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Research Article

# Intensity of hypermetabolic axillary lymph nodes in oncologic patients in relation to timeline following COVID-19 vaccination

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## ABSTRACT

**Purpose:** First discovered in Wuhan, China in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a highly contagious and deadly novel virus that quickly wreaked havoc throughout the world. As mass vaccination are now underway worldwide, clinicians have started to encounter a new clinical entity, COVID-19 vaccine-associated axillary lymphadenopathy. This presents a unique challenge to medical imagers, particularly in oncologic patients.

**Methods:** In this retrospective study, we assessed metabolic activity, size, and timeline of COVID-19 vaccine-associated axillary hypermetabolic lymph nodes in 202 oncologic patients post vaccination with 18-fluorodeoxyglucose positron emission tomography (18-FDG PET).

**Results:** When present, COVID-19 vaccine-associated hypermetabolic lymph nodes demonstrate a mean maximum standard uptake value ($SUV_{max}$) of 2.5 ± 0.3, and more common in younger patients. The metabolic activity is the most intense in the first two weeks post vaccination and diminishes over time. By approximately 5-6 weeks, only about half of the patients demonstrated appreciable, low grade uptake compared to background.

**Conclusion:** Based on our preliminary results, we would recommend correlation with a history and time of vaccination and routine use of a pre-study patient questionnaire to guide interpretation to prevent over-diagnosis of axillary nodal metastases and/or unnecessary work-up in oncologic patients.

## RÉSUMÉ

**Bute:** Découvert pour la première fois à Wuhan, en Chine, en décembre 2019, le coronavirus 2 du syndrome respiratoire aigu sévère (SRAS-COV-2) est un nouveau virus très contagieux et mortel qui a rapidement fait des ravages dans le monde entier. Alors que la vaccination de masse est en cours dans le monde entier, les cliniciens ont commencé à rencontrer une nouvelle entité clinique, la lymphadénopathie axillaire associée au vaccin COVID-19. Cela représente un défi unique pour les imageurs médicaux, en particulier chez les patients oncologiques.

**Méthodologie:** Dans cette étude rétrospective, nous avons évalué l'activité métabolique, la taille et la chronologie des ganglions lymphatiques axillaires hypermétaboliques associés au vaccin COVID-19 chez 202 patients oncologiques après la vaccination, à l'aide de la tomographie par émission de positrons au 18-fluorodésoxyglucose. (TEP 18-FDG).

**Résultats:** Lorsqu'ils sont présents, les ganglions lymphatiques hypermétaboliques associés au vaccin COVID-19 présentent une valeur de captation standard maximale moyenne (SUV max) de 2,5 ± 0,3, et sont plus fréquents chez les jeunes patients. L'activité métabolique est la plus intense dans les deux premières semaines suivant la vaccination

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et diminue avec le temps. Au bout de 5 à 6 semaines environ, seule la moitié des patients présentait une captation appréciable et de faible intensité par rapport au bruit de fond.

**Conclusion:** Sur la base de nos résultats préliminaires, nous recommandons une corrélation avec les antécédents et le moment de la vaccination et l'utilisation systématique d'un questionnaire préalable au patient pour guider l'interprétation afin d'éviter un surdiagnostic des métastases ganglionnaires axillaires et/ou des examens inutiles chez les patients oncologiques.

*Keywords:* FDG PET/CT; lymphadenopathy; COVID-19; coronavirus

## Background

Functional imaging with 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) has become an integral component of modern medical imaging, with increasing utility in and beyond oncology, especially when combined with conventional anatomical imaging modalities such as conventional transmission computed tomography (CT).

As our world enters a new phase of COVID-19 pandemic with mass vaccination, an ever-increasing number of people, especially people with chronic conditions (including oncologic patients), received, or are soon to receive COVID-19 vaccines. As of July 1, 2021, over 2.95 billion vaccine doses have been administered worldwide [1].

Health Canada has approved five COVID-19 vaccines for human use under emergency authorization. Over 25 million Canadians (65.9% of the population) have received at least one dose, and over 7.3 million Canadians, or 19.3% of the population are fully vaccinated, with over 38.2 million doses administered [2]. Among those five vaccines, two messenger RNA (mRNA) vaccines, Pfizer-BioNTech (tozinameran) and Moderna (mRNA-1273 SARS-CoV-2) and a viral vector vaccine made by Oxford–AstraZeneca saw particularly rapid nationwide deployment.

