Novel $^{68}$Ga-FAPI PET/CT Offers Oncologic Staging Without COVID-19 Vaccine–Related Pitfalls

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In the setting of ongoing coronavirus disease 2019 vaccination, vaccine-related tracer uptake in locoregional lymph nodes has become a well-known issue in tumor staging by $^{18}$F-FDG PET/CT. $^{68}$Ga-fibroblast-activation protein inhibitor (FAPI) PET/CT is a new oncologic imaging tool that may overcome this limitation. **Methods:** We assessed postvaccine head-to-head and same-day $^{18}$F-FDG and $^{68}$Ga-FAPI-46 PET/CT findings in a series of 11 patients from a large, prospective imaging registry. All patients with documented tracer uptake in locoregional lymph nodes on PET/CT or PET/MRI, after vaccination within 6 wk, were eligible for investigation. **Result:** Significant visual lymph node uptake adjacent to the injection site was noted in 11 of 11 (100%) patients with $^{18}$F-FDG PET/CT, versus 0 of 11 (0%) with $^{68}$Ga-FAPI PET/CT. $^{18}$F-FDG detected 73% and $^{68}$Ga-FAPI PET/CT 94% of all tumor lesions. **Conclusion:** In this case-series study, $^{68}$Ga-FAPI showed its potential to avoid $^{18}$F-FDG PET/CT postvaccination pitfalls and presented superior tumor localization.

Key Words: PET; PET/CT; COVID-19; tumor staging; vaccine-related pitfalls

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Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic in 2019 and the start of global mass vaccination in November 2020, several clinical studies have addressed the issue of reactive tracer accumulation in locoregional lymph nodes and upper-arm muscles (1). At local sites, $^{18}$F-FDG is taken up by immune cells responding to the messenger RNA inflammatory stimulus (2–4). This observation is concerning because vulnerable groups, such as oncologic patients, undergo both regular booster shots and medical imaging. False-positive findings on $^{18}$F-FDG PET due to uptake in inflammatory cells may trigger false management decisions.

$^{68}$Ga-fibroblast-activation protein inhibitor (FAPI) PET/CT is a novel imaging test directed at cancer-associated fibroblasts in the tumor stroma. Because of its unique mechanism targeting only activated fibroblasts and subtypes of cancer-associated fibroblasts, $^{68}$Ga-FAPI PET/CT may be able to avoid false-positive postvaccine uptake. $^{68}$Ga-FAPI PET/CT has emerged as a potential alternative to $^{18}$F-FDG PET/CT in many tumor types and may avoid locoregional pitfalls caused by vaccination. Here, we assess same-day head-to-head postvaccine $^{18}$F-FDG and $^{68}$Ga-FAPI PET/CT uptake in patients from a large, prospective registry of oncologic imaging collected during the ongoing mass vaccination campaign in Germany.

**MATERIALS AND METHODS**

We selected 11 patients with $^{68}$Ga-FAPI and $^{18}$F-FDG PET/CT (May 2021 to April 2022) from our prospective database, which is part of a large, prospective observational study (NCT04571086). Enrollment is offered to all patients who undergo $^{68}$Ga-FAPI-46 PET in our department. Eleven patients met the following criteria: same-day $^{68}$Ga-FAPI and $^{18}$F-FDG PET for oncologic staging or restaging, with $^{18}$F-FDG at least 4 h after $^{68}$Ga-FAPI PET; $^{68}$Ga-FAPI or $^{18}$F-FDG tracer uptake in locoregional lymph nodes, with a visually positive target-to-background ratio on PET/CT; COVID-19 vaccination within 6 wk; and no change in treatment between PET and vaccination (Fig. 1).

The study was approved by the ethics committee (approvals 20-9485-BO and 19-8991-BO), and all patients gave written informed consent for enrollment into a prospective observational trial (NCT04571086).

Lymph nodes were considered positive when demonstrating visually focal uptake above the background level. Visual readings were performed by 2 nuclear medicine physicians in consensus. The median injected dose was 333 MBq (interquartile range [IQR], 245–421 MBq) for $^{18}$F-FDG and 102 MBq (IQR, 79–125 MBq) for $^{68}$Ga-FAPI. Follow-up data included imaging and clinical information. All patients fasted for 6 h before the $^{18}$F-FDG scan, and blood glucose level ($<$200 mg/dL) was measured. Descriptive statistics are provided. An ANOVA was applied for assessing differences on SUV among the different time frames after vaccination. The SUV was measured in the center of each lymph node, determined on PET/CT images.

