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ORIGINAL ARTICLE

Inactivated and mRNA COVID-19 Vaccines Affect ^{18}F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Oncology Patients

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ABSTRACT

Introduction: *We aimed to analyse the effect of coronavirus disease 2019 (COVID-19) vaccination on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging findings in cancer patients.*

Methods: *A total of 165 oncology patients who underwent FDG PET/CT between 1 May 2021 and 30 September 2021 after their first or second COVID-19 vaccination with were included in this retrospective study. The occurrence and pattern of FDG uptake at the injection site (usually deltoid), ipsilateral axillary and other regional lymph nodes, were measured.*

Results: *Overall, the incidence of FDG-avid ipsilateral regional nodal uptake was 26.7% (44/165), with a median maximal standardised uptake value of 3.2 (range, 1.7-13.8). Vaccine-associated hypermetabolic lymphadenopathy (VAHL) was found in 11.4% (5/44) of the subjects beyond 6 weeks after vaccination. VAHL was more common in patients receiving BioNTech-Fosun mRNA vaccine (compared with patients receiving the Sinovac CoronaVac inactivated vaccine), and in women ($p < 0.05$).*

Conclusion: *VAHL is common and can be observed beyond 6 weeks after vaccination. It was seen more frequently in women and in patients receiving the mRNA-based vaccine. Proper vaccination history documentation, locating the vaccination site contralateral to the primary cancer, and appropriate scheduling of FDG PET/CT are advisable for correct image interpretation.*

Key Words: *COVID-19 vaccines; Lymphadenopathy; Fluorodeoxyglucose F18; Positron emission tomography computed tomography*

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Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: The study was approved by the Hong Kong Hospital Authority Kowloon Central Cluster / Kowloon East Cluster Research Ethics Committee (Ref (KC/KE)-21-0245/ER-2), and the requirement for informed consent was waived. The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

Declaration: Preliminary results of the present study were presented in part at the 9th Joint Scientific Meeting of the Royal College of Radiologists (RCR) & the Hong Kong College of Radiologists (HKCR) and 29th Annual Scientific Meeting of HKCR on 13-14 November 2021.

中文摘要

滅活和mRNA新冠疫苗接種對腫瘤患者^{18}F-氟脫氧葡萄糖PET/CT掃描的影響

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引言：旨在分析新冠疫苗接種對癌症患者^{18}F-氟脫氧葡萄糖（FDG）PET/CT成像結果的影響。

方法：本回顧研究納入165名第一次或第二次新冠疫苗接種後，於2021年5月1日至2021年9月30日期間接受FDG PET/CT檢查的腫瘤患者。測量注射部位（通常是三角肌）、同側腋窩和其他區域淋巴結以及脾臟產生FDG攝取極其模式。

結果：整體而言，同側區域淋巴結FDG-強烈攝取的發生率為26.7%（47/165），最大標準化攝取值中位數為3.2（介乎1.7-13.8）。接種疫苗6 週後，11.4%名受試者（5/44）出現與疫苗相關高代謝性淋巴結改變(VAHL)。與接受科興滅活疫苗的患者相比，VAHL在接受 BioNTech-復星mRNA疫苗的患者和女性中更為常見（$p < 0.05$）。

結論：VAHL常見，可在疫苗接種後6週後觀察到，在女性和接種mRNA疫苗的患者中更常見。正確的圖像解釋須參考疫苗接種記錄、考慮原發癌對側部位接種疫苗、以及適當安排FDG PET/CT檢查日期。

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in a tremendous burden on public health and the economy; universal vaccination is an important measure against the pathogen, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), to lessen serious infections and hospitalisation. There are currently two types of COVID-19 vaccine available in Hong Kong: Sinovac CoronaVac (inactivated vaccine) and Comirnaty (BNT162b2 mRNA vaccine, manufactured by BioNTech in collaboration with Fosun Pharma); both have been validated by World Health Organization for emergency use, and both require two doses to induce adequate protection against SARS-CoV-2.[1]

Reactive axillary, supraclavicular, and lower cervical lymphadenopathy following COVID-19 vaccination has been reported in several case reports and cohort studies on different imaging modalities.[2-6] Being an essential imaging tool for various types of cancers, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) is no exception. Increased FDG uptake at vaccine inoculation site and spleen after COVID-19 vaccination has also been described. Nevertheless, compared with mRNA vaccine, fewer reports about after vaccination imaging findings for other types of COVID-19 vaccines have been found.[7] In addition, vaccine-associated hypermetabolic lymphadenopathy (VAHL) on FDG PET/CT in the Chinese population has rarely been reported in the English-language literature.

