2022 SNMMI Highlights Lecture: Oncology and Therapy, Part 1

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From the Newsline Editor: The Highlights Lecture, presented at the closing session of each SNMMI Annual Meeting, was originated and presented for more than 30 years by Henry N. Wagner, Jr., MD. Beginning in 2010, the duties of summarizing selected significant presentations at the meeting were divided annually among 4 distinguished nuclear and molecular medicine subject matter experts. Each year Newsline publishes these lectures and selected images. The 2022 Highlights Lectures were delivered on June 14 at the SNMMI Annual Meeting in Vancouver, Canada. In this issue we feature the first part of the lecture by Heiko Schöder, MD, MBA, Chief of the Molecular Imaging and Therapy Service in the Department of Radiology at Memorial Sloan Kettering Cancer Center and professor of radiology at Weill Cornell Medical College (both in New York, NY), who spoke on oncology and therapy topics at the meeting. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2022;63[suppl 2]).*

It is a pleasure to present the highlights in oncology and therapy from the SNMMI Annual Meeting, and I thank the organizers for reinviting me. More than 400 abstracts were considered in preparing this lecture, and, needless to say, only a few could be included in the limited presentation time. I want to thank all the researchers who provided me with slides.

Trends

At the 2022 SNMMI Annual Meeting we saw a new trend in geographic origins of oncology abstracts, with almost half coming from Asia and Australia (48%) and smaller contributions from the United States (25%), Europe (18%), Canada (5%), Africa (2%), and South America (1.5%). Major representation from countries in this category came from China (105 abstracts), the United States (103), Italy (39), India (39), and Germany (29). Quantity is not always or necessarily quality; the majority of the highest rated abstracts came from North America (42%), followed by Asia/Australia (35%), and Europe (23%). In contrast to last year, when the subject-matter distribution was about 80% diagnostic and 20% therapeutic, this year we saw 76% diagnostic- and 24% therapeutic-related abstracts. This may indicate a general trend, part of the growing interest in nuclear medicine therapies that will be reflected in this lecture.

It is always interesting to look at general trends in subject matter. In terms of keywords in titles of oncologic and therapeutic presentations at this meeting, FDG was still dominant (105 abstracts). However, it was followed closely by prostate-specific membrane antigen (PSMA) (101), with fibroblast-activation protein inhibitor (FAPI) rapidly rising (29). (This trend is also reflected in the published literature). Top radiolabels represented in abstract titles included ^{18}F (121), ^{68}Ga (78), ^{177}Lu (37), and ^{225}Ac (11).

Heiko Schöder, MD, MBA

Clinical Diagnostics

FAPI Imaging

We will begin with the youngest and newest kid on the block, FAPI, and then review notable PSMA and FDG presentations. A large number of studies focused on FAPI, many of which were conducted in smaller patient samples. In general, these studies reported that FAPI has 1 or more advantages over FDG for disease detection and, in some instances, for staging. The studies provided evidence of FAPI benefit in differentiated thyroid cancer, gastrointestinal (GI) malignancies, breast cancer, hepatocellular carcinoma, and others. The theme is basically the same: FAPI provides very interesting data, but what we clearly need are more and larger prospective studies looking systematically at its utility in these diseases.

I have chosen only 1 of these FAPI abstracts to highlight here as an example. Chen et al. from the First Affiliated Hospital of Xiamen University (China) reported on "Comparison of ^{68}Ga-FAPI and ^{18}F-FDG uptake in patients with gastric signet-ring cell carcinoma: A multicenter retrospective study" [2370]. As you know, this disease is difficult to image with ^{18}F-FDG PET. Figure 1 highlights the higher uptake intensity and greater tumor-to-background ratios of the ^{68}Ga-FAPI agent. When compared with ^{18}F-FDG in 34 patients (16 men, 18 women; median age, 51 y [range, 25–85 y]), the FAPI agent had higher detection rates in primary tumors (73% vs 18%), local recurrence (100% vs 29%), nodal metastases (77% vs 23%), and distant metastases (93% vs 39%). (Both modalities missed 6 smaller [(0.3–1.1-cm] primary tumors.) More interesting, perhaps, is the fact that there were no lesion sites in which FDG provided an advantage over FAPI. In the majority of lesions FAPI provided more information. The authors concluded that their data suggest that "^{68}Ga-FAPI PET has the potential to replace ^{18}F-FDG PET in the diagnosis of patients with gastric signet-ring cell carcinoma."

