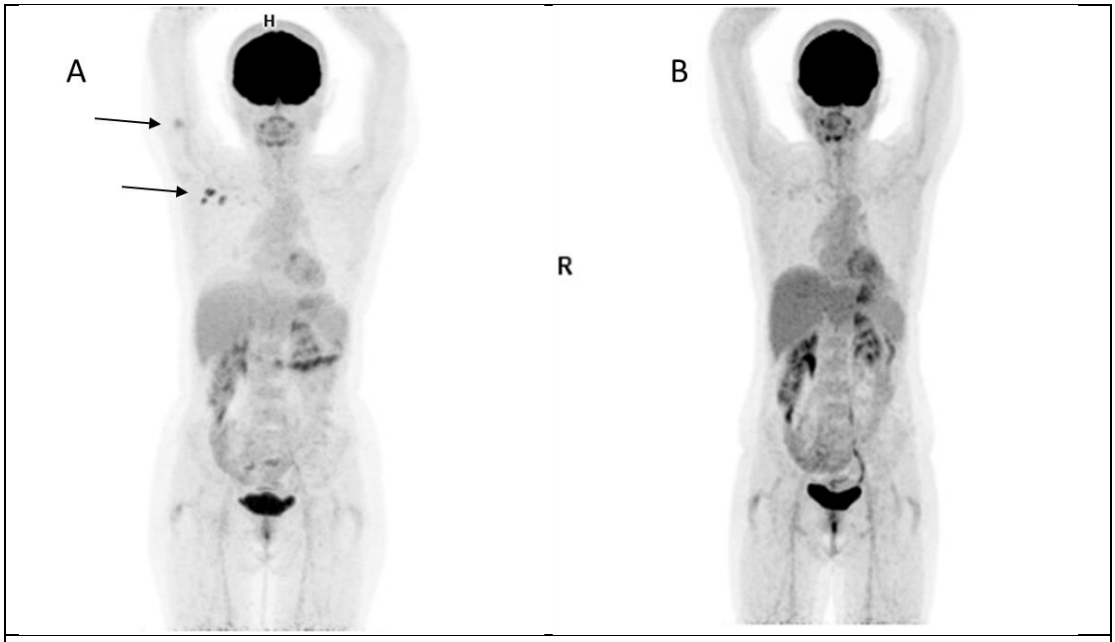
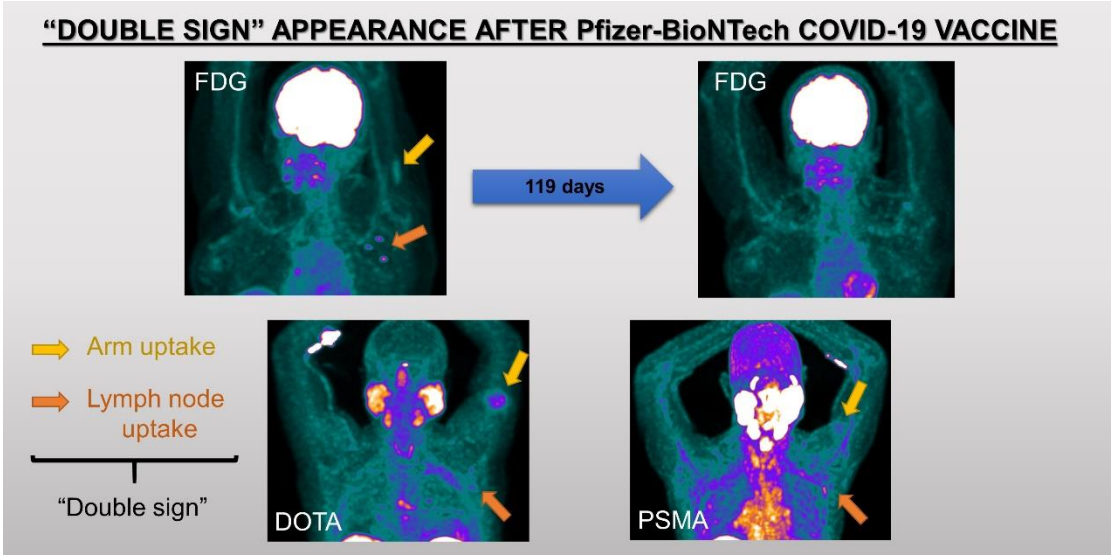
