Large-scale worldwide vaccination programs against the 2019 coronavirus diseases (COVID-19) are being rapidly deployed. As this vaccination is becoming more widespread, we are observing an increase of patients with previous vaccination against COVID-19 who underwent 18F-FDG PET/CT for different indications (i.e., cancer staging or restaging or evaluation of inflammatory diseases). Knowledge of vaccination-related effects is important to prevent wrong interpretations and alleviate patient concern during diagnostic imaging procedures. The earliest publications on this topic occurred in the field of breast imaging, where COVID-19 vaccine-induced lymphadenopathy was cited as a cause of unilateral axillary lymphadenopathy [1].

Taking into account recent literature data, we are also observing a rapid increase of published scientific articles reporting PET findings with different radiotracers in patients with previous vaccination against COVID-19 [2–21, 27, 28]. Overall, these articles are mainly case reports or small case series recently published by research groups from different countries worldwide reporting PET findings in COVID-19 vaccine recipients who underwent PET/CT or PET/MRI with different radiotracers for several indications [2–21] (Table 1). Most of the described patients underwent vaccination against COVID-19 from 1 day to 3 weeks before 18F-FDG PET/CT. About the 18F-FDG PET findings after COVID-19 vaccination, most of the published articles reported increased radiopharmaceutical uptake in axillary and subpectoral lymph nodes at the same side of the vaccine inoculation. Increased uptake in deltoid muscle corresponding to the vaccine inoculation site was also frequently described. Beyond the axilla, increased radiopharmaceutical uptake in supraclavicular and lower cervical lymph nodes was also illustrated in some reports. The hypermetabolic lymph nodes were normal-sized or enlarged. Less frequently, diffuse splenic 18F-FDG-uptake was also described. All these described sites of increased radiopharmaceutical uptake were interpreted as reactive due to immune response after recent vaccination against COVID-19 [2–10, 12–15, 17–21].

Radiopharmaceutical uptake in axillary lymph nodes was also described after PET/CT with radiolabelled choline or somatostatin analogues in COVID-19 vaccination recipients [11, 16].

We would like to underline that the main advantages of these case reports and small case series is to inform the nuclear medicine community about the increasing appearance of these PET findings following COVID-19 vaccination.

On the other hand, these findings are not surprising for the nuclear medicine physicians for several reasons [22, 23]. First of all, it is well known that inflammatory cells may take up 18F-FDG due to their increased glucose uptake and glycolytic activity. Therefore, 18F-FDG is not a specific tracer for cancer cells and reactive lymph nodes may take up 18F-FDG mimicking neoplastic lesions at PET. For these reason, 18F-FDG PET/CT may also be used to evaluate inflammatory and infectious diseases with good diagnostic accuracy as demonstrated by several evidence-based manuscripts [24].