In this study, we aimed to analyse the incidence, pattern, and potential clinical effects of VAHL and other imaging findings on FDG PET/CT in patients with cancer who previously received inactivated or mRNA COVID-19 vaccine.

METHODS

Study Population

This was a retrospective single-centre study. All consecutive cases with suspected or known malignancy, who had received at least one dose of COVID-19 vaccine (either Sinovac inactivated or BioNTech-Fosun mRNA vaccine), and subsequently undergone whole-body FDG PET/CT at our centre between 1 May 2021 and 30 September 2021 were enrolled in the current study. Exclusion criteria included: (1) non-whole body PET/CT studies; (2) incomplete vaccination records; (3) non-oncology patients; (4) known malignancy

that involved or was likely to involve the draining lymph nodes of the vaccine injection site (axillary, supraclavicular or lower cervical lymph nodes ipsilateral to the vaccine injection site in the deltoid muscle; for instance, ipsilateral breast cancer); (5) conditions and interventions that may affect lymphatic drainage pattern ipsilateral to the vaccine injection site (e.g., lymphoedema, local infection, axillary lymph node dissection, radiotherapy); and (6) patients with vaccinations in both deltoid muscles, and vaccination sites outside the upper extremities. For lymphoma, additional exclusion criteria included: no baseline PET/CT, no treatment response of previously identified lymphoma(s), and new lymphomatous lesion(s) detected in the rest of body. COVID-19 vaccination history (such as vaccine type, number of doses, vaccination date[s], injection site) and other relevant demographic and clinical data (including age, sex, and indication for PET/CT exam) were obtained from the electronic medical record as well as direct inquiry of each patient upon arrival for PET/CT.

Positron Emission Tomography/Computed Tomography

Imaging studies were performed on a PET/CT system (Discovery 710, GE Healthcare, Milwaukee [WI], US) according to our centre's scanning protocol. Patients fasted for at least 6 hours prior to FDG injection. Blood glucose levels were required to be <11 mmol/L. 370 MBq of FDG was injected intravenously (550 MBq for patients with body weight >80 kg). It was a standard procedure in our centre to inject tracer into the limb contralateral to the primary tumour, or via the lower extremities (e.g., in cases of bilateral breast tumours) whenever possible. A total of 19 patients had FDG administration and vaccination into the same limb. No patient experienced tracer extravasation or local infection.

Image acquisition started approximately 60 minutes following FDG injection. Spiral CT was first obtained for attenuation correction and anatomical localisation using the following technical parameters: tube voltage 120 kVp, modulated tube current 80 to 300 mA, gantry rotation speed 0.5 s per rotation, pitch 0.984. Emission PET scan was then acquired from the skull vertex to mid-thigh (or to toes, depending on clinical indications) with 2 minutes per bed position in three-dimensional mode. PET image datasets were reconstructed using a time-of-flight ordered subset expectation maximisation algorithm with point spread function modelling (4 iterations, 18 subsets, 5.5-mm cut-off filter).

Image Analysis

PET/CT images were reviewed using AW Volume Viewer (version 12.3, Ext 8, GE Healthcare, Milwaukee [WI], US) by a reader with 4 years of experience in nuclear medicine and molecular imaging. Results of previous imaging studies, type, and site of primary tumours, and location of regional nodal or distant metastases were taken into account for image interpretation.

The maximal standardised uptake value (SUVmax, normalised for body weight) was measured by placing spherical volumes of interest at the vaccine injection site (usually the deltoid muscle), at ipsilateral draining lymph nodes (e.g., axillary, supraclavicular, lower cervical lymph nodes for vaccination at deltoid muscle), and at the contralateral deltoid (or other injected) muscle and draining lymph nodes. Positive lymph node and deltoid muscle uptake was defined as having an SUVmax ≥1.5 × that of its contralateral counterpart.[4,5,7,8] The short axis of each lymph node was measured on the CT images.

