2021 SNMMI Highlights Lecture: General Nuclear Medicine

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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 2021 Highlights Lectures were delivered on June 15 as part of the SNMMI Virtual Annual Meeting. In this issue we feature the lecture by Andrei Iagaru, MD, Professor of Radiology–Nuclear Medicine at Stanford University School of Medicine (CA) and Chief of the Division of Nuclear Medicine and Molecular Imaging at Stanford HealthCare, who spoke on general nuclear medicine highlights from the meeting. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in The Journal of Nuclear Medicine *(2021;62[suppl 1]).*

I am grateful for the opportunity to participate in my favorite part of the SNMMI Annual Meeting and honored to be a part of the Henry N. Wagner, Jr., MD, Highlights Symposium. I had the privilege to meet Dr. Wagner, who was a monumental figure in our field. In 2009 I received first an email and then a phone call from him, asking questions about our abstract submission that year. I was next to him at the June 15 press conference in Toronto (Canada), where he announced that figures from our submission had been named as the 2009 Image of the Year—an incredible honor that I cherish to this day.

COVID-19 and Nuclear Medicine

This has been a terrible year for so many people, and, although we are doing better here in the United States, much suffering is still associated with the COVID-19 pandemic. Many lives have been lost, including in the medical community and in nuclear medicine. These lives will not be forgotten. However, out of this darkness also came moments of solidarity. I am sure you have seen many institutions (like my own) at which the local fire department, police department, and public showed up to honor frontline health care workers. Let us hope that this solidarity will carry us forward and that together we will make a better world.

Among the effects of the pandemic in many nuclear medicine departments were temporary closures and reduced numbers of procedures. Pulmonary ventilation scans were among the most affected procedures. Gayed et al. from the University of Texas Health Science Center at Houston/Memorial–Hermann Hospital (Houston) and the University of Arkansas for Medical Sciences (Fayetteville), reported on "Perfusion lung scans without ventilation part: COVID 19 experience in a large trauma hospital" [145]. They evaluated the results of perfusion-only lung scans in 128 patients and the frequency with which the ventilation part of the scans was necessary to diagnose acute pulmonary embolism. They found that certainty was achieved in 122 patients (95.3%), even when the ventilation portion of the study was not performed, and concluded that the perfusion part of lung scans is sufficient for evaluation of acute pulmonary embolism in most patients. This illustrates one way in which we were able to do more with less, as well as how adaptable the nuclear medicine community has been and continues to be in the face of this extraordinary challenge.

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Zhang et al. from Stanford University (CA) reported on "Perfusion-only scans with and without SPECT/CT in the era of COVID-19" [1390]. Figure 1 is an image demonstrating perfusion defects on planar images as well as on the ^{99m}Tc–macroaggregated albumin SPECT fused with the normal chest CT. Sensitivity was increased with the addition of SPECT/CT to perfusion only, while accuracy was not significantly impacted. The authors concluded that "Given the tradeoff of detecting more false-negatives for more false-positives and the cost of performing SPECT/CT, the utilization of SPECT/CT may be selectively limited to higher-risk patients with high pretest probability or equivocal planar imaging." With the limitations imposed by COVID-19 on concurrent ventilation scans, these findings suggested a more "nuanced role for SPECT/CT" in the pandemic.

One very important question being looked at by scientists and clinicians around the world involves identifying and addressing the long-term implications of COVID, and fibrosis is among these concerns. Sultan et al. from the Washington University School of Medicine in St. Louis/Mallinckrodt Institute of Radiology (MO) reported at this meeting on "Chemokine receptor 2 (CCR2)–targeted PET imaging in pulmonary fibrosis" [1695]. The authors described the development of ^{64}Cu-DOTA-ECL1i, a radiotracer that targets the extracellular loop 1 of CCR2, which they used to track CCR2 expression in mouse models of fibrosis in progression of disease and after treatment. They also reported on imaging in both healthy volunteers and patients with idiopathic pulmonary fibrosis (IPF). Figure 2 shows minimal lung uptake and reasonable dosimetry in a healthy volunteer and specific uptake in patients with IPF. A close association was found