Vaccine-associated lymphadenopathy is a known clinical entity long before the current pandemic [3]. As COVID-19 vaccines are typically administered intramuscularly in the deltoid muscle, regional lymphadenopathy in the axilla has become an increasingly common clinical scenario, considering the sheer number of people who are either partially or fully vaccinated. This also presents a unique challenge to medical imagers, especially in patients with certain malignancy with a predilection to axillary nodal spread, such as breast cancer, lymphoma, and melanoma. Therefore, it is crucial for medical imagers to recognize this potential imaging pitfall as an incidental finding in oncologic settings, with consideration of the intensity of FDG uptake in relation to the timeline of COVID-19 vaccination, to prevent over-diagnosis.

Although there are multiple studies recognizing COVID-19 vaccine associated lymphadenopathy [4-7], to our knowledge, to date, there is no current detailed study addressing its timeline and the degree of metabolic activity. Locally, COVID-19 vaccine associated lymphadenopathy is a commonly encountered clinical scenario. Given Canada's unique situation currently, having one of the highest rates of vaccination worldwide especially with mRNA vaccines, we aim to conduct a retrospective chart review to address this gap in knowledge, and to help guide clinical management. The objective of the study was to assess timeline and degree of 18-FDG avidity axillary lymph node in patients post COVID-19 vaccination.

## Methods

This is a retrospective single-center study, approved by the local Research Ethics Board.

### Patients

All adult patients who underwent an 18-FDG PET/CT study from May 13$^{th}$ to July 8$^{th}$, 2021, with a history of COVID-19 vaccination identified on patient pre-study questionnaire were also included in the study. Basic demographic information including age and sex, as well as prior oncologic history was recorded. In addition, the date of administration, type of COVID-19 vaccine, vaccination site, and number of COVID-19 vaccine doses received (first versus second), were recorded using the data provided from the patients' electronic medical records. Other basic demographic information including age, sex and type of malignancy was also recorded.

### Exclusion criteria

Patients with unknown vaccination date or type, and patients who had vaccines not yet approved in Canada were excluded. The presence of extensive FDG-avid metastatic lymphadenopathy, or suspected FDG-avid axillary nodal metastatic disease were the two other criteria for exclusion.

### Imaging protocol and analysis

Patient preparation and 18-FDG PET/CT image acquisition followed standard institutional protocol. After intravenous administration of 4.99 MBq per kilogram to a maximum of 444 MBq and an initial uptake phase of approximately 60 minutes, a low dose CT scan without IV contrast was acquired for attenuation correction and localization purposes. Subsequently, PET images were acquired on GE PET/CT Discovery 710 scanner and reconstructed using OSEM with 2 iterations, 24 subsets and corrections for time-of-flight, point-spread function, scatter, and attenuation. CT, PET, and fused images were reconstructed in the transaxial, coronal, and sagittal projections.

