Challenging Axillary Lymph-Nodes on F-18-FDG, F-18-Choline and Ga-68-DOTATOC PET/CT in Cancer Patients throughout Covid-19 Vaccination Era

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Abstract

Objectives: unexpected detection of axillary lymphadenopathy (AxL) in cancer patients (Pts) represents a real concern during COVID-19 vaccination era. Benign reactions may take place after vaccine inoculation, confounding image interpretation in patients undergoing F-18-FDG, F-18-Choline and Ga-68-DOTATOC PET/CT. It may simulate loco-regional metastases/disease. To assess PET/CT findings after COVID-19 vaccination in cancer patients and the consequent impact on their management.

Methods: we evaluated 333 patients undergoing PET/CT (257 F-18-FDG, 54 F-18-Choline and 23 Ga-68 DOTATOC) scans after first vaccination with mRNA vaccine (Pfizer-BioNTech). Uptake index (SUVmax) of suspected AxL was defined significant when the ratio >1.5 as compared to the contralateral inoculation site. Besides, co-registered CT (Co-CT) features of target lymph-nodes were evaluated. Nodes with aggregate positivity were further investigated.

Results: overall, the prevalence of apparently positive lymph-nodes on PET scans was 17.1% during vaccination era. 107 Pts had undergone PET/CT before COVID-19 pandemic and only 3 shown reactive lymph-nodes with a prevalence of 2.8% ($p<0.001$ as compared to vaccination era). 84.2% exhibited benign characteristics on Co-CT images and only 9 Pts needed additional appraisal.

Conclusions: the correct interpretation of images is crucial to avoid unnecessary management changes and to rule out invasive procedures in cancer Pts undergoing diagnostics. An accurate anamnestic interview and the precise assessment of nodes' Co-CT characteristics when performing PET/CT may help to address the diagnostic hypothesis.

Key Points

1. The correct interpretation of PET/CT images avoid unnecessary management changes in cancer patients undergoing SARS-CoV-2 vaccination
2. The prevalence of apparently positive lymph-nodes on PET scans was higher during vaccination era as compared to that of patients who had undergone PET/CT before COVID-19 pandemic.
3. A significant number of patients exhibited benign characteristics on Co-registered-CT images and only few needed additional appraisals.

1. Introduction

The coronavirus disease 2019 (Covid-19) pandemic has caused millions of deaths with great commitment by world health services [1]. The scientific endeavor has led to the development of vaccines useful to reduce infections, transmissibility, and mortality [2]. The Pfizer/BioNTech vaccine was the first SARS-CoV-2 (Covid-19) vaccine to be approved by Regulatory Agencies [3–4], followed by the Oxford/AstraZeneca and Moderna vaccines [5]. The administration of vaccines has been a priority for health workers and the most fragile patients such as elderly and immunosuppressed [6].

Mild systemic symptoms like fatigue, myalgia, and headache along with locoregional adverse reactions, such as shoulder pain and erythema have been reported after COVID-19 vaccination, as for other types of vaccines [7–8]. However, recent data have suggested a higher incidence of local reactive lymphadenopathy in the axillary and neck regions at the side of injection as compared to other vaccines [9]. With the increasing use of vaccines, the presence of lymphadenopathies has become a diagnostic dilemma for cancer patients. In this setting the differential diagnosis concerning adenopathy is mandatory to exclude metastatic or recurrent cancers [10]. Accordingly, the United States Society of Breast Imaging, the Canadian Society of Breast Imaging, the Canadian Association of Radiologists, and a multidisciplinary team (MDT) of experts from three leading cancer centers in USA [11] have released recommendations about the management of lymphadenopathy due to Covid-19 vaccination. Cases of ipsilateral adenopathy in the axillary and supraclavicular regions following deltoid Covid-19 vaccinations are quickly emerging in the international literature and are being increasingly referred to healthcare services for advice and management [12].