Other notable studies on FAPI PET/CT were presented by: Fu et al. from the First Affiliated Hospital of Xiamen University (China), who reported on "^{68}Ga-FAPI PET/CT in metastatic differentiated thyroid cancer detection: Comparison with ^{18}F-FDG PET/CT" [2361]; Ballal et al. from the All India Institute of Medical Sciences (New Delhi) and the TRIGA Research Reactor/Johannes Gutenberg Universität Mainz (Germany), who reported on "Head-to-head comparison of ^{68}Ga-DOTA.SA.FAPi versus ^{18}F-FDG PET/CT in

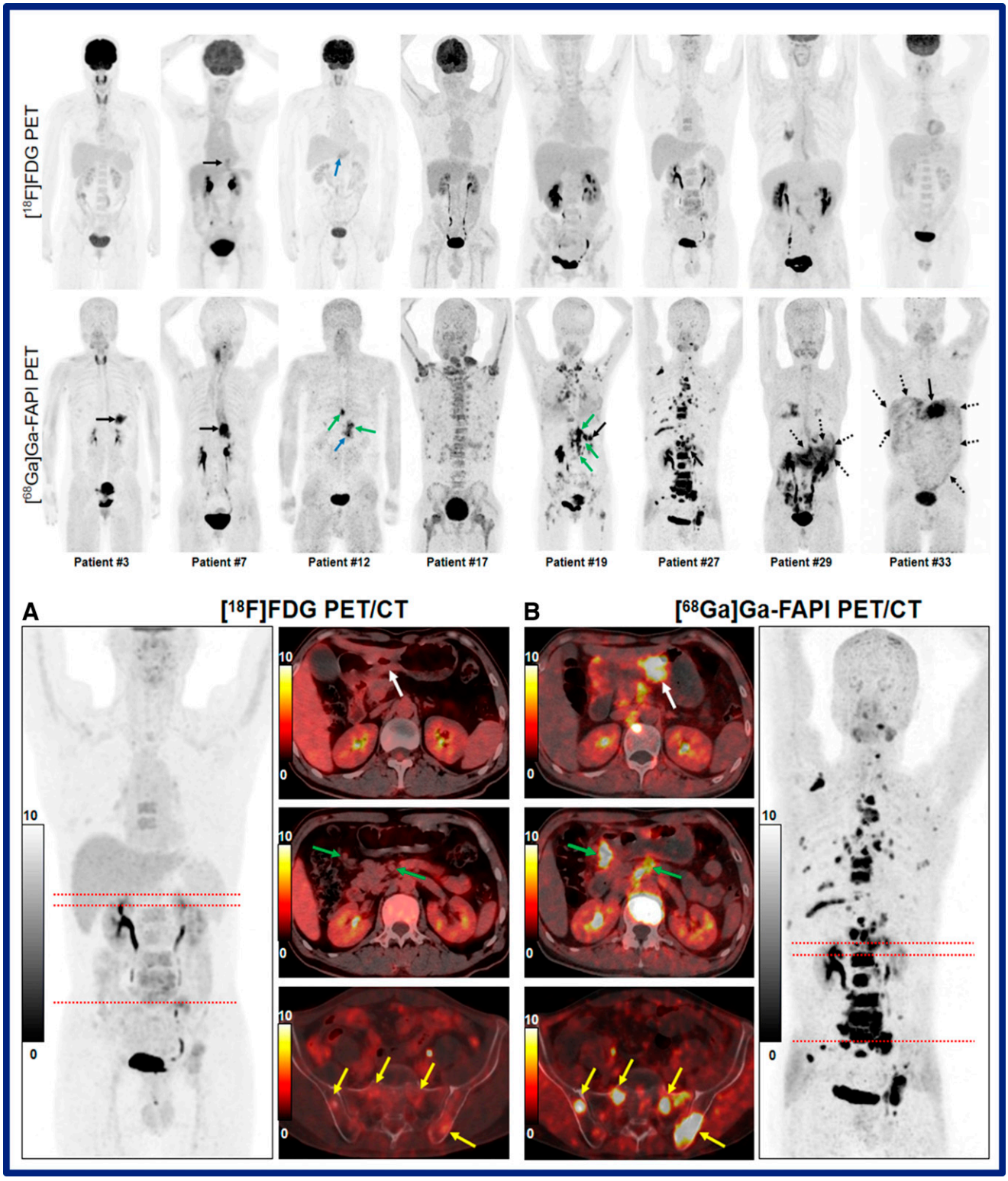

FIGURE 1. Comparison of ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in gastric signet-ring cell carcinoma. Top: Example patients imaged with ^{18}F-FDG (top row) and ^{68}Ga-FAPI (bottom row) PET/CT. Bottom: Comparative imaging in a single patient with ^{18}F-FDG (left) and ^{68}Ga-FAPI (right) PET/CT. ^{68}Ga-FAPI imaging resulted in higher detection rates in primary tumors (73% vs 18%), local recurrence (100% vs 29%), nodal metastases (77% vs 23%), and distant metastases (93% vs 39%).

radioiodine refractory differentiated thyroid cancer patients" [2371]; Li et al. from Peking Union Medical College Hospital and the Chinese Academy of Medical Sciences (Beijing, China), who reported on "^{68}Ga-FAPI-04 and ^{18}F-FDG PET/CT for identifying primary and metastatic lesions in patients with gastrointestinal cancer: A comparative study"