It is also not surprising that reactive lymph nodes may show increased 18F-FDG uptake and normal size in some
| First author | Year | Country | Age/sex of patients | Vaccine manufacturer | Inoculation site | Time from vaccine to PET scan | PET indication | PET tomograph | PET tracer | PET findings |
|--------------|------|---------|---------------------|----------------------|------------------|-----------------------------|----------------|---------------|------------|-------------|
| Ahmed [2]    | 2021 | UK/Kuwait | 86/F | Pfizer | Left deltoid muscle | 6 days** | Melanoma (restaging) | PET/CT | **18**F-FDG | Uptake in left deltoid muscle and in normal-sized left subpectoral LN |
| Avner [3]    | 2021 | Israel  | 57/F | Pfizer | Left arm | 6 days** | Melanoma (restaging) | PET/CT | **18**F-FDG | Uptake in left proximal arm, enlarged left axillary and subpectoral LN |
| Bauckneht [4] | 2021 | Italy  | 44/M | Pfizer | Left arm | 1 day** | Target for LN biopsy | PET/CT | **18**F-FDG | Uptake in left proximal arm and in enlarged left axillary LN |
| Brown [5]    | 2021 | UK     | 67/F | NR | Left arm | 2 weeks | Breast cancer (restaging) | PET/CT | **18**F-FDG | Uptake in normal-sized left axillary and subpectoral LN |
|              |      |         | 48/F | NR | Right arm | 3 weeks | Breast cancer (restaging) | PET/CT | **18**F-FDG | Uptake in right proximal arm and in normal-sized right axillary LN |
|              |      |         | 83/F | NR | Left arm | 2 weeks | Breast cancer (restaging) | PET/CT | **18**F-FDG | Uptake in normal-sized left axillary and subpectoral LN |
|              |      |         | 66/F | NR | Left arm | <3 weeks | Breast cancer (restaging) | PET/CT | **18**F-FDG | Uptake in a normal-sized left subpectoral LN |
| Doss [6]     | 2021 | USA     | 70/F | Pfizer | Left arm | 2 days** | Lymphoma (restaging) | PET/CT | **18**F-FDG | Uptake in left deltoid muscle and in normal-sized left axillary LN |
| Eifer [7]    | 2021 | Israel  | 72/F | Pfizer | Right deltoid muscle | 10 days | Breast cancer (restaging) | PET/CT | **18**F-FDG | Uptake in right deltoid muscle and in normal-sized right axillary LN |
| Finnegon [8] | 2021 | Ireland | 50/M | Pfizer | Left arm | 10 days** | NR (staging) | PET/CT | **18**F-FDG | Uptake in left axillary LN |
| Hanneman [9] | 2021 | Canada  | 56/F | Pfizer | Left deltoid muscle | 1 day** | Cardiac diseases (research) | PET/MRI | **18**F-FDG | Uptake in enlarged left axillary LN |
| First author | Year  | Country | Age/sex of patients | Vaccine manufacturer | Inoculation site | Time from vaccine to PET scan | PET indication            | PET tomograph | PET tracer | PET findings                                                                 |
|-------------|-------|---------|---------------------|----------------------|-----------------|-------------------------------|--------------------------|---------------|------------|--------------------------------------------------------------------------------|
| Johnson     | 2021  | USA     | NR/F                | Moderna              | Left deltoid muscle | 10 days*                      | Parotid cancer (staging) | PET/CT       | 18F-FDG    | Uptake in left axillary and supraclavicular LN                                |
|             |       |         | NR/F                | NR                   | Left deltoid muscle | 2 weeks*                      | Oropharyngeal cancer (restaging) | PET/CT       | 18F-FDG    | Uptake in left axillary and supraclavicular LN                                |
| Lu          | 2021  | USA     | 64/F                | Pfizer               | Both arms          | 6 weeks* and 3 weeks**         | Carcinoid (restaging)     | PET/CT       | 68Ga-DOTATATE | Uptake in bilateral axillary and subpectoral LN                                |
| McIntosh    | 2021  | USA     | 40/F                | Moderna              | Left deltoid muscle | 3 days                        | Breast cancer (staging)   | PET/CT       | 18F-FDG    | Uptake in left axillary, supraclavicular and lower cervical LN                |
|             |       |         | 72/F                | Pfizer               | Right deltoid muscle | 11 days*                      | Breast cancer (restaging) | PET/CT       | 18F-FDG    | Uptake in normal-sized right axillary LN                                     |
|             |       |         | 72/F                | NR                   | NR                | 4 days**                      | Lung nodule (characterization) | PET/CT       | 18F-FDG    | Uptake in right axillary LN                                                   |
|             |       |         | 40/F                | Moderna              | NR                | 3 days                        | NR                        | PET/CT       | 18F-FDG    | Uptake in enlarged left axillary LN                                           |
|             |       |         | 59/M                | NR                   | NR                | 14 days                       | Lung cancer (staging)     | PET/CT       | 18F-FDG    | Uptake in enlarged left axillary, supraclavicular and lower cervical LN       |
|             |       |         | 68/F                | Moderna              | Left deltoid muscle | 9 days                        | Cervical cancer (restaging) | PET/CT       | 18F-FDG    | Uptake in left axillary LN                                                    |
| Moghimi     | 2021  | Canada  | 71/M                | NR                   | Left deltoid muscle | 6 days                        | Melanoma (staging)        | PET/CT       | 18F-FDG    | Uptake in left deltoid muscle and left axillary and lower cervical LN         |
| Nawwar      | 2021  | UK/Egypt| 76/F                | AstraZeneca          | Left arm           | 14 days                       | Myeloma (restaging)       | PET/CT       | 18F-FDG    | Uptake in left deltoid muscle and left axillary LN                            |
| Nawwar      | 2021  | UK/Egypt| 70/M                | AstraZeneca          | Left arm           | 7 days                        | Lung cancer (staging)     | PET/CT       | 18F-FDG    | Uptake in left axillary LN                                                    |
| Nawwar      | 2021  | UK/Egypt| 75/M                | AstraZeneca          | Left arm           | 3 days                        | Prostate cancer (restaging) | PET/CT       | 18F-choline | Uptake in left deltoid muscle and left axillary LN                            |
| First author | Year | Country | Age/sex of patients | Vaccine manufacturer | Inoculation site | Time from vaccine to PET scan | PET indication | PET tomograph | PET tracer | PET findings |
|--------------|------|---------|---------------------|----------------------|-----------------|-------------------------------|----------------|---------------|------------|-------------|
| Özütemiz [17] | 2021 | Turkey  | 32/F                | Pfizer               | Left arm        | 6 days**                      | Melanoma (restaging) | PET/CT       | 18F-FDG    | Uptake in left arm and enlarged left axillary LN |
|               |      |         |                     |                      | 46/F            | 7 days**                      | Breast cancer (restaging) | PET/CT       | 18F-FDG    | Uptake in left deltoid muscle and enlarged left axillary and supraclavicular LN |
| Smith [18]    | 2021 | USA     | 40/F                | Pfizer               | Left arm        | 1 day**                       | Osteosarcoma (restaging) | PET/CT       | 18F-FDG    | Uptake in left deltoid muscle and in normal-sized left axillary and supraclavicular LN |
| Steinberg [19]| 2021 | USA     | 65/F                | Moderna              | Right deltoid muscle | 5 days*                       | Lung nodules (characterization) | PET/CT       | 18F-FDG    | Uptake in right deltoid muscle, right axillary LN and diffuse splenic uptake |
| Ulaner [20]   | 2021 | USA     | 68/M                | Moderna              | Left arm        | 3 weeks*                      | Melanoma (restaging)    | PET/CT       | 18F-FDG    | Uptake in left axillary LN |
| Xu [21]       | 2021 | USA     | 72/M                | Pfizer               | Left arm        | 2 days                        | Lymphoma (restaging)    | PET/CT       | 18F-FDG    | Uptake in left deltoid muscle and left axillary LN |