The PET/CT (Positron Emission Tomography - Computed Tomography) holds a widely validated and recognized role in cancer diagnostics [13–15]. On the other hand, the most common radiotracers used in PET/CT imaging are not cancer specific at all [13]. Among the others the radio-labeled glucose analogue F-18-2-fluoro-2-deoxyglucose (F-18-FDG) is the most employed tracer in PET imaging. It accumulates both in cancer and non-cancer cells having high rate of glycolysis, such as activated leukocytes in inflammatory conditions [16]. As a result, the clinical use of (F-18-FDG) PET/CT for assessing inflammatory and infectious diseases is increasing worldwide [17]. Moreover, the tracer F-18-Choline is used for the appraisal of prostate cancer. It is a radiolabeled precursor of phosphatidylcholine, an essential phospholipid of cell membranes. Both in cancer cells and reactive lymph-nodes the enhanced choline uptake is explained by the increased mitogenic activity, which requires more membrane precursors [18]. Finally, radiolabeled somatostatin analogues, such as Ga-68-DOTATOC, -DOTANOC and -DOTATATE are utilized to assess neuroendocrine tumors expressing somatostatin receptors. Nevertheless, lymphatic tissues including reactive lymph-nodes might accumulate this radioligand [19–20].

We aimed to study PET/CT findings after COVID-19 vaccination in cancer patients and the consequent impact on their management.

2. Materials And Methods

2.1 Patients

We assessed 333 oncological patients (overall; 143 women; 65 ± 13 years) who underwent F-18-FDG (132 women; 63 ± 13 years), or F18-Choline (all men; 74 ± 8 years) or Ga-68-DOTATOC (11 women; 60 ± 13 years) PET/CT scans from March to May 2021 for staging, re-staging or follow-up assessment. Aggregated individual data are presented in table 1.

Table 1

Patients' individual data

Characteristics	Values
Total number of patients	333
Age at enrollment, year, median (range)	65 (21-97)
Sex M:F	190:143
Cancer diagnosis, pts (%)	
<i>Prostate</i>	56 (16.8)
<i>Gastro-enteric</i>	44 (13.2)
<i>Breast</i>	42 (12.6)
<i>Lymphomas and hematological diseases</i>	39 (11.7)
<i>Lung</i>	38 (11.4)
<i>Gynecologic</i>	28 (8.4)
<i>Head and Neck</i>	25 (7.5)
<i>GEP/non-GEP NET</i>	23 (6.9)
<i>Melanomas</i>	9 (2.7)
<i>Urothelial</i>	9 (2.7)
<i>Testis</i>	5 (1.5)
<i>Thyroid</i>	4 (1.2)
<i>Others</i>	11 (3.3)
PET/CT diagnostic inquiry, pts (%)	
<i>Staging</i>	93 (27.9)
<i>Re-staging</i>	156 (46.9)
<i>Follow-up</i>	84 (25.2)
PET suspected lymphadenopathy (<i>female/male</i>)	
<i>F-18-FDG</i>	31/16
<i>F-18-FCH</i>	0/8
<i>Ga-68-DOTATATE</i>	0/2

GEP, Gastroenteropancreatic; NET, Neuroendocrine Tumors; Others, Thymus cancer, Sarcomas, Unknown origin; PET/CT, Positron Emission Tomography/Computed Tomography; F-18-FDG, F-18-2-fluoro-2-

deoxyglucose; F-18-FCH, F-18-fluoro-choline; Ga-68-DOTATATE, Gallium-68-DOTA-0-Tyr3-Octreotate

From the beginning of COVID-19 vaccination era, all patients referred either for F-18-FDG, F-18-Choline or Ga-68-DOTATOC PET/CT scans were invited to report about the COVID-19 vaccination type they received, as well as timing and anatomical site of inoculation. To make our observations as homogeneous as possible, only patients vaccinated with the first dose of Pfizer-BioNTech, presenting age at entry of 18 years or older and negative pregnancy test were evaluated. Patients had undergone comprehensive re-evaluation including clinical and oncological data. Insufficient information about the kind of vaccine and/or the anatomical region of injection constituted a reason for exclusion. Patients whose lymph-node sites were previously treated by recent external radiotherapy before PET/CT imaging were excluded from this study to avoid confounding items.

We also collected data from PET/CT scans in the same patients before COVID 19 pandemic, if any, as reference.