[2369]; Novruzov et al. from the Azerbaijan National Centre of Oncology (Baku, Azerbaijan), who reported on "Head-to-head comparison of ^{68}Ga-FAPI-46 PET/CT and ^{18}F-FDG PET/CT in breast carcinoma staging: A clinical trial update from Azerbaijan" [2372]; Wu et al. from Peking Union Medical College Hospital and the Chinese Academy of Medical Sciences (both in Beijing, China), who reported on "^{68}Ga-FAPI and ^{18}F-FDG PET/CT in evaluation of primary and metastatic lesions in late-stage hepatocellular carcinoma" [2373]; and Pang et al. from the First Affiliated Hospital of Xiamen University/Xiamen University (China), who reported that "^{68}Ga-FAPI PET/CT improves tumor detection and staging in patients with pancreatic cancer and comparison with ^{18}F-FDG PET/CT" [2374].

Prostate Cancer

Prostate cancer remains a challenging problem worldwide. It is the dominant malignancy in the male population in 112 countries: all of North and South America, Australia, and much of Africa and Europe. *The Lancet* Commission on Prostate Cancer, introduced in 2021 (James et al., *The Lancet*. 2021;397[10288]:1865–1866), cites "genomic tools and imaging, particularly PSMA PET/CT" as "likely to be increasingly important in treatment decisions in the future." The commission will assess these and other diagnostic and treatment developments to determine "what is likely to constitute the best approach in different health care settings [including in lower middle–income countries] and make policy and clinical practice recommendations."