Statistical Analysis

Categorical data are expressed as frequency and percentage. Continuous data are presented as mean ± standard deviation if they are normally distributed; otherwise, they are expressed as median (range). An unpaired Student's *t* test was used to compare means between groups for normally distributed data; a non-parametric Mann-Whitney *U* test was used to compare non-normally distributed data. The Chi-square test was used to compare proportions between groups (e.g., comparing proportions of patients with first dose of vaccine only between Sinovac and BioNTech-Fosun groups). All statistical tests were carried out using commercial software (MedCalc version 20.019; MedCalc Software, Ostend, Belgium). Graphs were composed using commercial software (Excel version 16.43, Microsoft, Redmond [WA], US). A p value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Among 2259 consecutive cases undergoing whole-body FDG PET/CT during the study period, 221 (9.8%) had received at least one dose of COVID-19 vaccine before PET/CT. Figure 1 shows the numbers of cases meeting exclusion criteria. A total of 165 cases were finally included in the study population (mean age, 60.8 ± 11.1 years; 45.5% women). Eighty-seven patients (52.7%) had received Sinovac inactivated vaccine, and the other 78 were vaccinated with BioNTech-Fosun mRNA

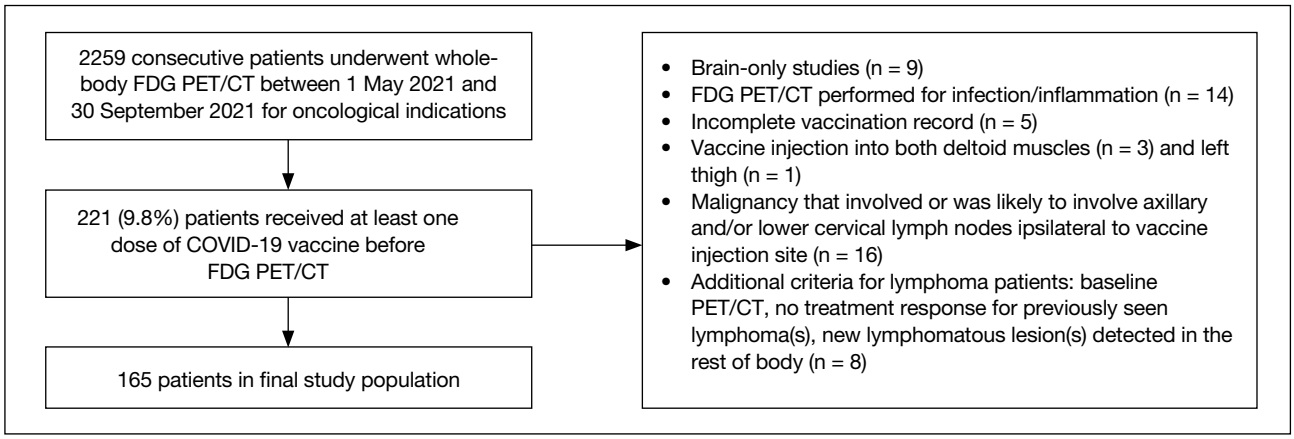

Figure 1. Flowchart showing how patients are selected.
Abbreviations: COVID-19 = coronavirus disease 2019; FDG = ^{18}F-fluorodeoxyglucose; PET/CT=positron emission tomography/computed tomography.

vaccine. In all, 24.8% of subjects (41/165) had received one vaccine dose, and 75.2% of subjects (124/165) had received two doses of vaccine. The median time interval between vaccination and FDG PET/CT was 41.0 days (range, 2-176). Details of patient demographics are illustrated in Table 1.

^{18}F-fluorodeoxyglucose-avid Lymph Nodes Ipsilateral to COVID-19 Vaccination

Overall, 26.7% (44/165; 29 women and 15 men) of cases had positive uptake in axillary and lower cervical lymph nodes ipsilateral to the vaccine injection site. A representative case is shown in Figure 2. The median SUVmax of VAHL was 3.2 (range, 1.7-13.8). Most of them were of normal size (88.6% were <10 mm; median, 7 mm; range, 3-17 mm). The number of FDG-avid lymph nodes ranged from 1-15 (median, 3). VAHL was most frequently seen in ipsilateral axillary level I nodes (52.1%, 86/165; while 27.3% (45/165) and 2.4% (4/165) were detected in ipsilateral axillary levels II and III, respectively. In all, 20.5% of cases (9/44) also showed positive ipsilateral extra-axillary nodal uptake (including interpectoral [located between the pectoralis major and pectoralis minor muscles], infraclavicular, supraclavicular, lower cervical, and mediastinal regions).