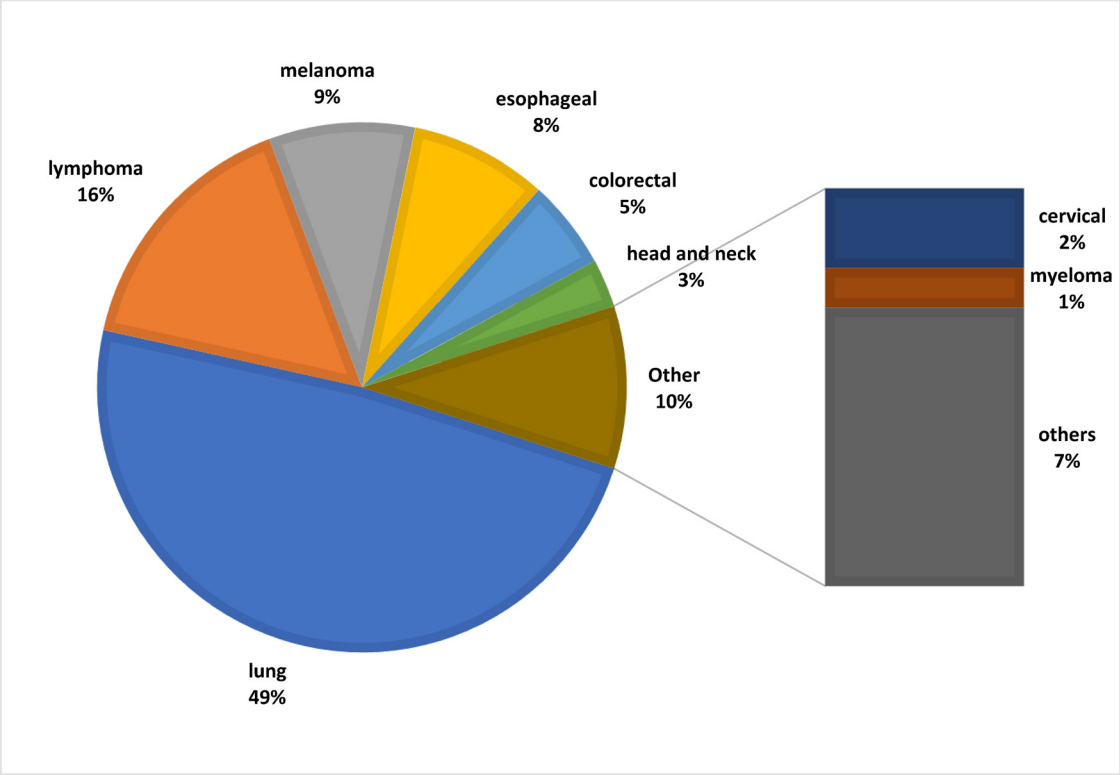


Fig. 1. Primary lung cancer, lymphoma, or esophageal cancer are the top three most common malignancy in the sample population (n=202 patients), followed by melanoma, colorectal cancer, cancer of the head and neck region, cervical cancer, and myeloma. Other, rarer malignancies encountered not presented in this chart include adrenocortical carcinoma, sarcoma, gastroenteropancreatic neuroendocrine neoplasms, germ cell tumors, and ovarian cancer, as well as malignancy of unknown origin.

For each patient, PET/CT images were re-evaluated on a HERMES workstation by one of the two board-certified Nuclear Medicine physicians, each with more than 5 years of experience. The most intense ipsilateral axillary lymph node against background was first identified visually, with its maximum standard uptake value ($SUV_{max}$) recorded. This lymph node was measured on the low dose transaxial CT images in the maximal short dimension and recorded in millimetres. Liver $SUV_{max}$ was also measured as an internal reference. The patients were divided in two groups for comparison purposes: (1) $\geq$ 1 FDG avid lymph node and (2) absence of FDG avid lymph node. The avidity of the lymph nodes ($SUV_{max}$) was then correlated with the time post-injection (0 to 2, 3 to 4 and greater than 5 weeks). The effects of the different vaccines were also evaluated.

Statistical analysis was performed using IBM SPSS platform. Standard errors were reported in 95 percent confidence interval (CI) unless stated otherwise. Averages were compared using two-tailed student t-test. Ratios were compared using the two-proportions z-test. P-values less than 0.05 were considered statistically significant.

## Results

In total, 202 patients, the mean age of 66.9 $\pm$ 1.9 and male to female ratio of 1:1.1, met the inclusion criteria. Lung cancer was the most encountered primary malignancy and accounted for half of the patients, followed by lymphoma (16%), melanoma (9%) and esophageal carcinoma (8%) (Fig. 1).

The average number of days between the most recent dose of vaccine and PET/CT study was 31.0 $\pm$ 3.3 days (range 0-108 days). In terms of the vaccination status, 116 patients (57.4%) had received one dose of COVID-19 vaccine, and the rest (42.6%) had received two doses. Most of the patients, 194 out of 202, or 96.5%, received at least one dose of mRNA vaccine, either Pfizer-BioNTech (152) or Moderna (42). Three patients received their first dose of the Pfizer-BioNTech vaccine followed by a second dose of the Moderna vaccine. Five patients received at least one dose of the Oxford–AstraZeneca vaccine. No one in the sample population had received any of the other two vaccines currently approved in Canada (COVISHIELD Verity/Serum Institute of India (SII) (COVISHIELD) and Janssen).