Six (55%) patients underwent imaging on a Siemens Biograph Vision and 5 (45%) on a Siemens Biograph mCT device. SUVpeak was selected on the basis of phantom cross-calibration for the PET/CT devices to achieve reproducible results.
RESULTS

Patient characteristics are shown in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org). After database screening, 11 patients (5 men and 6 women) were included. The mean age was 44 y (IQR, 34–54 y). Three (27%) underwent PET for staging and 8 (73%) for restaging. Five (45%) patients had sarcoma, and 6 (55%) patients had carcinoma. When combined findings from 68Ga-FAPI and 18F-FDG scans were considered, 3 (27%) patients showed primary lesions only, 1 (9%) patient showed locoregional lesions, and 7 (64%) patients showed distant metastases. Distant metastatic disease was noted in visceral organs, bone, and soft tissue in 5 (45%), 1 (9%), and 1 (9%) patients, respectively. The thoracic cavity was tumor-free in 7 (64%) patients. Before chemotherapy, 2 (18%) of 11 patients had a thoracic primary tumor, that is, lung (n = 1) and breast cancer (n = 1), which have a higher likelihood of axillary nodal involvement (Supplemental Table 2).

Ten (91%) patients received BNT162b2 vaccine and 1 (9%) received messenger RNA1273 vaccine at a median interval of 19 d (IQR, 8–30 d) before PET/CT. Eleven (100%) patients demonstrated focal 18F-FDG tracer uptake in axillary lymph nodes on PET/CT; none of the patients had focal 68Ga-FAPI uptake. Details are listed in Supplemental Table 3. SUV at different times after vaccination (Fig. 2A) demonstrated the highest 18F-FDG accumulation in lymph nodes at 2–4 wk after vaccination (ANOVA P = 0.002), whereas no increase in uptake on 68Ga-FAPI was observed at any of the time points (Fig. 2B, ANOVA P = 0.79).

Imaging follow-up data at an average of 120 d (IQR, 44–196 d) confirmed reactive nodal uptake in all patients: a decrease in uptake was documented in all 4 (100%) lymph nodes of the patient who underwent follow-up 18F-FDG PET/CT. A decrease in lymph node size was documented for all patients (on CT, n = 5 [100%]; on ultrasound, n = 4 [100%]). One patient underwent a biopsy confirming reactive lymphoid hyperplasia with no evidence of malignancy (Supplemental Fig. 1). Further tracer accumulation at the injection site in the deltoid muscle was detected in 5 (45%) patients (Supplemental Fig. 2.2). Another patient showed generalized tracer accumulation in the bone marrow on 18F-FDG PET in addition to splenic uptake above the level of liver uptake, indicating reactive bone marrow and splenic activation by a vaccine-induced immune response (Supplemental Fig. 3). According to combined 18F-FDG and 68Ga-FAPI PET/CT reports, none of the patients had tumor involvement of the arm or axillary lymph nodes. One patient with breast cancer demonstrated new bone metastases 4 y after initial therapy. Local recurrence was not noted, and focal nodal uptake was seen ipsilateral to the vaccination site and contralateral to the former tumor site.

The combined analysis of 68Ga-FAPI and 18F-FDG scans detected, in total, 102 (100%) tumor lesions (primary, 6 [6%]; locoregional, 26 [25%]; distant nodal, 10 [10%]; lung, 7 [7%]; liver, 18 [18%]; bone, 28 [27%]; and soft tissue, 7 [7%]). Lesion detection efficacy was higher for 68Ga-FAPI than for 18F-FDG PET (96 [94%] vs. 74 [73%]). 68Ga-FAPI PET detected additional tumor lesions in the lung (7 [100%] vs. 5 [71%]), liver (17 [94%] vs. 9 [50%]), and bone (28 [100%] vs. 23 [82%]). The superior efficacy was based on a higher detection rate in 3 patients with different tumor entities (ovarian cancer, solitary fibrous tumor, and breast cancer). There was no 18F-FDG–positive, 68Ga-FAPI–negative primary tumor lesion (Supplemental Table 4).

DISCUSSION

The COVID-19 pandemic is active globally, with an estimated 12.8 billion vaccine doses given and 627.1 million registered infections as of October 21, 2022 (5). Vaccines aim to decrease COVID-19 spread and severe disease, protecting vulnerable groups, including cancer patients (6). Repeat vaccinations have been endorsed by the
Completely understood. Transforming growth factor (17). Fittingly, none of the patients demonstrated focal 68Ga-FAPI uptake in locoregional lymph nodes after vaccination. In addition, 68Ga-FAPI PET demonstrated higher detection efficacy when compared with 18F-FDG PET/CT both for locoregional and for distant staging. Tumor detection was based on the PET/CT findings; however, lesions were not verified by imaging follow-up, and findings are limited by a low sample size. Superior detection for 68Ga-FAPI versus 18F-FDG PET is in line with previous reports on carcinoma of unknown primary, sarcoma, and breast carcinoma imaging (18). Our findings indicate that 68Ga-FAPI PET delivers oncologic staging with accuracy equal or superior to that of 18F-FDG PET but with no risk of a false diagnosis after vaccination (19).

An ongoing prospective trial at our institution aims to assess accuracy and correlation with histopathology for various types of cancer (clinicaltrials.gov, NCT05160051). Our study was limited by a low number of patients and a low histopathologic confirmation rate for lymph node findings.

**CONCLUSION**

Increased annual vaccinations are expected for vulnerable groups, including cancer patients. 18F-FDG may trigger costly follow-up investigations and false management decisions. In our study, 68Ga-FAPI PET, a promising novel imaging tool, avoided postvaccination lymph node and bone marrow pitfalls and provided accurate oncologic staging. 68Ga-FAPI PET should be assessed as an alternative to 18F-FDG PET in ongoing (NCT05160051) and future prospective studies.