The proportion of VAHL at various time intervals following vaccination is shown in Figure 3. The greatest percentage of vaccinated cases with VAHL was seen within first 2 weeks (59.3%), and there was still a significantly larger proportion of cases with VAHL within the first 4 weeks after vaccination compared with

Table 1. Summary of patient demographic and clinical characteristics.*

	Study population (n = 165)
Age, mean ± SD, y	60.8 ± 11.1
Sex	
Male	90 (54.5%)
Female	75 (45.5%)
Type of vaccine	
Sinovac (inactivated)	87 (52.7%)
BioNTech-Fosun (mRNA)	78 (47.3%)
No. of dose(s) of vaccine received	
First dose only	41 (24.8%)
First and second doses	124 (75.2%)
Days between last vaccination and PET/CT, median (range)	41 (2-176)
Site of vaccine injection	
Left deltoid	143 (86.7%)
Right deltoid	22 (13.3%)
Laterality of FDG injection to COVID-19 vaccination	
Ipsilateral†	17 (10.3%)
Contralateral	148 (89.7%)
PET/CT scan indication	
Lung cancer or nodule	40 (24.2%)
Gastrointestinal cancers‡	18 (10.9%)
Head and neck cancers	17 (10.3%)
Breast cancer	13 (7.9%)
Lymphoma	10 (6.1%)
Other malignancies	42 (25.5%)
Elevated tumour markers or non-specific symptoms	27 (16.4%)

Abbreviations: COVID-19 = coronavirus disease 2019; FDG = ^{18}F-fluorodeoxyglucose; PET/CT = positron emission tomography/computed tomography; SD = standard deviation.
* Data are shown as No. (%), unless otherwise specified.
† There was no documentation of tracer extravasation in all subjects in the present study.
‡ Oesophageal, gastric, colorectal, pancreatic and hepatic cancers.

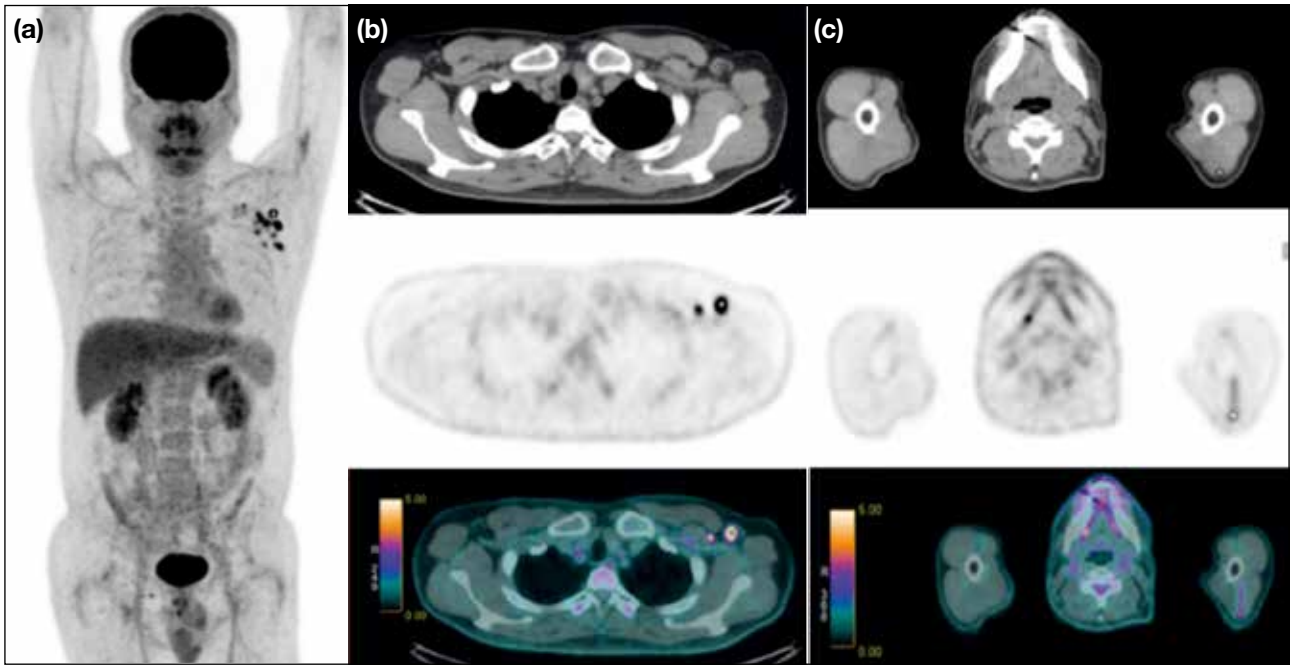

Figure 2. Representative images of a 55-year-old man with unexplained weight loss for 6 months underwent ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) exam 3 days after the second dose of BioNTech-Fosun mRNA vaccine into the left deltoid muscle. (a) Maximum intensity projection (MIP) image, axial CT, PET and fused PET/CT images (from top to bottom) showing (b) increased uptake in multiple left axillary lymph nodes with a maximal standardised uptake value (SUVmax) of 13.8, short-axis diameter 17 mm, and (c) elongated uptake at left deltoid with SUVmax = 3.2, indicating vaccine injection site. The patient was found to have bladder cancer. Hypermetabolic left axillary lymph nodes were not visualised on subsequent FDG PET/CT images.