Procedures included in the study were submitted to our institutional review board for approval. All patients who underwent the study signed an informed consent form in accordance with the Declaration of Helsinki.

2.2 Imaging technique

The patients were well-hydrated before receiving F-18-FDG (370–555 MBq), F-18-Choline (230–300 MBq) or Ga-68-DOTATOC (250–300 MBq) via a peripheral venous catheter on the contralateral site of vaccination. Sixty minutes after the tracer injection, PET and modulated low dose CT were carried out with a commercial PET/CT scanner (GE Discovery VCT scanner) that combined a PET scanner and a Light Speed VCT sixty-four row MDCT system. MDCT (pitchx 1.5; 120 mAs; 120 kVp) was performed without contrast medium. The PET scanning was subsequently performed, acquiring 3 min per bed position and six to eight bed per patient depending on patient height encompassing the whole body. The raw CT data were reconstructed into transverse images with a 3.75-mm section thickness. Sagittal and coronal CT images were generated by reconstruction of the transverse data. Raw PET data were reconstructed with and without attenuation correction into transverse, sagittal, and coronal images. Attenuation correction was based on CT attenuation coefficients, which were determined by iterative reconstruction. Patients were fasted and blood glucose levels were determined only before F-18 FDG administration (cut-off value of less than 8.3 mmol/L; 150 mg/dL).

2.3 Imaging evaluation

All hybrid images were reviewed by using PET/CT fusion software (Volumetrix for PET-CT and AW volume share 4.5, GE Healthcare). The PET studies were evaluated both visually and semi-quantitatively by SUVmax by two nuclear medicine physicians with 20 yrs of expertise. Then, the SUVmax body weight

corrected values were determined by using the vendor-provided software. According to the method previously used by Thomassen et al. [21], only vaccine-draining lymph-nodes (target lesion) that had shown a SUVmax ratio ≥ 1.5 when compared to the contralateral site, were circumspectly studied on CT.

Bilaterality and multi-centricity were assessed, if any. All target lesions were visually assessed for shape and hilus characteristics and measured at CT in one maximum diameter at least, in short axis images by using the above-mentioned vendor-provided software. A target lesion was defined as reactive lymph-node if two of the three abovementioned features indicated a benign nature (oval in shape; clearly evident hilus; $<10\text{mm}$ diameter) with soft-tissue/mediastinal window settings, along with metabolic findings. Patients with lesions mismatching with normal anatomy or physiology and suspected of disease recurrence/relapse were referred for ultrasound and biopsy, if any. Study algorithm is reported in figure 1.

2.4 Follow-up assessment

Patients for whom a short follow-up PET/CT imaging was scheduled according to clinical needs, were re-evaluated for both metabolic and morphological findings.

3. Statistical Analysis

Statistical analysis was performed using MedCalc Software version 20.014. Numeric variables and frequencies of categorical variables were calculated. Fisher’s exact test was used to evaluate the proportions of incidental findings observed before and after vaccinations. A p value < 0.05 was considered statistically significant.

4. Results

Two hundred fifty-six patients who underwent F-18- FDG PET/CT scan, 54 who received F-18-Choline and 23 referred for Ga-68-DOTATOC were eligible, respectively.

Overall, the prevalence of apparently positive axillary lymph-nodes on PET scans was 17.1% during vaccination era whereas it was 18.3% for patients who received F-18-FDG, 14.8% for F-18-Choline and 8.7% Ga-68-DOTATOC, respectively.

Among the 333 patients 107 had undergone PET/CT before COVID-19 pandemic and only 3 shown reactive lymph-nodes with a prevalence of 2.8% ($p < 0.001$ as compared to vaccination era).

The range of SUVmax in positive lymph-nodes, irrespective of the tracer used, was 1.8 to 4.7, with a mean SUVmax of 2.8 ± 1.1 . Data of the metabolic results according to the tracer employed are shown in table 2. The average time elapsed from vaccination was of 16 ± 7 days for F-18- FDG, 22 ± 5 days for the F-18-Choline and 26 ± 7 days Ga-68-DOTATOC, respectively.