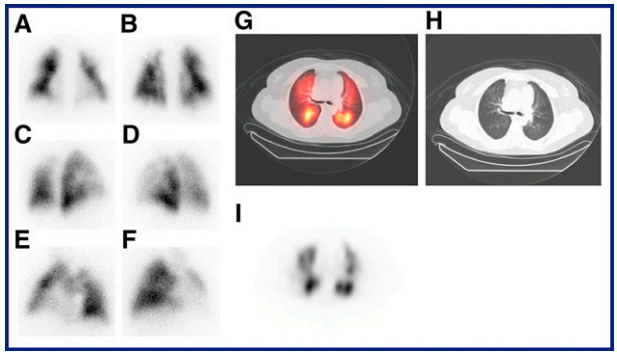

FIGURE 1. Perfusion-only imaging and SPECT/CT in the era of COVID-19. 46-y-old woman presenting with acute onset dyspnea after recent surgery. Left: Planar perfusion images in the anterior, posterior (A,B), left anterior oblique, right posterior oblique (C,D), right anterior oblique, and left posterior oblique (E,F) orientations demonstrated a segmental perfusion defect of the lateral segments of the right middle lobe. Right: SPECT/CT imaging more clearly demonstrated the right middle lobe segmental defect (G–H).

between ^{64}Cu-DOTA-ECL1i uptake on PET and fibrotic activity/changes on CT. The authors concluded that their preclinical and human studies "support a role for imaging CCR2 cells within the fibrogenic niche in IPF to provide a molecular target for personalized therapy and monitoring." This is novel work and may be quite useful in the future, as we continue to evaluate patients who have had COVID, long after (hopefully) the pandemic is over.

Novel Applications of Existing Technologies

Last year was daunting as a result of the pandemic and terrible for us at Stanford and for the global nuclear medicine community because we lost our colleague, friend, mentor, and significant luminary, Sanjiv Sam Gambhir, MD, PhD (Fig. 3). The following 2 parts of my presentation are based on quotations from Sam, who had not only great wisdom but an ability to express his insights in memorable ways. He once said, "Innovation is not always a new device or technology, but simply finding a new/novel way to use an existing technology." This observation was seen in many presentations at the SNMMI 2021 meeting, and I will review several here.

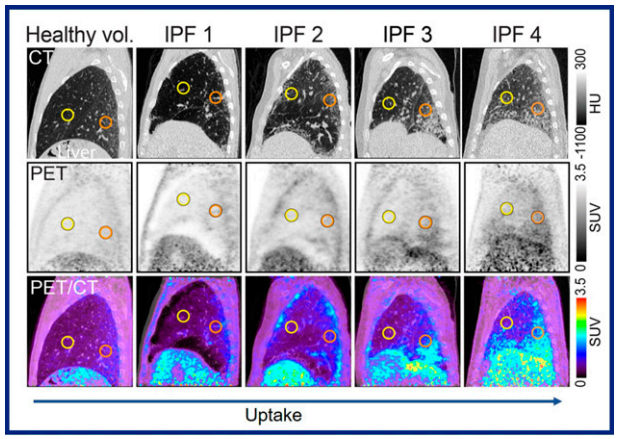

FIGURE 2. ^{64}Cu PET/CT in patients with idiopathic pulmonary fibrosis (IPF). Top row: CT; middle row: PET; bottom row: PET/CT in (left) a healthy volunteer and 4 patients with IPF.

FIGURE 3. Sanjiv Sam Gambhir, MD, PhD (1962–2020).