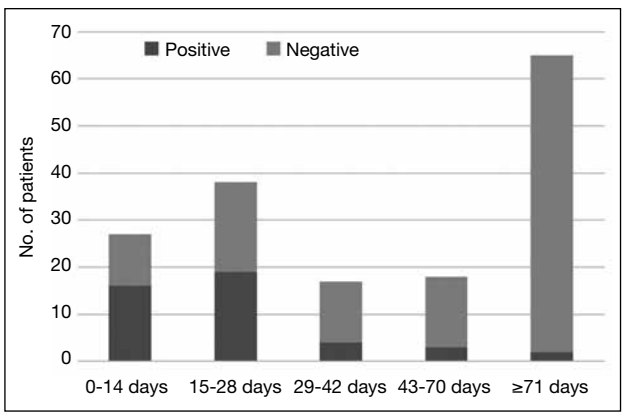

Figure 3. Proportion of vaccine-associated hypermetabolic lymphadenopathy of oncology patients in various time points postvaccination.

those beyond 4 weeks after vaccination ($p < 0.001$). In total, 11.4% of cases (5/44) with FDG-avid axillary lymph nodes were found >6 weeks after vaccination.

In a subgroup analysis of cases undergoing FDG PET/CT exam within 87 days following vaccination (because no benign VAHL was seen 87 days after vaccination), BioNTech-Fosun mRNA vaccine was significantly associated with a higher incidence ($p < 0.001$) and larger number ($p = 0.038$) of FDG-avid ipsilateral lymph nodes compared with Sinovac inactivated vaccine, but there was no significant association with size ($p = 0.142$) or SUVmax ($p = 0.153$) [Table 2]. In addition, VAHL was more frequently seen in women ($p = 0.004$) [Table 3]. There was no statistically significant difference in the incidence, SUVmax, short-axis diameter or number of VAHL nodes between those cases that had received the first dose only and those that had received first and second doses (Table 4).

DISCUSSION

Overall, 26.7% of subjects showed hypermetabolic ipsilateral lymph nodes. Within 2 weeks after vaccination, VAHL was seen in 59.3% of patients. Such findings were postulated to be associated with the inflammatory response to vaccine components at the inoculation site and draining lymph nodes.[9] Indeed, VAHL was previously reported after vaccines against other pathogens (such as influenza virus, human papillomavirus, and pneumococcus), and was also observed in various non-FDG PET exams

Table 2. Subgroup analysis of patients' characteristics and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography findings of vaccine-associated hypermetabolic lymphadenopathy in patients with Sinovac (inactivated) or BioNTech-Fosun (mRNA) COVID-19 vaccine.*

	Sinovac (n = 57)	BioNTech-Fosun (n = 64)	p Value
No. of dose(s) of vaccine received			0.952
First dose only	19 (33.3%)	21 (32.8%)	
First and second doses	38 (66.7%)	43 (67.2%)	
Days between last vaccination and PET/CT, median (range)	31 (2-85)	21.5 (3-87)	0.211
VAHL			
Presence	9 (15.8%)	35 (54.7%)	<0.001
SUVmax, median (range)	2.7 (1.9-6.3)	3.6 (1.7-13.8)	0.153
Number, median (range)	2 (1-3)	3 (1-15)	0.038
Size, median (range), mm	5 (3-8)	7 (3-17)	0.142

Abbreviations: COVID-19 = coronavirus disease 2019; PET/CT = positron emission tomography/computed tomography; SUVmax = maximal standardised uptake value; VAHL = vaccine-associated hypermetabolic lymphadenopathy.
* Data are shown as No. (%), unless otherwise specified.