At this meeting, as in the peer-reviewed literature, some studies on PSMA agents in prostate cancer are exciting and others, although possibly less exciting, are essential for regulatory approval and for conduct of clinical trials. Kuo et al. from the University of Arizona (Tucson), Invicro (Needham, MA), Medstar Georgetown University Hospital (Washington, DC), Warren Alpert Medical School of Brown University (Providence, RI), and McMaster University (Hamilton, Canada), on behalf of the SPOTLIGHT Study Group, reported on "Inter- and intrareader reproducibility of ^{18}F-rhPSMA-7.3 PET image interpretation in patients with suspected prostate cancer recurrence: Results from a phase 3, prospective, multicenter study (SPOTLIGHT)" [2539]. Their data indicated a high degree of inter- and intrareader agreement across 3 blinded readers given the same set of scans after completing the same training. Interreader agreement was >75% overall and greatest for the pelvic lymph node region, with 87% concordance. Intrareader agreement was >85% overall. Although reproducibility was lower for the prostate/prostate bed than other regions, the substantial reproducibility in regions outside the prostate fossa is of clinical importance because of the potential to influence treatment selection. These types of studies are important for creation and validation of the large clinical trial data needed to obtain regulatory approval and reimbursement for PSMA agents and other novel radiopharmaceuticals and techniques.

Olivier et al. from the Centre Hospitalier Universitaire Nancy (France), the Centre Léon Bérard (Lyon, France), Centre Jean Perrin (Clermont-Ferrand, France), Hôpital Européen Georges-Pompidou (Paris, France), and ABX Advanced Biochemical Compounds (Radeberg, Germany) reported on a "Phase III study of ^{18}F-PSMA-1007 versus ^{18}F-fluorocholine PET to compare the detection rate of prostate cancer lesions in patients with biochemical recurrence after previous definitive treatment for localized prostate cancer" [2537]. This study contributed to the regulatory approval of PSMA-1007 in France. We all know instinctively that PSMA is a better imaging agent than others we have had available in prostate cancer, but it is important to have the hard data for regulatory approval. The design of this multicenter study is interesting. Patients (n = 190) in an intent-to-treat population with suspected prostate cancer recurrence underwent both choline and PSMA imaging in a random order. Blinded readers used a 3-point qualitative scale (no recurrence, undetermined, recurrence) to report findings. In 172 patients, PET imaging resulted in a more accurate diagnosis as determined by an independent panel of experts and additional data. Of these more accurate diagnoses, 72% were attributed to ^{18}F-PSMA-1007, 5% to ^{18}F-fluorocholine, and 23% to the 2 tracers equally. ^{18}F-PSMA-1007 PET/CT identified disease relapse in more patients than did ^{18}F-fluorocholine PET/CT, especially at low prostate-specific serum antigen levels.

In developing clinical trials to assess and validate PSMA imaging, it will be important to move beyond counting and measuring each individual lesion to the increasing application of artificial intelligence (AI) tools that facilitate lesion identification, tracking, activity measurement, and even assessment of volume change over time. Calais et al. from the University of California Los Angeles, Technical University of Munich (Germany), Stanford University (CA), EXINI Diagnostics AB (Lund, Sweden), Lund University (Sweden), Veterans Affairs Greater Los Angeles (CA), and Memorial Sloan Kettering Cancer Center (New York, NY) reported on a "Prospectively planned and independent validation of aPROMISE in a phase III CONDOR study for rapid lesion detection and standardized quantitative evaluation for ^{18}F-DCFPyL (PSMA) imaging in prostate cancer" [2496]. The aPROMISE tool performs both AI-based CT segmentation of bone and soft tissue and hotspot detection/segmentation to yield total PSMA SUV_{mean}, total PSMA tumor volume, and a total PSMA score (Fig. 2). The AI tool required relatively little observer interaction and was comparable or superior in accuracy to manual assessment. The time needed to score an ^{18}F-DCFPyL scan using aPROMISE in a patient with metastatic disease was dramatically shorter (median, 1.4 min) than manual reading time in the original CONDOR study (~15 min). The authors concluded that the AI-based total PSMA score "warrants future clinical investigation to define its clinical context of use as an imaging biomarker."