Kersting et al. from University Hospital Essen and University of Duisburg–Essen (Germany) reported on "Dynamic ^{68}Ga-DOTA PET/CT and compartmental modeling to noninvasively estimate the glomerular filtration rate" [88]. They asked whether it was possible to estimate renal function from dynamic PET/CT without laboratory assessment of glomerular filtration rate (GFR) or dedicated renal imaging. Datasets were included from 12 patients who underwent dynamic ^{68}Ga-DOTA PET imaging prior to ^{177}Lu-DOTATOC or ^{177}Lu–prostate-specific membrane antigen therapy. In addition to visual interpretation of renal cortical transition time–activity curves, the authors estimated GFR using single-compartmental kinetic modeling of the PET data. The results were compared with those from serum creatinine–derived GFR. In the 9 patients with undisturbed urinary efflux, reproducibility analyses showed good agreement and a linear correlation between PET-assessed GFR and serum creatinine results as well as dedicated renal scintigraphy. In 3 patients with urinary obstruction, however, PET-assessed GFR provided a significant underestimation compared with serum results. These same 3 patients had been diagnosed with urinary obstruction in previous renal scintigraphy. Figure 4 shows images from dynamic PET in a patient with normal renal function (left) and a patient with a urinary obstruction (right). This is a novel use of dynamic DOTATE PET to evaluate renal function.

Eberhardt et al. from Ulm University Medical Center and SI Praxisklinik Riedlingen (both in Germany) reported on "Evaluation of ^{11}C-methionine PET/MRI in primary hyperparathyroidism" [1026]. This is a novel use for this tracer, which was not developed for this indication. In this retrospective study, PET/MRI images were retrospectively evaluated from 12 patients with laboratory evidence of primary hyperparathyroidism, and levels of diagnostic certainty for PET findings alone and for combined PET/MRI were assessed. PET showed at least 1 suspicious finding for parathyroid adenoma in every case (2 in 1 patient). MR provided excellent anatomic correlation and localization, with the best identification of parathyroid adenomas by early arterial enhancement in the dynamic contrast-enhanced (DCE) sequence improving overall diagnostic certainty. PET/MRI, in addition to resulting in no false-positive findings at surgery, substantially reduced radiation exposure compared with PET/CT

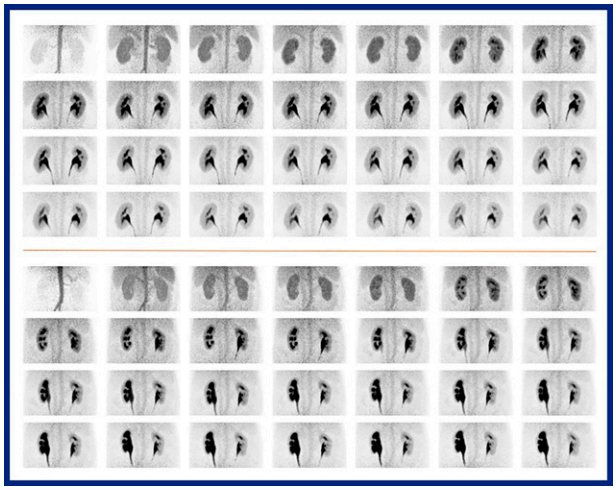

FIGURE 4. Renal dynamic ^{68}Ga-DOTA PET. Maximum-intensity projections (frontal view) of dynamic PET images of undisturbed urinary efflux (top block) and right-sided urinary obstruction (bottom block). In each block, left 12 frames of 30 s and right 16 frames of 90 s. Images are shown in the anterior projection, differing from data acquired in the posterior position in renal scans.

(by 65%–80%). In Figure 5, a parathyroid adenoma located posterior to the left thyroid globe is easily appreciated on the PET and fused PET/MR images, as well as the DCE sequence shown.

"Fast" imaging is an important, novel, and rapidly expanding focus of research, particularly in PET/CT. Reasons for this are many: elderly patients, for example, may have difficulty lying flat in the scanner for long periods of time; in the youngest patients, avoiding or limiting sedation is desirable; and patients with claustrophobia benefit from shorter scans. Esmail et al. from the Jaber Alahmad Center for Nuclear Medicine and Molecular Imaging (Kuwait) reported on "Fast NaF PET/CT acquisition with digital PET/CT system: Single initial experience" [1160]. They compared independent interpretations of fast whole-body (≤3.5 min) and routine (≤16 min) image acquisitions with a silicon photomultiplier–based scanner to assess the presence of osteoblastic bone metastases in 14 patients (7 obese but with body mass index <40.1)