Table 3. Subgroup analysis of demographic and clinical characteristics of patients with and without vaccine-associated hypermetabolic lymphadenopathy following COVID-19 vaccination.*

	With VAHL (n = 44)	Without VAHL (n = 77)	p Value
Age			0.777
Elderly patients (≥61 y)	16 (36.4%)	30 (39.0%)	
Non-elderly patients (<61 y)	28 (63.6%)	47 (61.0%)	
Female sex	29 (65.9%)	30 (39.0%)	0.004
Type of vaccine			<0.001
Sinovac (inactivated)	9 (20.5%)	48 (62.3%)	
BioNTech-Fosun (mRNA)	35 (79.5%)	29 (37.7%)	
No. of vaccination(s) received			0.324
One dose	17 (38.6%)	23 (29.9%)	
Two doses	27 (61.4%)	54 (70.1%)	
Days between last vaccination and PET/CT, median (range)	17 (3-87)	33 (2-87)	<0.001
Types of cancers			
Lung cancer or nodule	10 (22.7%)	17 (22.1%)	
Head and neck cancers	4 (9.1%)	9 (11.7%)	
Breast cancer	4 (9.1%)	6 (7.8%)	
Gastrointestinal cancers	3 (6.8%)	10 (13.0%)	
Lymphoma	3 (6.8%)	6 (7.8%)	

Abbreviations: COVID-19 = coronavirus disease 2019; PET/CT = positron emission tomography/computed tomography; VAHL = vaccine-associated hypermetabolic lymphadenopathy.
* Data are shown as No. (%), unless otherwise specified.

(e.g., ^{68}Ga-DOTATATE, ^{18}F- or ^{68}Ga-PSMA).[4,10,11] VAHL can become enlarged,[2,3,12] as in 11.4% of cases in our study, which could not be readily distinguished from nodal metastases based on CT alone. Follow-up scan showed that such enlargement did not persist.

The definitions of positive draining lymph node and deltoid uptake after vaccination in the current study (i.e. having a SUVmax ratio of ≥1.5 between ipsilateral to contralateral reference sites) were used previously by other research groups for COVID-19 and influenza vaccines.[4,5,7,8] Compared with other criteria (e.g., using blood pool SUVmax or surrounding background as reference),[2,3,6] these criteria were relatively more quantitative, reproducible and took into account that lymphadenopathy contralateral to vaccine injection is extremely rare. Lim et al[13] reviewed 67 published reports and found that only four out of 3072 cases (0.13%) showed lymphadenopathy outside ipsilateral axillary and cervical regions (including contralateral axilla). There are other criteria of lymph node or deltoid uptake in the literature as mentioned above[2,3,6] and caution should be taken when comparing results of different studies.

Table 4. Subgroup analysis of characterisation of vaccine associated hypermetabolic lymphadenopathy in patients following first dose versus first and second doses of COVID-19 vaccination.*

	First dose (n = 40)	First and second doses (n = 81)	p Value
VAHL			
Presence	17 (42.5%)	27 (33.3%)	0.324
SUVmax, median (range)	4.0 (1.8-9.2)	3.0 (1.5-13.8)	0.093
No., median (range)	3 (1-6)	2 (1-15)	0.749
Size, median (range), mm	7 (4-11)	7 (3-17)	0.689

Abbreviations: COVID-19 = coronavirus disease 2019; SUVmax = maximal standardised uptake value; VAHL = vaccine-associated hypermetabolic lymphadenopathy.
* Data are shown as No. (%), unless otherwise specified.

Although many studies focused on VAHL in the ipsilateral axillary region, our findings showed that 20.5% of patients had ipsilateral extra-axillary lymph nodal uptake, which should not be ignored by interpreting physicians. Furthermore, in spite of several recommendations advising to delay nonurgent imaging 4 to 6 weeks after the recent dose of vaccination,[12,14,15] Eshet et al[5] demonstrated that VAHL was still found in 29% of subjects 7 to 10 weeks after the second dose of vaccination. Similarly, we also observed 11.4% of patients having VAHL beyond 6 weeks after vaccination (the longest duration was 87 days) in the current study. Therefore, a delay of 4 to 6 weeks of a nonurgent scan is useful but cannot completely avoid the occurrence of VAHL.