Many studies and guidelines have been published highlighting the importance of PET imaging for radiation treatment planning in lung, cervix, and other cancers. It comes as no surprise that PSMA can also contribute to radiation treatment planning in prostate cancer. In salvage radiotherapy, radiation

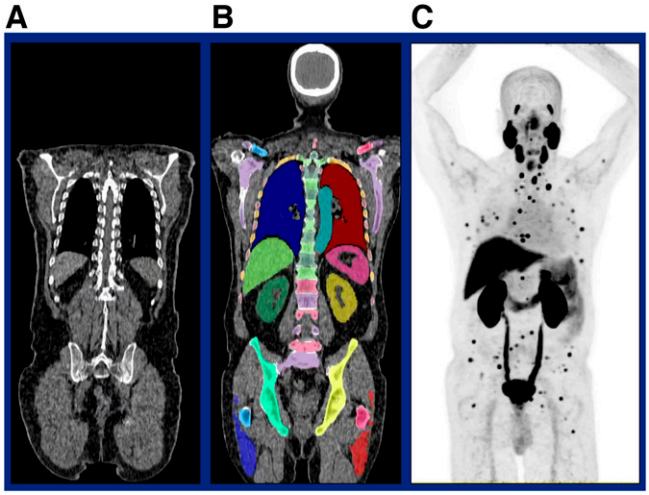

FIGURE 2. aPROMISE for rapid lesion detection and standardized quantitative evaluation for ^{18}F-DCFPyL (PSMA) imaging in prostate cancer. In this example ^{18}F-DCFPyL image (A), the aPROMISE tool performed both AI-based CT segmentation of bone and soft tissue (B) and hotspot detection/segmentation (C) to yield total PSMA SUV_{mean}, total PSMA tumor volume, and a total PSMA score. The time needed to score an ^{18}F-DCFPyL scan using aPROMISE in metastatic disease was dramatically shorter (median, 1.4 min) than average manual reading time (~15 min).

oncologists currently use contouring guidelines based on expert consensus (e.g., those from RTOG) to determine the volume to be irradiated, without reference to information from patterns of recurrence seen on advanced imaging such as PSMA PET. Can PSMA PET imaging contribute to refining planning treatment volumes? Sonni et al. from the University of California Los Angeles, the University of Miami Miller School of Medicine (FL), and the VA Greater Los Angeles Healthcare System (CA) looked at "PSMA PET mapping of postoperative local recurrence and impact on prostate fossa contouring guidelines for salvage radiation therapy" [2538]. This study analyzed the typical patterns of prostate fossa recurrence after radical prostatectomy using ^{68}Ga-PSMA-11 PET/CT and evaluated the location of recurrences as compared to RTOG clinical target volume (CTV) definitions. In 127 patients, the authors found that PSMA-positive prostate fossa recurrences were fully covered by the CTV in 68 (54%) patients, partially covered in 43 (34%), and fully outside the CTV in 16 (13%). Recurrences were in close proximity to the rectal wall in 9% and bladder wall in 3% of all patients. The heatmaps in the example in Figure 3 clearly show that the standard volume (green), would not have included disease as shown on the PSMA PET. The authors concluded that PSMA PET–based data should inform the update of commonly used prostate bed contouring guidelines and that new contouring guidelines should consider reducing coverage at the anterior and superior borders (near pubic bone) and extending coverage at the posterior, posterolateral, and inferior borders.

Duan et al. from Stanford University (CA) recently published data on a ^{68}Ga-labeled bombesin antagonist (^{68}Ga-RM2) targeting gastrin-releasing peptide receptors (GRPRs), which are overexpressed in prostate cancer (*J Nucl Med.* 2022; May 12 ahead of print). Their results showed high agreement between ^{68}Ga-PSMA-11 and ^{68}Ga-RM2 imaging in patients with newly diagnosed intermediate- or high-risk prostate cancer. Against this background we heard a presentation at this meeting that found somewhat different results (perhaps related to patient selection). Tang et al. from Xiangya Hospital/Central South University (Changsha City, China) reported on "Comparison of ^{68}Ga-GRPR PET/CT with ^{68}Ga-PSMA PET/CT in initial diagnosing of prostate cancer using histopathology: Results from 207 participants" [2540]. Overall, ^{68}Ga-PSMA PET/CT performed better than ^{68}Ga-GRPR PET/CT. Although ^{68}Ga-GRPR PET/CT showed higher sensitivity in imaging low-risk disease, uptake in benign prostatic hyperplasia and early clinically insignificant prostate cancer was greater. The authors concluded that ^{68}Ga-GRPR PET/CT "may not be a direct competitor or have a complementary role" to that of PSMA PET/CT in fully characterizing prostate cancer at different stages. They added that the fact that ^{68}Ga-GRPR uptake was not specific for prostate cancer may suggest that GRPR may not be an imaging target for initial diagnosis. This raises a number of questions about the role of GRPR in prostate cancer diagnosis and indicates that we need more data.