### *Clinical and imaging features of FDG avid ipsilateral axillary lymph nodes*

In total, 126 patients (62.4%) had one or more FDG avid axillary lymph nodes. The mean age was 63.4 $\pm$ 2.4 years old, with a male to female ratio of 1:1.1. When present, most patients had two or more FDG avid axillary lymph nodes. The mean $SUV_{max}$ value was 2.5 $\pm$ 0.3 (range: 1.0 – 9.2). The mean size of the most hypermetabolic lymph node was 6.2 $\pm$ 0.4 mm in the short axis.

Table 1
Demographic and imaging characteristics of patients with ≥ 1 FDG-avid lymph node over time post-vaccination. When patients with at least one FDG-avid lymph node is subcategorized in order of time to the most recent vaccination, an apparent trend start to emerge. Although the basic demographic information stays approximately the same between the subgroups, $SUV_{max}$ value of the most avid ipsilateral lymph node diminish significantly over time, with the highest value seen in the first two weeks ($p < 0.05$).

| | Week 0 – 2 | Week 3 – 4 | > Week 5 |
|---|---|---|---|
| Number of patients with ≥ 1 FDG-avid lymph node | 46 | 34 | 46 |
| Number of patients without FDG-avid lymph node | 19 | 14 | 43 |
| Percentage of patients with no FDG-avid lymph node | 9.4% | 9.4% | 21.3%* |
| Age | 63.8 ± 4.3 | 61.1 ± 4.3 | 64.8 ± 3.9 |
| M:F | 1:1.6 | 1.4:1* | 1:1.2 |
| $SUV_{max}$ | 3.5 ± 0.6* | 2.4 ± 0.5* | 1.7 ± 0.2* |
| Lymph node size (mm) | 6.6 ± 0.6 | 5.8 ± 0.6 | 5.8 ± 0.8 |