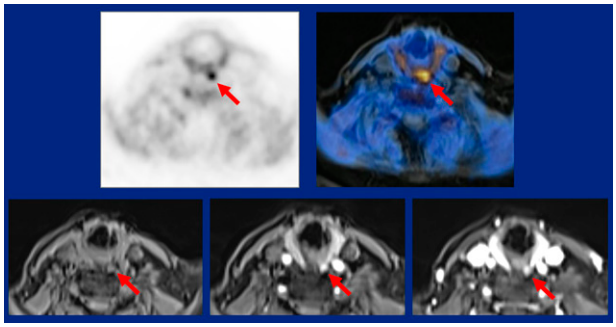

FIGURE 5. PET/MR imaging of parathyroid adenoma (arrows) with early arterial enhancement. Top left: PET; top right: MRI. Bottom: Dynamic contrast-enhanced MRI sequence (left to right): native phase, early arterial phase, and arteriovenous phase.

(Fig. 6). The authors concluded that using fast PET acquisition for NaF PET/CT in a digital system is possible and feasible, reducing scan time by 80% or more. This is encouraging news about what we can do with advanced technology and how we can make the imaging experience better for patients while enhancing workflow.

No review of recent innovations in PET would be complete without mentioning the great work of the EXPLORER team at the University of California Davis (Sacramento) and colleagues elsewhere. Among multiple reports of innovations with this scanner at the 2021 SNMMI meeting, Abdelhafez et al. from the University of California Davis reported on "Ultra-low-dose total-body ^{18}F-FDG PET/CT in patients with autoimmune inflammatory arthritis (AIA): Evaluation of image quality with shorter scan time" [1697]. The study included 11 men with an established AIA condition (rheumatoid arthritis, 3; psoriatic arthritis, 8) and 3 non-AIA controls (osteoarthritis). Imaging data were subsampled for reconstruction as a single frame (20 min), 4 5-min frames, and 20 1-min frames, looking specifically at coefficients of variance (COVs) in parameters associated with volumes of interest in the ascending aorta blood pool and liver and uptake in the most active arthritic lesion. Initial results indicated that scan times as short as 5 min, with ~75.5 MBq ^{18}F-FDG injected dose, appeared to provide COVs below 15%. Despite some noise, even the 1-min acquisition was quite good for diagnostic purposes, and the 5-min acquisitions were as clear as those at 20 min (Fig. 7). The extent of disease involvement in the small joints is apparent even in the 1-min scan. For patients with arthritis, who cannot tolerate long scan times, this a welcome innovation. The authors also noted that analyses of temporal ^{18}F-FDG uptake characteristics in lesions of

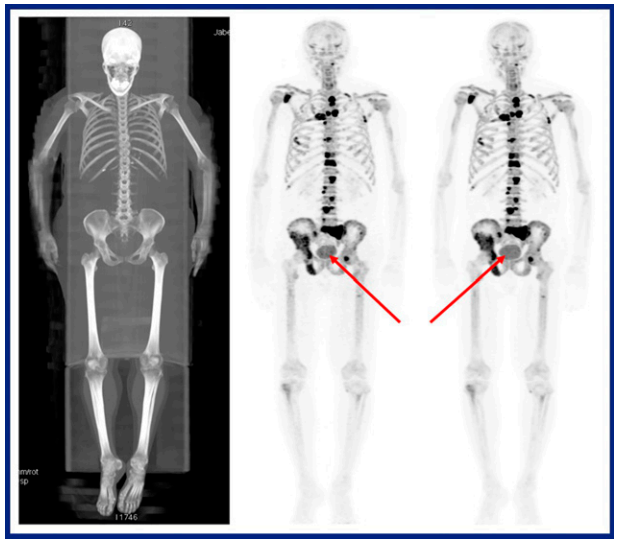

FIGURE 6. Fast NaF PET/CT acquisition with digital PET/CT system. Left: Low-dose, nonenhanced CT attenuation correction. Middle: Fast PET at ≤3.5 min (12–18 s/bed, based on body mass index). Right: Routine PET (up to 16 min, no motion allowed between acquisitions) in the same patient. Note the difference in urinary bladder size in the 2 PET images.