Other Cancers

Carlsen et al. from the Righospitalet/Copenhagen University (Copenhagen, Denmark) reported on a "Prospective phase II trial of prognostication by ^{68}Ga-NODAGA-E [c(RGDyK)]2 PET/CT for integrin $\alpha_v\beta_3$ imaging in patients with neuroendocrine neoplasms (NENs)" [2209]. The authors used this novel tracer in PET/CT imaging in 97 patients with NENs of all grades (78% low-grade, 22% high-grade disease), and tumor SUV_{max} for each patient was evaluated as a predictor of progression-free and overall survival at follow-up of at least 1 y (median, 32 mo). During follow-up, 62 patients (64%) experienced progressive disease and 26

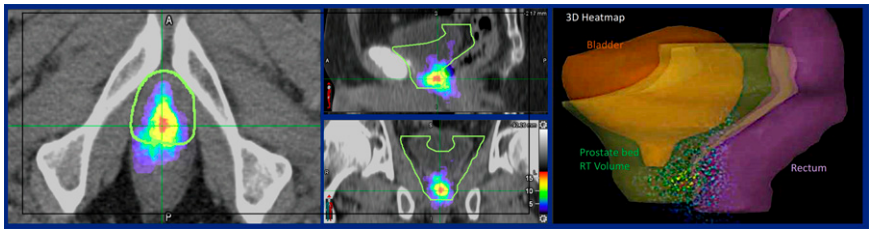

FIGURE 3. PSMA PET mapping of postoperative local recurrence compared with planning based on prostate fossa contouring guidelines for salvage radiation therapy. Patient example with: (left and middle) 2D heatmap of prostate bed recurrence on ^{68}Ga-PSMA-11 PET/CT and RTOG-based clinical treatment volume (CTV; green outline); (right) 3D heatmap of prostate bed recurrence on ^{68}Ga-PSMA-11 PET/CT and RTOG-based CTV, showing proximity to rectal and bladder walls. The authors concluded that PSMA PET–based data should inform the update of commonly used prostate bed contouring guidelines.

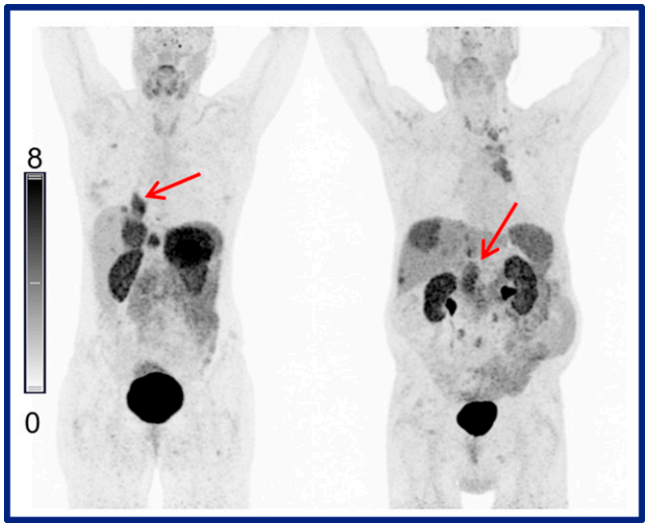

FIGURE 4. Prognostic utility of ^{68}Ga-NODAGA-E[c(RGDyK)]2 PET/CT integrin $\alpha_v\beta_3$ imaging in patients with neuroendocrine neoplasms (NENs). Example imaging in patients with a metastatic lung NEN (left) and a metastatic pancreatic NEN (right). Higher tracer uptake was significantly correlated with worse prognosis.