* indicates $p<0.05$ between groups

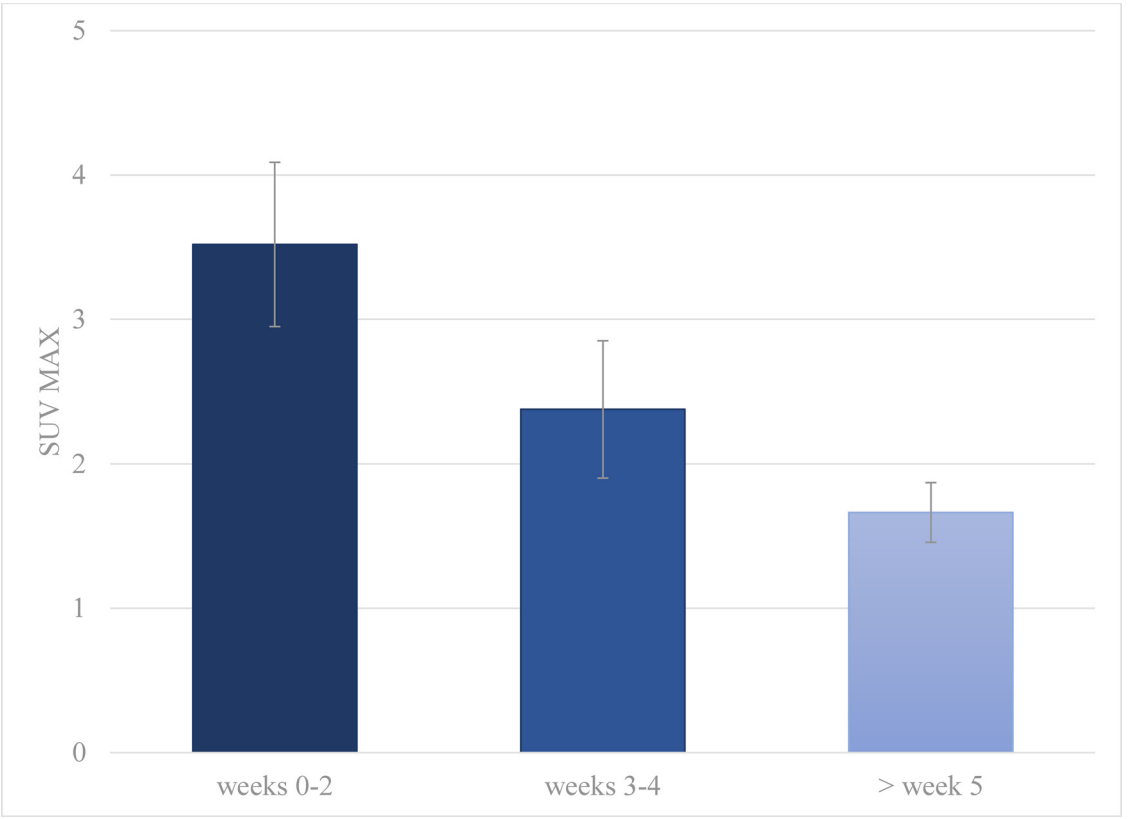


Fig. 2. $SUV_{max}$ of the most hypermetabolic lymph node over time post-vaccination. This figure demonstrates, visually, the diminishing $SUV_{max}$ values of the most FDG avid ipsilateral lymph node over time. The grey bars represent the calculated 95% CI.

*Evolution of FDG avid ipsilateral axillary lymphadenopathy over time*

The ipsilateral axillary lymphadenopathy was the most FDG-avid in the first two weeks post vaccination, with a mean $SUV_{max}$ value of 3.5 ± 0.6. There was a significant reduction in $SUV_{max}$ value two to four weeks post injection, with a mean $SUV_{max}$ value of 2.4 ± 0.5 ($p < 0.01$, Table 1). There was a further decrease in $SUV_{max}$ value beyond the fifth week ($SUV_{max} = 1.7 \pm 0.2$, $p < 0.01$, Table 1 and Fig. 2).

In term of lymph node size, there was an apparent decrease of nodal size over time, from 6.6 ± 0.6 mm in the short axis in the first two weeks, to 5.8 ± 0.8 mm beyond the fifth week ($p = 0.06$, Table 1). This subtle difference did not reach statistical significance. There were no statistical differences in mean patient age, prevalence of primary disease, but a higher ratio of male patients was noted for the weeks 3-4 group.

No FDG avid ipsilateral lymph node could be identified in 76 (37.6%) patients. These patients were statistically significantly older than the FDG avid group at 72.6 ± 2.6 years ($p < 0.001$, Table 1). The average number of days post vaccination was 38.0 ± 6.0 days, significantly longer than the average number of days post vaccination for the FDG-avid group, 25.4 ± 3.5 days ($p < 0.001$).