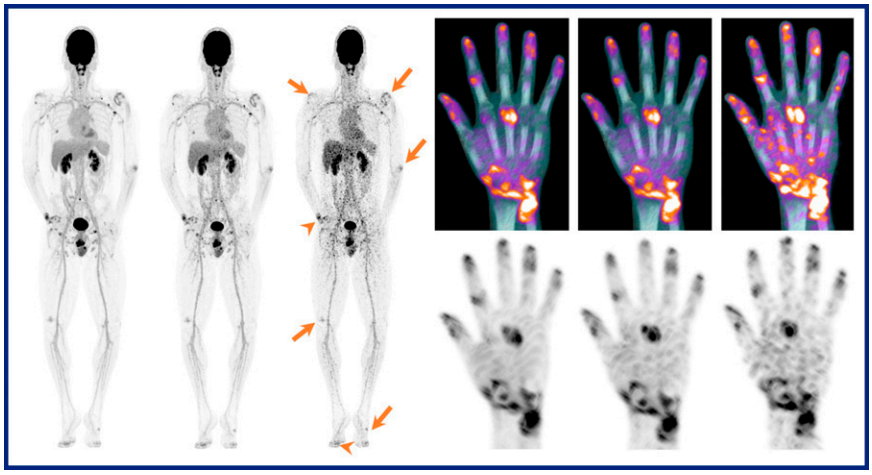

FIGURE 7. Ultra-low-dose total-body ^{18}F-FDG PET/CT with the EXPLORER in patients with autoimmune inflammatory arthritis. Left block: total-body maximum-intensity projection images (4-mm voxel) acquired at (left to right): 20 (40–60), 5 (55–60), and 1 (59–60) min. Right block: fused (top row) and PET (bottom row) maximum-intensity projection images of the right hand, acquired at (left to right) 20, 5, and 1 min.

different types of arthritis have the potential to provide insights into underlying pathologic processes.

Long-term neurologic effects of high-dose chemotherapy in pediatric patients are a significant challenge, particularly given the lack of predictive metrics and the special research needs associated with this population. Baratto et al. from Lucile Packard Children's Hospital (CA) reported on "Imaging chemotherapy-induced brain damage in pediatric cancer survivors" [89]. The study included 10 children (ages 2–24 y; mean, 17.5 ± 5.2 y) with osteosarcoma (6) or lymphoma (4), who underwent ^{18}F-FDG PET/MR imaging before and after intravenous chemotherapy with high-dose methotrexate (range, 3,000–144.000 mg/m^2; mean, 26,448 mg/m^2). Hyper- or hypometabolic brain areas were noted in Brodmann areas associated with executive functions and intelligence quotient in 8 patients, in areas related to attention ability in 3 patients, in areas related to academic function in 6 patients, and in areas related to reading ability in 9 patients (Fig. 8). The researchers are continuing to follow this group of patients to determine correlations between these findings and serial neuropsychological testing. In addition to indicating that PET/MRI can detect early signs of chemotherapy-induced brain damage in this vulnerable population, these results suggest that there is a window of time between drug exposure and morbidity. Early detection of chemotherapy-induced drug damage could guide changes in management that would improve long-term outcomes.

First-in-Humans and Early Development Research

Sam Gambhir also said, "It is called re-search for a good reason." Only rarely is a single experiment "successful" as a standalone achievement. Much more frequently, many experiments are required, and many of these may fail before they reach advanced research or clinical implementation. The following section of this lecture looks at presentations from the meeting in which researchers reported on novel, first-in-humans, or early development studies.