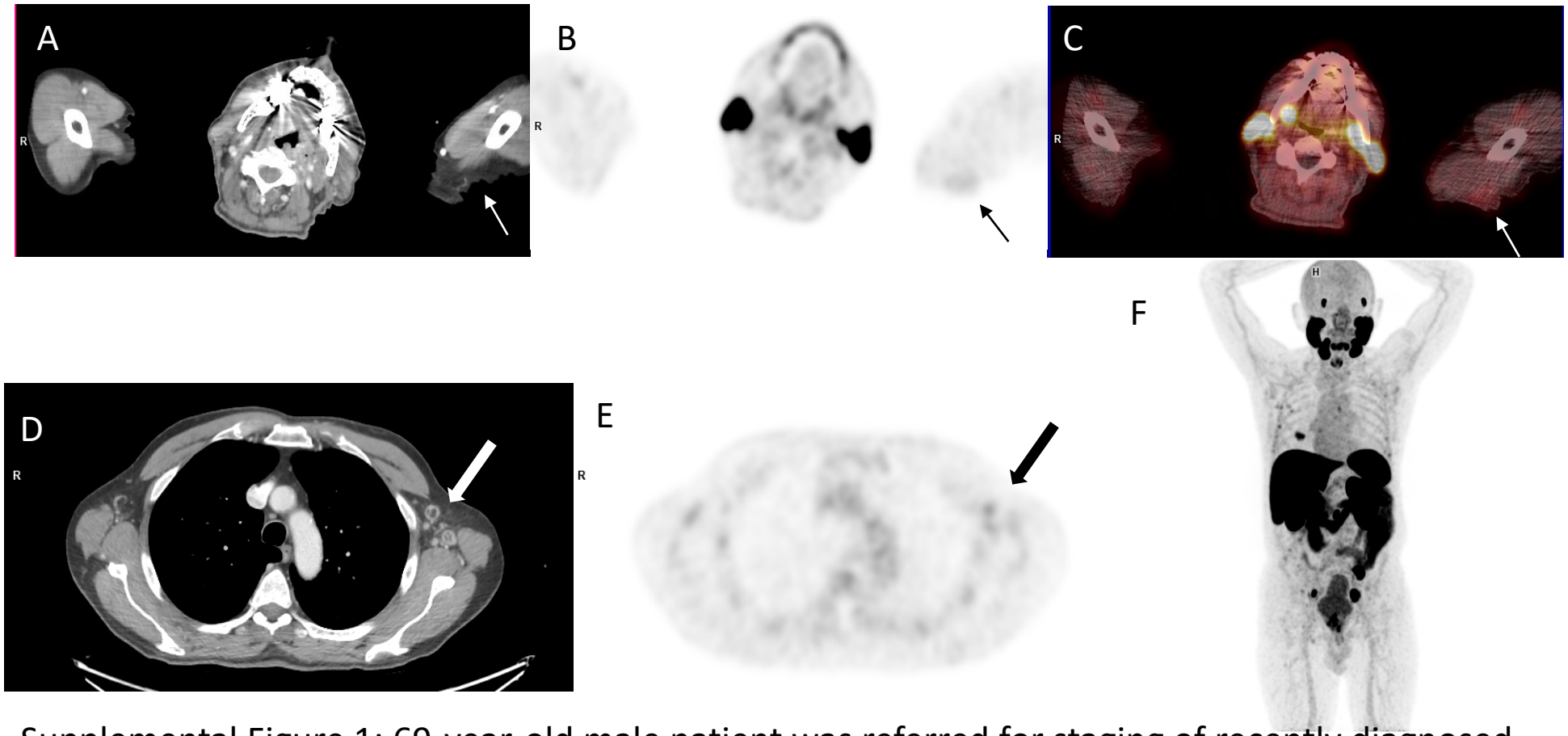