**DISCLOSURE**

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**KEY POINTS**

**QUESTION:** Can 68Ga-FAPI PET prevent COVID-19 vaccine-related reactive lymph node uptake?

**PERTINENT FINDINGS:** We compared 18F-FDG and 68Ga-FAPI PET/CT acquired on the same day within 6 wk of COVID-19 vaccination in 11 oncology patients. Although 18F-FDG was visually positive in 11 patients, 68Ga-FAPI had higher tumor detection efficacy and showed no vulnerability to vaccine-related tracer uptake in any patients. Additionally, the 18F-FDG uptake intensity was time-dependent on the vaccination interval. 68Ga-FAPI was visually negative at all time points.

**IMPLICATIONS FOR PATIENT CARE:** 68Ga-FAPI avoids vaccine-associated reactive lymph node uptake and is therefore superior to 18F-FDG in tumor staging up to 6 wk after COVID-19 vaccination.

**REFERENCES**

1. Eifer M, Eshet Y. Imaging of COVID-19 vaccination at FDG PET/CT. Radiology. 2021;299:E248.
2. Nawwar AA, Searle J, Lyburn ID. Features of systemic immune response from COVID-19 vaccination on 18F-FDG PET/CT: Clin Nucl Med. 2022;47:e89-e90.
3. Becker AS, Perez-Johnston R, Chikarmame SA, et al. Multidisciplinary recommendations regarding post-vaccine adenopathy and radiologic imaging: radiology scientific expert panel. Radiology. 2021;300:E323–E327.
4. 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;7:1241–1242.
5. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Johns Hopkins website. https://coronavirus.jhu.edu/map.html. Accessed October 21, 2022.
6. Wang Q, Berger NA, Xu R. Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection. JAMA Oncol. 2021;7:220–227.
7. Barrière J, Carles M, Audigier-Valette C, et al. Third dose of anti-SARS-CoV-2 vaccine for patients with cancer: should humoral responses be monitored? A position article. Eur J Cancer. 2022;162:182–193.
8. Rubin R. COVID-19 vaccine makers plan for annual boosters, but it’s not clear they’ll be needed. *JAMA*. 2021;326:2247–2249.

9. Chudasama RV, Khunti K, Ekezie WC, et al. COVID-19 vaccine uptake and hesitancy opinions from frontline health care and social care workers: Survey data from 37 countries. *Diabetes Metab Syndr*. 2022;16:102361

10. Bar-On YM, Goldberg Y, Mandel M, et al. Protection by 4th dose of BNT162b2 against omicron in Israel. medRxiv website. https://www.medrxiv.org/content/10.1101/2022.02.01.22270232v1. Published February 1, 2022. Accessed December 8, 2022.

11. Treglia G, Cuzzocrea M, Giovanella L, Elzi L, Muisio B. Prevalence and significance of hypermetabolic lymph nodes detected by 2-[18F]FDG PET/CT after COVID-19 vaccination: a systematic review and a meta-analysis. *Pharmaceuticals*. 2021;14:762.

12. Ozutemiz C, Krystosek LA, Church AL, et al. Lymphadenopathy in COVID-19 vaccine recipients: diagnostic dilemma in oncologic patients. *Radiology*. 2021;300:E296–E300.

13. 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;38:894–898.

14. Weeks JK, O’Brien SR, Rosenspire KC, Dubroff JG, Pantel AR. Evolving bilateral hypermetabolic axillary lymphadenopathy on FDG PET/CT following 2-dose COVID-19 vaccination. *Clin Nucl Med*. 2021;46:1011–1012.

15. Indini A, Costa S, Ierardi AM, Rjavec E, Passoni E, Grossi F. COVID-19 vaccination mimicking lymph-node progression in a patient with melanoma: a case report. *Melanoma Res.* 2021;31:490–493.

16. Andreesciani F, Ricci M, Grasso RF, Zobel BB, Quattrocci CC. COVID-19 vaccination simulating lymph node progression in a patient with prostate cancer. *Radiol Case Rep*. 2022;17:2996–2999.

17. Krepela E, Vanickova Z, Hrabal P, et al. Regulation of fibroblast activation protein by transforming growth factor beta-1 in glioblastoma microenvironment. *Int J Mol Sci*. 2021;22:1046.

18. Giesel FL, Kratochwil C, Schlittenhardt J, et al. Head-to-head intra-individual comparison of biodistribution and tumor uptake of 68Ga-FAPI and 18F-FDG PET/CT in cancer patients. *Eur J Nucl Med Mol Imaging*. 2021;48:4377–4385.

19. Cermik TF, Ergu L N, Yılmaz BA, Mercanog Lu GL. Tumor imaging with 68Ga-DOTA-FAPI-04 PET/CT: comparison with 18F-FDG PET/CT in 22 different cancer types. *Clin Nucl Med*. 2022;47:e333–e339.