(27%) died. The intensity of ^{68}Ga-NODAGA-E[c(RGDyK)]2 uptake increased from grade 1 to grade 2 and was positive in almost all grade 3 patients (Fig. 4). Higher uptake correlated with worse prognosis. The suggestion is not that this tracer will replace DOTATATE but that it provides interesting additional prognostic information and so could serve as a companion diagnostic for treatments targeting $\alpha_v\beta_3$.

Ulaner et al. from the Hoag Family Cancer Institute (Irvine, CA) and the University of Southern California (Los Angeles) reported on "A prospective clinical trial of ^{18}F-fluorestradiol (^{18}F-FES) PET/CT compared to standard-of-care imaging in patients with newly diagnosed and suspected recurrent breast cancer" [2590]. ^{18}F-FES is an estrogen receptor–targeting PET tracer approved by the FDA as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. Particular utility is expected in patients with lobular breast cancer and those with heterogeneous metastatic disease (to determine the extent of estrogen receptor–positive disease). The authors of this study plan to enroll a total of 120 patients in 2 cohorts: 1 with locally advanced stage 2B–3C cancer and 1 with treated breast cancer and suspected recurrence. Patients undergo both ^{18}F-FES PET/CT and standard-of-care imaging (either CT/bone scan or ^{18}F-FDG PET/CT). Preliminary results reported at the SNMMI meeting on the first 39 patients enrolled suggest that ^{18}F-FES PET/CT detects more unsuspected distant metastases at initial staging and also at the time of suspected recurrence and may outperform current imaging methods for detection of clinically significant and treatment-altering disease in patients in both study cohorts. These cohorts represent novel patient populations that could benefit from ^{18}F-FES PET/CT. Figure 5 shows comparative ^{18}F-FDG PET/CT and ^{18}F-FES PET/CT imaging in a 59-y-old woman with previously treated invasive lobular breast cancer and elevated tumor markers. Benign granulomatous inflammation produced false-positive findings for lung recurrence on ^{18}F-FDG PET/CT, but these lesions were not ^{18}F-FES avid. However, many ^{18}F-FES–avid nodal, GI, osseous, and peritoneal metastases were missed on ^{18}F-FDG imaging. Tissue sampling of a peritoneal lesion demonstrated recurrent lobular breast cancer.

One of the main applications for ^{18}F-FDG PET has been and remains lymphoma, in which the tracer is used for staging, restaging, response assessment, and (more than in any other disease) for the conduct of clinical trials. In these trials, we are increasingly interested in looking at more than just the number of lesions and visual criteria by applying radiomics principles to extract more information. Eertink et al. from Amsterdam University Medical Centers (The Netherlands), Erasmus Medical Centre (Rotterdam, The Netherlands), the Universitätsklinikum Essen (Germany), the University of Duisburg-Essen/University Hospital Essen (Germany), Universitätsklinikum Leipzig (Germany), Kings College (London, UK), Guy's and St. Thomas Hospital (London, UK), Istituto Imaging Della Svizzera Italiana/Ente Ospedaliero Cantonale, Semmelweis University (Budapest, Germany), and VU University Medical Center (Amsterdam, The Netherlands), on behalf of the PETRA Consortium, reported that "^{18}F-FDG PET radiomics features result in more accurate prediction of outcome for diffuse large B-cell lymphoma (DLBCL) patients than currently used International Prognostic Index (IPI) score" [2490]. This group has done remarkable work in collecting and analyzing these and