CT computed tomography, F female, 18F-FDG 18F-fluorodeoxyglucose, LN lymph nodes, M male, MRI magnetic resonance imaging, NR not reporte, PET positron emission tomography

* After the first dose of vaccine

** After the second dose of vaccine
cases, because functional abnormalities as revealed by $^{18}$F-FDG PET may precede morphological alterations detected by CT or MRI [24]. Similar to $^{18}$F-FDG, radiopharmaceutical uptake in reactive lymph nodes has been already widely described with PET using radiolabelled choline [25] or somatostatin analogues [26].

Moreover, increased $^{18}$F-FDG uptake in hypermetabolic lymph nodes due to vaccine-related immune response has been already described in several patients who underwent different types of vaccinations beyond those against COVID-19 [22], therefore this is not a significant novelty.

Furthermore, we should also take into account that a clear information about the prevalence of these PET findings in COVID-19 vaccine recipients cannot be obtained by using these case reports and small case series only, because these manuscripts are strongly affected by publication bias; in other words, positive results (presence of increased radiopharmaceutical uptake at PET with different radiotracers after vaccination) are more likely to be published compared to negative findings (absence of increased radiopharmaceutical uptake at PET with different radiotracers after vaccination).

Conversely, two interesting cohort studies from Israel demonstrated that the detection of hypermetabolic axillary lymph nodes at $^{18}$F-FDG PET/CT is quite common after vaccination against COVID-19, mainly after the inoculation of the second dose of COVID-19 vaccine (Table 2) [27, 28]. However, accurate data reporting the time required after COVID-19 vaccination to allow for resolution of $^{18}$F-FDG uptake in sites of vaccine-related immune response are currently lacking.

Notably, taking into account all the evidence-based data available so far, we cannot state that PET with $^{18}$F-FDG or other radiopharmaceuticals are really able or may be used to detect COVID-19 vaccination sequelae as well as for COVID-19 [29, 30]. It could be interesting to perform a trial in the future for evaluating if the increased $^{18}$F-FDG uptake associated with the vaccination could give some useful information on the immune response for vaccinated individuals (as example: duration of immunity) or showing different behaviours when using different types of vaccine.

To date, we can only state that, in a still unclear percentage of COVID-19 vaccine recipients, some radiopharmaceutical uptake patterns as those described in the available articles may be found and these may be due to vaccine-related immune response. These PET findings will likely increase in number in the next months due to the parallel increase of global immunization against COVID-19.

Nuclear medicine physicians should be (already) able to recognize the possible PET findings due to COVID-19 vaccination, in particular both hypermetabolic lymph nodes (mainly axillary) and ipsilateral increased radiopharmaceutical uptake in the deltoid muscle at $^{18}$F-FDG PET. Documenting vaccination history and vaccine injection location at the time of PET scan is (already) extremely useful for PET reporters to avoid false interpretation, useless further diagnostic examinations, unnecessary changes in management and additional patient anxiety and this should be valid for all (COVID-19 and beyond) vaccine recipients.

### Declarations

**Conflict of interest** The authors declare that they have no financial or non-financial competing interests.

**Ethical approval** This article does not contain any studies with human participants or animals.

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