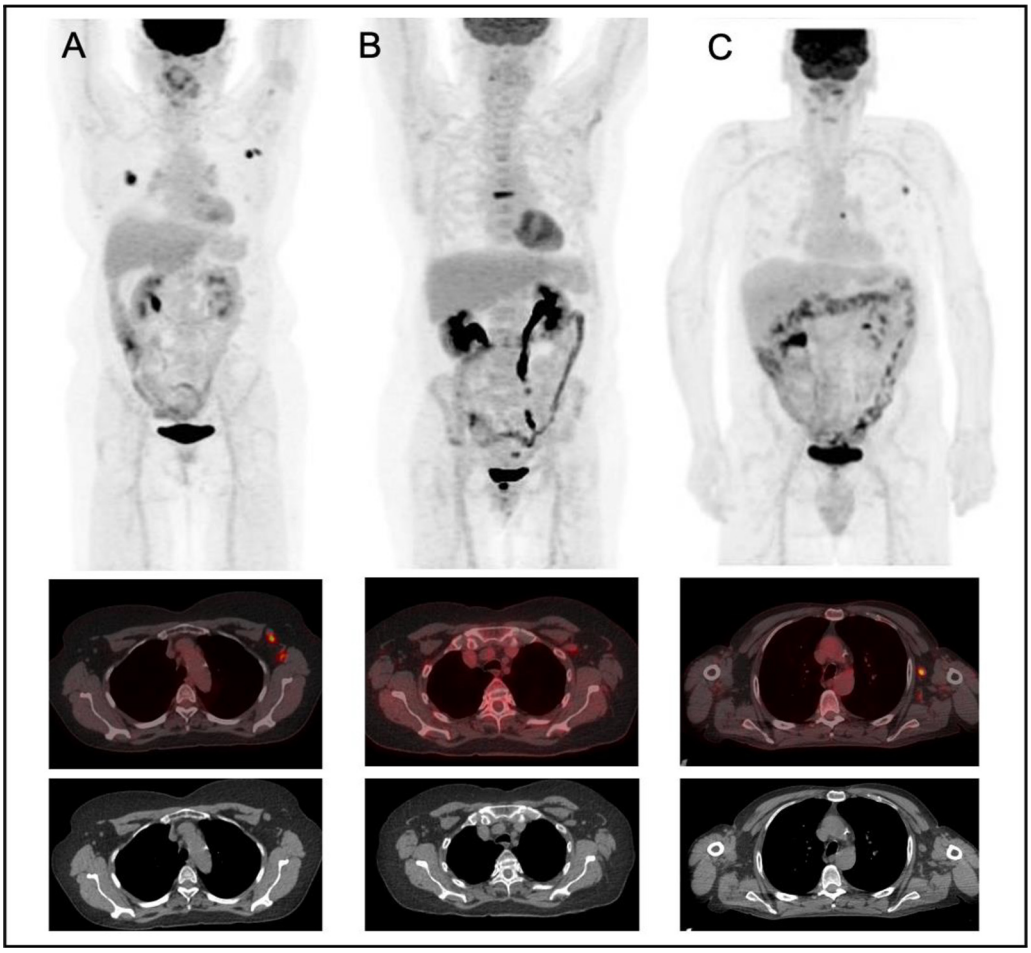


Fig. 3. Whole-body maximum intensity projection images and transaxial images of fused PET/CT and CT show: A) Multiple hypermetabolic axillary lymph nodes are identified, in this 66-year-old female patient with a primary adenocarcinoma of the right middle lobe, 9 days after the first dose of Moderna vaccine. The most intense lymph node demonstrates a $SUV_{max}$ of 13.1, and measures 9 mm in the short axis. These lymph nodes are ipsilateral to the vaccine injection and contralateral to the known primary malignancy and thought to be vaccine-related rather than metastatic disease. B) In comparison, this 69-year-old female patient with minimally FDG-avid left perihilar adenocarcinoma, 7 days after the first dose of Moderna vaccine, demonstrates a more typical PET/CT appearance. The most intense axillary lymph node is barely perceivable on the MIP image, measuring 7 mm in the short axis with a $SUV_{max}$ of 2.7. Incidental benign compression fracture in the midthoracic spine is also noted. C) In this 59- year-old male with primary adenocarcinoma in the left perihilar region, moderate hypermetabolic activity ($SUV_{max}$ 6.6) is noted in a 9 mm left axillary lymph node 10 days after the first dose of Pfizer-BioNTech vaccine.

Patients with non-FDG-avid lymph nodes were similarly subcategorized by weeks post-injection. The proportion of non-FDG-avid patients tended to increase with time post vaccination from 9.4% in the first four weeks, to 21.3% beyond the fifth week (Table 1). There was no statistically significant difference between the three groups, in term of patient's age and sex ratio. The top three most encountered malignancies in all three groups remained the same.

### *Effects of different vaccines and number of doses*

Between the two patient groups who received either one of the two mRNA vaccines, there was no statistically significant difference in basic demographics (Table 2). In terms of the PET/CT measurements, there was no statistically significant differences in $SUV_{max}$ measurements or nodal size between the two groups.

Table 2
Effect of different mRNA vaccination on PET/CT. There is no statistical significance in patient's basic demographics, number of days from vaccination, SUVmax values or nodal size between the two groups.

| | Pfizer-BioNTech | Moderna |
|---|---|---|
| Number of patients with ≥ 1 FDG avid lymph node | 93 | 29 |
| Age | 66.2 ± 2.3 | 67.7 ± 3.3 |
| Sex ratio (M:F) | 1:1.1 | 1:1 |
| Days from vaccination | 31.2 ± 3.9 | 27.8 ± 9.1 |
| SUVmax | 2.4 ± 0.3 | 2.7 ± 0.7 |
| Lymph node size (mm) | 6.3 ± 0.5 | 5.9 ± 0.7 |

There is a statistically significant difference in $SUV_{max}$ value in patients who received one or both doses of the mRNA vaccine. The average $SUV_{max}$ value in patients who received the first dose was 2.1 ± 0.3, versus an average $SUV_{max}$ value of 3.0

± 0.4 in patients who received both doses, although this is confounded by the fact that the PET/CT studies are done earlier in the second group (34.5 ± 4.9 days, versus 15.2 ± 3.2 days). There is no statistically significant difference in nodal size in these two groups (5.7 ± 0.5 mm versus 6.6 ± 0.6 mm).