Compared with mRNA COVID-19 vaccines, there are fewer studies about VAHL following other types of COVID-19 vaccines.[7,16] The current study illustrated that BioNTech-Fosun mRNA vaccine was associated with a higher incidence of VAHL compared with the Sinovac inactivated vaccine, which was similar to the results recently reported in Turkish patients (incidence of 9.9% for CoronaVac and 37.5% for BioNTech).[7] It can be explained by the fact that mRNA vaccines have inherently greater immunogenicity based on laboratory and clinical data.[17] Moreover, a higher incidence of VAHL was also observed in female patients. Such sex-related differences have been noted previously,[18] and could be explained by genetic factors as well as the immunostimulatory effect of oestrogens.[19]

From the results of the present study, 26.7% of subjects showed hypermetabolic ipsilateral regional lymph nodes after COVID-19 vaccination, suggesting that VAHL is common and distinguishing VAHL from true metastatic lymphadenopathy is important to avoid additional testing, unnecessary biopsy and even alteration of therapy. CT alone is not adequate, since some of these lymph nodes are enlarged (11.4% of cases in our study) and could not be readily differentiated from nodal metastases. Obtaining a detailed vaccination history before tracer injection is useful, which should at least include all the items recommended by the Society of Nuclear Medicine and Molecular Imaging COVID-19 Task Force and the Scientific Expert Panel of the journal *Radiology*: injection site(s), date(s) of vaccination and type(s) of vaccine.[12,14] Information on injection site(s) helps interpreting physicians determine which lymph nodes are more likely to be related to vaccine infection. Date(s) of vaccination is important because VAHL is transient and wanes with time. Knowing which type of vaccine has been injected is useful since incidence of VAHL differs among type of vaccine; for instance, our study showed that BioNTech-Fosun mRNA vaccine was associated with higher incidence and larger number of VAHL compared with Sinovac inactivated vaccine. Nevertheless, vaccination history should not be based on pre-injection questionnaire alone, since patients may not remember accurately, and some details may be omitted. Details of vaccination history should be readily found in medical records and electronic vaccination records, which can be accessed using smartphones (in some countries or regions where it is feasible). Such vaccination history should include injection site(s) apart from date(s) and type(s) of vaccination.[12,14] Furthermore, efforts should be made to avoid administration of vaccine on the side ipsilateral to the primary or suspected malignancy. First and second doses should be given in the same arm.[12,14,15] Promotion of awareness of referring physicians and patients and proper training of healthcare professionals who provide COVID-19 vaccination are possible measures to implement. Last but not least, scheduling of FDG PET/CT for a certain period after the last vaccination can allow for VAHL to resolve. The National Comprehensive Cancer Network COVID-19 Vaccination Advisory Committee suggests a delay of 4 to 6 weeks,[15] which is based on the recommendation of the Society of Breast Imaging.[20] On the other hand, the Scientific Expert Panel of the journal *Radiology* recommended a postponement of at least 6 weeks, because the preliminary experience of the panel members showed that the some enlarged lymph nodes persisted even after 4 weeks.[12] The present study provided further evidence that such recommendations can also

be applied to hypermetabolic lymphadenopathy seen on FDG PET/CT, since 79.5% (35/44) and 88.6% (39/44) of subjects demonstrated hypermetabolic lymph nodes within 4 weeks and 6 weeks postvaccination, respectively. Because women experience VAHL more commonly than men, and breast cancer is a common type of cancer among women, it may be necessary to inject breast cancer patients in the lower extremity, or at least in deltoid contralateral to the site of primary tumour. Given that the healthcare system is currently facing enormous strain due to the COVID-19 pandemic, some of the above measures to tackle FDG-avid lymph nodes may not be readily implemented and require cooperation of a multidisciplinary team.

There were several limitations in the present study. First, it was a retrospective single-centre study design. Second, recall bias of vaccination history existed. Furthermore, the study was conducted in a relative short study period. Follow-up FDG PET/CT of two subjects with VAHL demonstrated interval metabolic resolution/improvement of previously hypermetabolic lymph nodes. For the other cases, however, there was no biopsy or follow-up imaging to support the benignity of VAHL; follow-up or even biopsy of enlarged/hypermetabolic lymph nodes is necessary to confirm that VAHL was benign.

CONCLUSION

In summary, in view of emergence of new variants of the coronavirus, recommendation of additional booster shot as well as lowering the age limit of vaccination, the vaccination rate will continue to rise, and awareness of COVID-19 vaccine-associated imaging findings is important for interpreting physicians. In the present study, we found that 26.7% of subjects showed positive ipsilateral lymph node uptake more frequently with BioNTech-Fosun mRNA vaccine and in women. Some of the reactive nodes were enlarged and persisted beyond 6 weeks, which could not be readily distinguished from malignant lesions based on CT alone. Therefore, advising patients to get vaccination contralateral to primary tumour or in the lower extremity, proper vaccination history documentation, and recognition of co-occurrence of positive deltoid uptake with VAHL may help avoid misinterpretation.