Table 2

SUVmax and timing from vaccination in cancer patients with hyper-metabolic lymph-nodes according to radiotracers

PET/CT tracers	Total scans post vaccination March-May 2021	Suspected Axillary lymphadenopathy # (%)	SUVmax Mean (SD)	SUVmax Range	Average time elapsed from vaccination (days)
F¹⁸FDG	257	47 (18.3)	2.95 ± 1.2	2.0-4.7	16 ± 7
F¹⁸Choline	54	8 (14.8)	2.36 ± 0.9	1.8–2.9	22 ± 5
Ga⁶⁸DOTATOC	23	2 (8.7)	2.27 ± 0.7	1.9–2.6	26 ± 7
SUVmax, Standard Uptake Value; F-18-FDG, F-18-2-fluoro-2-deoxyglucose; F-18-FCH, F-18-fluoro-choline; Ga-68-DOTATATE, Gallium-68-DOTA-0-Tyr3-Octreotate					

Fifty-seven patients had an apparently positive lymph-node on PET/CT scan (hypermetabolic/receptor overexpression; Fig. 2), none bilateral, two patients shown multiple ipsilateral nodes.

Among them 48 (84.2%) showed benign characteristics on co-recorded CT images and were considered disease-free avoiding further investigations. Nine patients (15.8%) presented suspected CT features (round shape, max diameter > 10mm and/or not evident hilus), 7 patients underwent ultrasound appraisal that excluded adenopathy disease, two had a further mdc CT; only for one of them a metastatic disease was evoked.

Twenty-six of 57 (45.6%) patients who apparently presented positive lymph-node on PET scan throughout the vaccination era have had a PET/CT also before COVID-19 pandemic; none showed suspected axillary nodes at that time.

No muscular and subcutaneous uptake on the deltoid region were observed. The shortest time range from vaccination was 6 days, when normally the non-specific deltoid's muscular uptake has already disappeared.

Also, twenty-eight patients of 57 (49.1%) with previous target lesion received a negative short-term PET/CT follow-up within three months. Of note, 23/47 (49%) patients who underwent F-18-FDG PET/CT and exhibited suspected axillary nodes suffered from cancers such as breast, melanoma and lymphoma, where the presence or the absence of lymphatic spread would have really changed their management. None had disease confirmed.

5. Discussion

To our knowledge this is the first study assessing the PET/CT findings with different tracers after COVID-19 vaccination in cancer patients and the consequent impact on their management.

The prevalence of locoregional PET positive lymph-nodes after SARS-CoV-2 vaccine inoculation was significantly higher as compared to pre-COVID-19 era.

After recently vaccine administration reactive lymphadenopathy in the ipsilateral axillary and/or supraclavicular area is most likely to occur. Unfortunately, it represents a serious challenge in cancer patients who undergo F-18-FDG, since it might mimic disease onset, relapse, or recurrence [22–25] whereas for F-18-Choline and Ga-68 DOTATOC PET/CT scans it may constitute only an unusual finding. Our patients were referred for staging, re-staging or follow-up to PET/CT examinations with different radioligands according to their diagnostic inquiry. Incidentally, the rate of apparently positive lymph-nodes was significant in this setting. Although our findings may appear not astonishing, they deserve caution, particularly for cancer patients as recently reported by some other authors [23–25]. The correct interpretation of this secondary effect of vaccine is of primary importance to avoid unnecessary changes in patients' management and to rule out undue biopsies as well as to differentiate them from malignancies, recurrence and/or metastases.

We focused on the importance of a correct anamnestic interview concerning recent vaccination in oncological patients undergoing diagnostics and particularly on the precise appraisal of co-recorded CT features when they go through PET/CT scans. In this study patients were invited to report about vaccine inoculation from the beginning of COVID-19 vaccination era. In addition, suspected lymph-nodes on the PET scan were reviewed on co-registered CT for malignancy [25]. According to daily practice, nodes with aggregate positivity were further investigated by US or mdc CT, at least [26]. This approach avoided undue further investigations for most of patients and unnecessary invasive procedures [27] for those supposed positive. In fact, 84% of patients suspected positive on PET scan resulted to have benign features on co-recorded CT images. In only one case imaging confirmed malignancy.