Figure 5: 57-year-old female with vulvar melanoma was referred to FDG PET/CT for staging (A) and 53 days later for evaluation of treatment response (B). Increased FDG uptake seen in the right arm and in the ipsilateral axilla (black arrows) on the baseline PET MIP (A) has completely resolved on the second study. MIP=maximum intensity projection.

Graphical Abstract

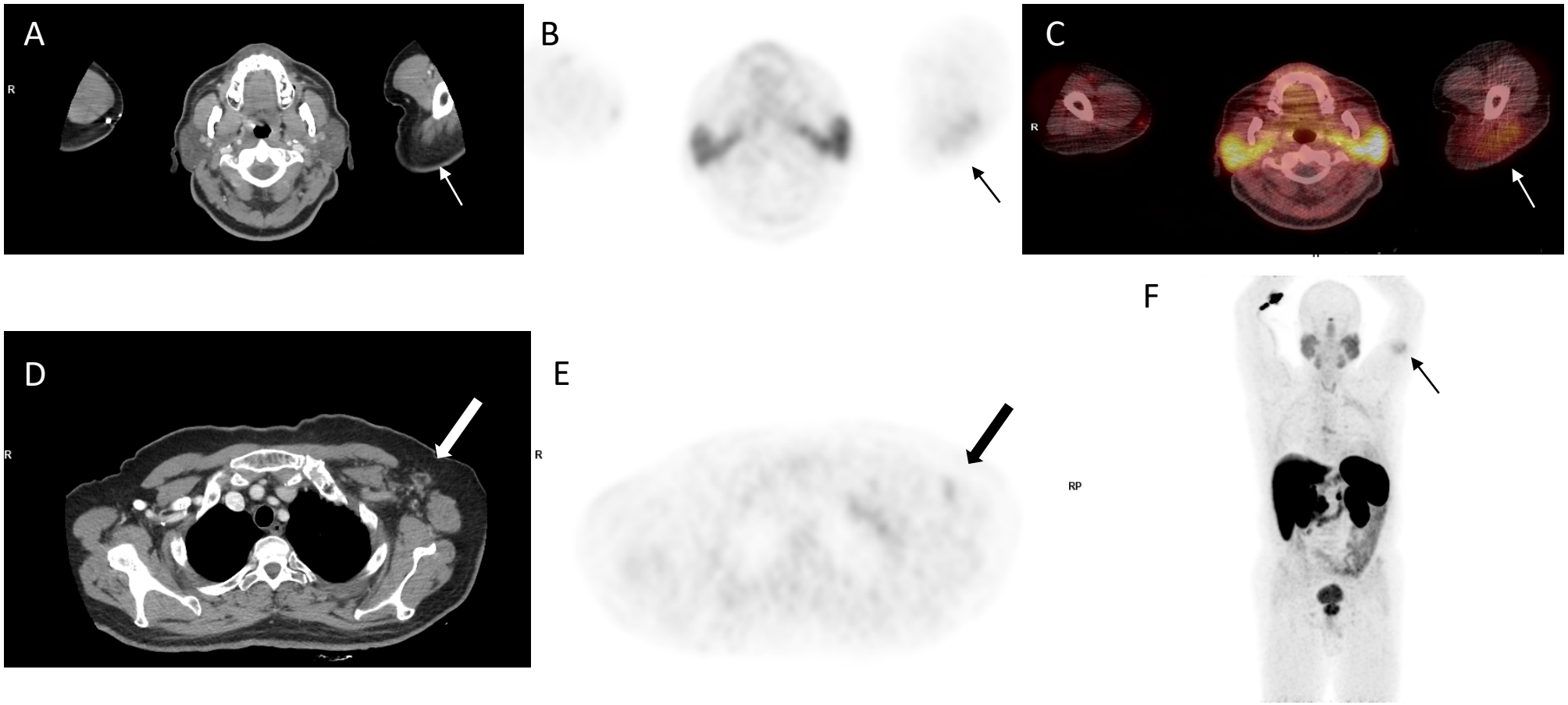


Supplemental Figure 1



Supplemental Figure 1: 69-year-old male patient was referred for staging of recently diagnosed prostate cancer. F18 PSMA PET/CT was performed one day after COVID19 vaccination. Selected transaxial CT (A, D), and PET (B, E) slices at the level of posterior arm uptake and axillary lymph nodes, fused image (C) at the level of posterior arm uptake and MIP (F) demonstrate low grade uptake in the left posterior arm, SUV max 1.0 (thin black and white arrows) and in left axillary lymph nodes measuring up to 1.5 cm in short axis (thick white arrow) with SUV max 2.1. The MIP also shows high grade activity in the prostate primary tumor, pelvic lymphadenopahty and bone metastases the pelvis and a right rib. MIP=maximum intensity projection.

Supplemental Figure 2



Supplemental Figure 2: 62-year-old male patient with pancreatic neuro-endocrine tumor was referred for a routine Ga68 DOTA TATE PET/CT follow up study. The study was performed two days after COVID19 vaccination. Selected transaxial CT (A, D), and PET (B, E) slices at the level of posterior arm uptake and axillary lymph nodes, fused image (C) at the level of posterior arm uptake and and MIP (F) demonstrate low grade uptake in the left posterior arm, SUV max 2.4 (thin black and white arrows) and in left axillary nodes measuring up to 0.9 cm in short axis with benign appearances (thick white and black arrows), SUV max 1.6. High tracer accumulation visualized in the prostate. MIP=maximum intensity projection.