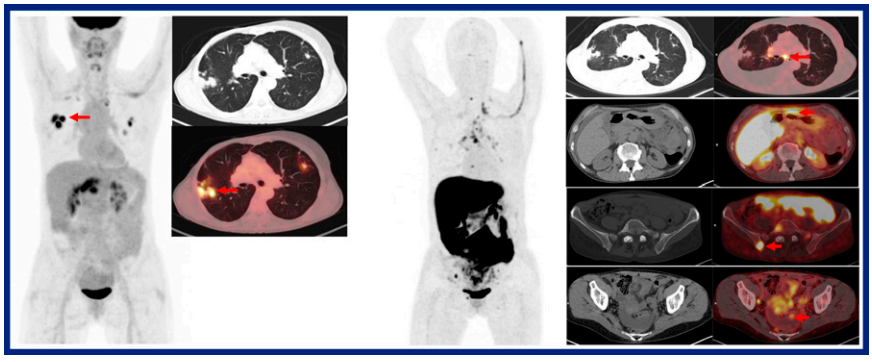

FIGURE 5. ^{18}F-fluorestradiol (^{18}F-FES) PET/CT vs standard-of-care imaging in newly diagnosed and suspected recurrent breast cancer. Comparative ^{18}F-FDG PET/CT (left) and ^{18}F-FES PET/CT (right) imaging in a 59-y-old woman with previously treated invasive lobular breast cancer and elevated tumor markers. Benign granulomatous inflammation produced false-positive findings for lung recurrence (arrows) on ^{18}F-FDG PET/CT; these lesions were not ^{18}F-FES avid. However, many ^{18}F FES-avid nodal, gastrointestinal, osseous, and peritoneal metastases (arrows) were missed on ^{18}F-FDG imaging. Tissue sampling of a peritoneal lesion demonstrated recurrent lobular breast cancer.

similar data and have already published a number of articles in this area. In their presentation at the SNMMI meeting, the authors reported on a study designed to externally validate the radiomics model developed in the HOVON-84 trial, using datasets from other DLBCL studies within the PETRA database, and to identify an optimal model to predict outcomes in that database by combining radiomics features and clinical parameters. They identified several criteria validated as providing prognostic information and applied these as model in other clinical trials including a total of 1,090 patients. The new PETRA model, combining quantitative radiomics features extracted from baseline ^{18}F-FDG PET/CT scans with components of the IPI score, significantly improved identification of patients at risk of relapse when treated with standard first-line treatment regimens compared with the IPI score alone. It is clear that these and other radiomics models will contribute to the use of multiple datapoints beyond SUV that will be crucial in the conduct of future clinical trials, particularly those drawing on multiple studies and very large patient populations.

We are often told that we are either not doing enough or are doing too much ^{18}F-FDG PET imaging. It is important that we address such criticisms with data on usage, utility, and compliance with validated guidelines. Sterbis et al. from the University of Colorado Medical Center (Aurora, CO) and the Edward Hines Jr. VA Hospital (Hines, IL) reported on "Lack of adherence to guideline-based imaging prior to adjuvant radiation in patients with non–small cell lung cancer (NSCLC)" [2596]. The authors used National Cancer Institute Surveillance, Epidemiology, and End Results program data (which should be taken with a grain of salt) in patients with NSCLC who had received adjuvant radiation therapy and undergone imaging with CT angiography or CT and/or PET with or without CT. They looked at adherence to National Comprehensive Cancer Network guidelines for imaging in this setting prior to adjuvant radiation therapy, which recommend that "PET/CT should be obtained preferably within 4 wk before treatment," ideally in the treatment position. In this study, only 56.3% of patients had preradiation imaging with PET. Predictors of decreased PET/CT usage included stage III or IV disease, initial treatment with chemotherapy or chemoradiation, black or other/unknown ethnicity, initial diagnosis with CT or CT angiography alone, and/or neuroendocrine or squamous cell biology. Both inferior overall survival and inferior cancer-specific survival were associated with decreased preradiation PET/CT usage. It is a challenge and an area of great concern that this modern and timely imaging technology is not widely enough available or routinely and equitably offered across all populations.

Dr. Schöder's lecture will be continued in the next issue of The Journal of Nuclear Medicine *and will cover clinical radionuclide therapy and experimental studies.*