The prevalence of the abovementioned incidental findings was significant for all the tracers investigated according to their different frequency in use (see Ga-68 peptides). From a physio-pathological point of view, F-18 FDG, as glucose analogue, distributes in both cancer and inflammatory glucose-utilizing cells [16–17, 28] and, with different pathways, inflammatory cells may concentrate the F-18-Choline and Ga-68-DOTATOC [18–20].

Recently, some authors [23–25] have reported similar results but, in smaller cohorts, sometimes in form of case report, using one tracer and after adenovirus-based vaccine which is known to elicit inflammatory response [29]. Our study was conducted collecting data from 333 consecutive patients, irrespective of the tracer used, who underwent mRNA SARS-CoV-2 vaccination and reporting on findings both in pre-COVID-19 period and thereafter in a subset of patients. Almost 50% of patients had PET/CT scan negative in this two moments confirming the incidental nature of the observations during vaccination age.

Moreover, we renew the importance of the correct interpretation of these incidental findings during metabolic imaging in cancer patients to prevent unjustified misapprehension and the temporal enlargement of diagnostic path, as well as unnecessary changes in therapy and management.

When PET positive, the uptake index (SUVmax) was significant in all the three radiotracers satisfying the method of Thomassen [21] and justifying the need for further caution.

Concerning the nodes' metabolic positivity duration few information are still available. It seems that reactive processes to vaccination may last up to 70 days [30–31]. Indeed, the longer the time elapsed the lower the tracers' uptake intensity once scans performed newly. Accordingly, in our patients the difference in SUVmax values between the radiotracers could be explained by the time elapsed from vaccination and the different pharmacodynamic characteristics as showed in table 2.

Finally, we suggest careful interpretation of PET/CT data in cancer patients who recently undergo SARS-CoV-2 vaccine (and others vaccine as well) [32–36] considering the vaccine site of injection and addressing for subsequent imaging appraisal for the ambiguous lymph-nodes to confirm or reject the diagnostic hypothesis. In doubtful cases, the biopsy remains the last useful tool.

6. Perspectives

We aim to collect more data, especially from patients vaccinated with different vaccines, to evaluate any differences in terms of uptake's intensity and duration as well as from patients after the second and/or the booster dose.

Abbreviations

AxL: axillary lymphadenopathy

Pts: patients

F-18-FDG: fluoride-18-2-fluoro-2-deoxyglucose

Ga-68 DOTATOC: gallium-68 DOTA-D-Phe1-Tyr3-octreotide

PET/CT: positron emission tomography/computed tomography

SUVmax: maximum standardized uptake

Co-CT: co-registered computed tomography

-DOTANOC:(1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid)-1-Nal3-octreotide

-DOTATATE: DOTA-0-Tyr3-Octreotate

Declarations

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

Figure 1

study algorithm. PET/CT: positron emission tomography/computed tomography; F-18-FDG: F-18-2-fluoro-2-deoxyglucose; F-18-FCH: F-18-Choline; Ga-68-DOTATOC: Ga-68 somatostatin analogue; Co-registered CT: CT acquired during hybrid PET/CT; CT benign features: maximum diameter <10 mm, evident hilus, oval shape; outsource CT: additional CT scan.

Figure 2

PET/CT scans (A;C;D) in cancer patients showing doubtful axillary lymphadenopathy after mRNA SARS-CoV-2 vaccination. A: F-18-FDG scan in 35 yrs-old Hodgkin lymphoma woman with suspected lymph-nodes in right axilla on PET and benign features on both co-registered CT and subsequent ultrasound (B, diameters are shown). C: F-18-Choline in 83 yrs-old man complying with castrate sensitive metastatic prostate cancer presenting left axillar lymph-node uptake and benign characteristics on co-registered CT. D: Ga-68-DOTATOC in 72 yrs-old man exhibiting gastroenteropancreatic (GEP-NET) cancer, with PET positive right axillary lymph-node and negative co-registered CT.