Imaging pain is an unmet need that many investigators continue to explore. Yoon et al. from Stanford University School of Medicine (CA) reported that "Sigma-1 receptor (S1R) PET/MRI of patients with chronic knee pain reveals potential pain generators not otherwise identified with standard care: Early experience" [143]. These researchers looked at the potential of ^{18}F-FTC-146 PET and MR imaging in elucidating the etiology of chronic knee pain. The study included 10 patients whose pain was of >6 mo duration, had pain levels >4/10, and who had failed standard medical and surgical

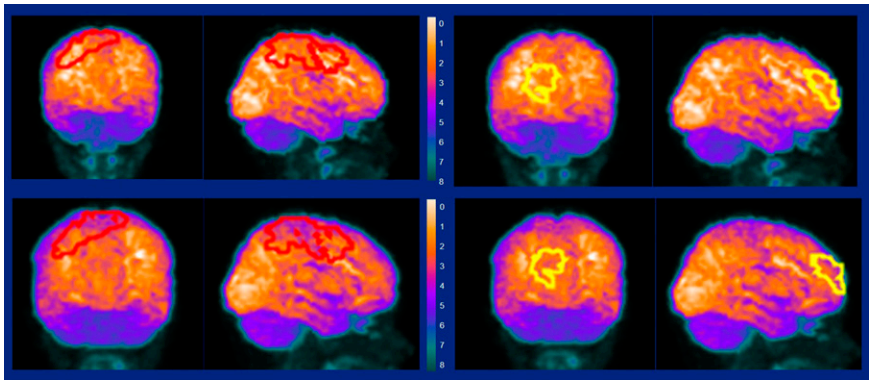

FIGURE 8. Imaging chemotherapy-induced brain damage in pediatric cancer survivors. Left block: hypermetabolic area in the right frontal lobe (Brodmann areas 8, 9) at baseline (top; SUV_{max}, 12.29) and follow-up (bottom; SUV_{max}, 11). Right block: hypermetabolic area in the right frontal lobe (Brodmann areas 9, 10) at baseline (top; SUV_{max}, 10.9) and follow-up (bottom; SUV_{max}, 9.88).

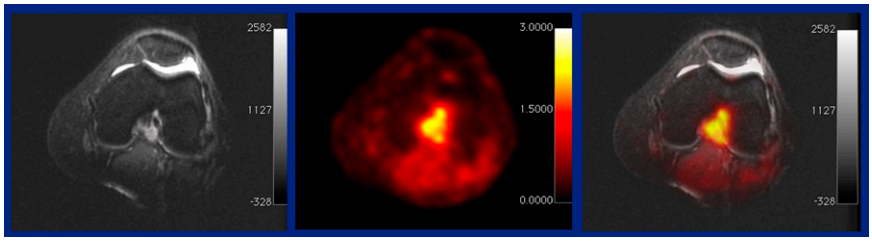

FIGURE 9. Sigma-1 receptor (S1R) ^{18}F-FTC-146 PET/MR imaging in patients with knee pain. Example of S1R PET abnormality in the intercondylar notch of the knee (middle), where no corresponding abnormality was visualized on MR imaging (left). S1R PET/MR (right) guided arthroscopic surgical resection of the synovial mass resulting in complete resolution of pain.

management. Patients underwent whole-body, time-of-flight ^{18}F-FTC-146 PET/MR imaging, and results were compared with those from 9 asymptomatic individuals, assessing both uptake on PET and evaluating MR separately. PET showed significant abnormal uptake in all 10 patients in a variety of locations (joint, bone, muscle, synovia, menisci, and others). On MRI alone, only 6 patients showed an anatomic correlate (3 with expected postsurgical changes on MRI that were deemed to be unrelated to the pain and 3 with findings consistent with osteoarthritis and/or meniscal tear). MR often did not show abnormalities at sites of abnormal PET uptake, most notably in the bones and muscles. Clinical follow-up indicated that a subgroup of these patients benefited from PET/MR guidance in terms of treatment. Figure 9 is an example in which a synovial mass demonstrated uptake of the S1R on PET. After arthroscopic surgical resection based on PET, the patient saw complete resolution of long-term pain. This is a research area with great potential for larger group studies and expansion to other indications.