REFERENCES

1. Chan WL, Ho YH, Wong CK, Choi HC, Lam KO, Yuen KK, et al. Acceptance of COVID-19 vaccination in cancer patients in Hong Kong: approaches to improve the vaccination rate. Vaccines (Basel). 2021;9:792.
2. Bernstine H, Priss M, Anati T, Turko O, Gorenberg M, Stenmetz AP, et al. 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.
3. Cohen D, Krauthammer SH, Wolf I, Even-Sapir E. Hypermetabolic lymphadenopathy following administration of BNT162b2 mRNA Covid-19 vaccine: Incidence assessed by [18F]FDG PET-CT and relevance to study interpretation. Eur J Nucl Med Mol Imaging. 2021;48:1854-63.
4. Eifer M, Tau N, Alhoubani, Y, Kanana N, Domachevsky L, Shams J, et al. COVID-19 mRNA vaccination: age and immune status and its association with axillary lymph node PET/CT Uptake. J Nucl Med. 2021;63:134-9.
5. 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;300:E345-7.
6. Schroeder DG, Jang S, Johnson DR, Takahashi H, Navin PJ, Broski SM, et al. Frequency and characteristics of nodal and deltoid FDG and 11C-choline uptake on PET imaging performed after COVID-19 vaccination. AJR Am J Roentgenol. 2021;217:1206-16.
7. Sahin O. Hypermetabolic axillary lymphadenopathy on FDG PET/CT Due to COVID-19 vaccination. Selcuk Med J. 2021;37:269-75.
8. 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.
9. Youn H, Hong KJ. Non-invasive molecular imaging of immune cell dynamics for vaccine research. Clin Exp Vaccine Res. 2019;8:89-93.
10. McIntosh LJ, Bankier AA, Vijayaraghavan GR, Licho R, Rosen MP. COVID-19 vaccination-related uptake on FDG PET/CT: an emerging dilemma and suggestions for management. AJR Am J Roentgenol. 2021;217:975-83.
11. Treglia G, Cuzzocrea M, Muoio B, Elzi L. PET findings after COVID-19 vaccination: "Keep calm and carry on". Clin Transl Imaging. 2021;9:209-14.
12. Becker AS, Perez-Johnston R, Chikarmane SA, Chen MM, El Homsi M, Feigin KN, et al. Multidisciplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: *Radiology* Scientific Expert Panel. Radiology. 2021;300:E323-7.
13. Lim J, Lee SA, Khil EK, Byeon SJ, Kang HJ, Choi JA. COVID-19 vaccine-related axillary lymphadenopathy in breast cancer patients: Case series with a review of literature. Semin Oncol. 2021;48:283-91.
14. Society of Nuclear Medicine and Molecular Imaging (SNMMI). SNMMI statement: the effect of COVID-19 vaccination on FDG PET/CT. J Nucl Med. 2021;62:30N.
15. National Comprehensive Cancer Network. Recommendations of the e National Comprehensive Cancer Network® (NCCN®) Advisory Committee on COVID-19 vaccination and pre-exposure prophylaxis. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v4-0.pdf?sfvrsn=b483da2b_70. Accessed 7 Dec 2021.
16. Shin M, Hyun CY, Choi YH, Choi JY, Lee KH, Cho YS. COVID-19 vaccination-associated lymphadenopathy on FDG PET/CT: distinctive features in adenovirus-vectored vaccine. Clin Nucl Med. 2021;46:814-9.
17. Mingos M, Howard S, Giacalone N, Kozono D, Jacene H. Systemic immune response to vaccination on FDG-PET/CT. Nucl Med Mol Imaging. 2016;50:358-61.
18. Adin ME, Isufi E, Kulon M, Pucar D. Association of COVID-19

mRNA Vaccine with ipsilateral axillary lymph node reactivity on imaging. JAMA Oncol. 2021;7:1241-2.
19. Giefing-Kröll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging cell. 2015;14:309-21.
20. Grimm L, Destounis S, Dogan B, Nicholson B, Dontchos, Sonnenblick E, et al. Society of Breast Imaging: SBI recommendations for the management of axillary adenopathy in patients with recent COVID-19 vaccination. Available from: https://www.sbi-online.org/Portals/0/Position%20Statements/2021/SBI-recommendations-for-managing-axillary-adenopathy-post-COVID-vaccination.pdf. Accessed 7 Dec 2021.