*Rare exceptions*

The typical FDG uptake in the axillary lymph nodes post COVID-19 vaccination was mild to moderate in our study (Fig. 3B and C). However, there were notable exceptions.

In a patient with biopsy-proven lung cancer in the right middle lobe ($SUV_{max}$=12.5), there were no other abnormal findings except two hypermetabolic lymph nodes in the left axilla (index node 0.9 × 1.1 cm, $SUV_{max}$=13.1). The patient was 9 days post vaccination with Moderna vaccine in the left deltoid (Fig. 3A). The case was discussed at our local thorax tumor board and the lymphatic activity was considered to be vaccine-related.

## Discussion and Conclusion

Vaccine-associated lymphadenopathy is a well-established clinical scenario. In the published COVID-19 vaccine clinical trial data, axillary swelling or tenderness occurs in 10.1% and 14.2% of patients after first and second doses in receipts of Moderna vaccine [8]. In the Pfizer-BioNTech cohort, the incidence of possible vaccine related lymphadenopathy is reported to be 0.3% in all participants, slightly more common in the younger age group, age 16-55, at 0.5% [9].

Our data suggests that vaccine-associated lymph node inflammation is a more common clinical entity than what has been reported previously; 62.4% of the patients with a history of COVID-19 vaccination demonstrated at least one FDG-avid lymph node. The discrepancy between the clinical findings and our imaging findings may suggest the activity may be physiologic. Alternatively, if inflammation is present, it is most likely subclinical and low grade.

Regarding the time course, we found that the FDG activity was the most intense in the first two weeks. The activity decreases and gradually resolves over time, which suggests that it is likely transient. From our data, this activity likely returns to background level 5 to 6 weeks post vaccination. This could be considered as a reasonable time point for follow up in case of any diagnostic uncertainty, such as in the special case presented above. There is an apparent further downward trend in axillary nodal metabolic activity beyond the end of the fourth week although it might not be statistically significant. This could serve as a starting point for future research, by recruiting more patients and improving statistics.

In term of patient's age, we found that younger vaccinated patients were more likely to develop FDG-avid axillary lymph node, which mirrors the clinical findings published in the Pfizer-BioNTech vaccine trial [9]. Low grade axillary nodal FDG activity may simply reflect increased physiologic activity post vaccination, rather than true inflammation. Our data also suggests that there is no set size criterion to predict metabolic activity.

There are several limitations in the study. Firstly, as the axillary lymph nodes are often sub-centimeter in size, partial volume average artifact may result in underestimation of the true metabolic activity. Secondly, as most of the patients have an underlying malignancy, diagnosis of vaccine related hypermetabolic axillary lymph nodes is usually based on clinical consensus, without definite pathologic confirmation. At the same time, pathologic diagnosis might be difficult to obtain for a patient population large enough to acquire statistical significance. Follow-up imaging may be difficult to justify as well for most of the patients, due to radiation and financial concerns, as the activity is often mild and can only be seen on PET/CT studies. Thirdly, we have only encountered the three vaccines approved by Health Canada. Unfortunately, the number of patients who had received the Oxford–AstraZeneca vaccine, or a mixture of different vaccines, is too small for us to draw any useful conclusions. The other adenovirus vector-based vaccines were not encountered during this study and their effects remain unknown. Finally, further expansion to include all vaccinated patients who had a PET/CT study in the entire study period would likely improve statistical significance of findings in the non-FDG avid group. Nevertheless, even in this relatively small sample size statistically significant findings between the two groups were demonstrated.

In conclusion, vaccine related ipsilateral hypermetabolic lymph nodes are a common incidental finding on 18-FDG PET/CT post COVID-19 vaccination. The typical intensity of the FDG uptake is mild to moderate and it tends to decrease over time, the majority resolving by the fourth to fifth weeks post vaccination. Vaccine related ipsilateral hypermetabolic lymph nodes are more likely to occur in younger patients, and often subclinical. Medical imagers should be aware of this entity to avoid over-diagnosis. Careful patient history in the form of a pre-PET/CT questionnaire may be helpful.

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