Horikawa et al. from the National Center for Global Health and Medicine (Tokyo, Japan) reported on "SUV-based quantification of ^{131}I-6-β-iodomethyl-norcholesterol (NCL-6-I) SPECT/CT for the diagnosis of the responsible adrenal glands in patient with primary hyperaldosteronism: A preliminary result" [1025]. The study included 10 patients (ages 49 ± 8 y; 7 women, 3 men) with adrenal nodules ≥10 mm in diameter who underwent hormone tests, abdominal CT, adrenal vein catheterization with aldosterone sampling, and NCL-6-I SPECT/CT with pharmacologic adrenosuppression on d 3 and 7. SUV_{max} and SUV_{mean} of the adrenal region were compared to cortisol and aldosterone concentrations. Adrenal gland SUV changes between d 3 and 7 were assessed and compared with visual interpretation. This is a novel and promising approach to quantifying data.

Imaging is an increasing focus of research and a clear clinical need for the future. Dearling et al. from Boston Children's Hospital/Harvard Medical School (Boston, MA) and Tel Aviv University (Israel) reported on "Colonic uptake of a ^{64}Cu-labeled immunoprotein incorporating mucosal addressin cell adhesion molecule (MAdCAM) correlates with the degree of colitis" [1208]. As part of an effort to develop an immunoPET agent for colitis detection and quantification, they constructed an antibody that incorporates MAdCAM, which interacts with β7 integrins to recruit lymphocytes to regions of colitis. ^{64}Cu-labeled MAdCAM and a nonbinding control were assessed for biodistribution in healthy mice and mice with induced colitis. They found that tracer uptake was increased in mice with colitis proportionally to colon density, a measure of disease severity, and decreased in disease-free controls. It is hoped that this work will successfully transition to human and then clinical use, where it could prove to be quite valuable.

Fibroblast activation protein inhibitor (FAPI) was a focus of multiple oncologic lectures at this meeting, and we are all interested as well. Ballal et al. from the All India Institute of Medical Sciences (New Delhi) and the Johannes Gutenberg University (Mainz, Germany) reported on "First clinical experience and initial outcomes of ^{177}Lu-DOTAGA $(SA.FAPi)_2$ therapy in patients with end-stage radioiodine-refractory differentiated thyroid cancer: A salvage treatment option" [1701]. The study included 6 patients (4 women, 2 men; median age, 61.5 y; range, 46–67 y) with metastatic disease who were prospectively recruited after disease progression after standard treatments (>22.2 GBq of radioiodine, sorafenib followed by lenvatinib). Patients were screened with ^{68}Ga-DOTAGA $(SA.FAPi)_2$ and ^{18}F-FDG-PET/CT imaging to confirm high cancer-associated fibroblast expression. They then received intravenous ^{177}Lu-DOTAGA $(SA.FAPi)_2$ at 8 weekly intervals. The biodistribution of this radiotherapeutic agent was normal in the oral mucosa, salivary glands, liver, gall bladder, pancreas, colon, and kidneys, with the desirable characteristics of high tumor affinity and long retention (an effective half-life in tumors of 86 h). In this small cohort of patients the authors identified biochemical response (thyroglobulin decrease) as well as clinical response (pain palliation), with no grade III or IV toxicities. The authors concluded that this new radiopharmaceutical opens new fronters for treatment of end-stage thyroid cancer refractory to standard treatment. In the patient in Figure 10, the FDG scan shows the aggressiveness of disease in uptake in a lesion in the left shoulder as well as elsewhere in the skeleton. A post-^{131}I therapy scan had shown some of these as avid, but the FAPI PET/CT identified significant uptake in those lesions as well as others not seen on previous imaging. ^{177}Lu-DOTAGA $(SA.FAPi)_2$ uptake was retained and visualized up to 168 hours. The authors concluded that this therapy "adds a new dimension to the treatment of radioiodine-refractory differentiated thyroid cancer patients who have exhausted all standard line treatment options." This is an area of unmet need, and we look forward to future results on the utility of this approach in salvage therapy as well as in wider applications.

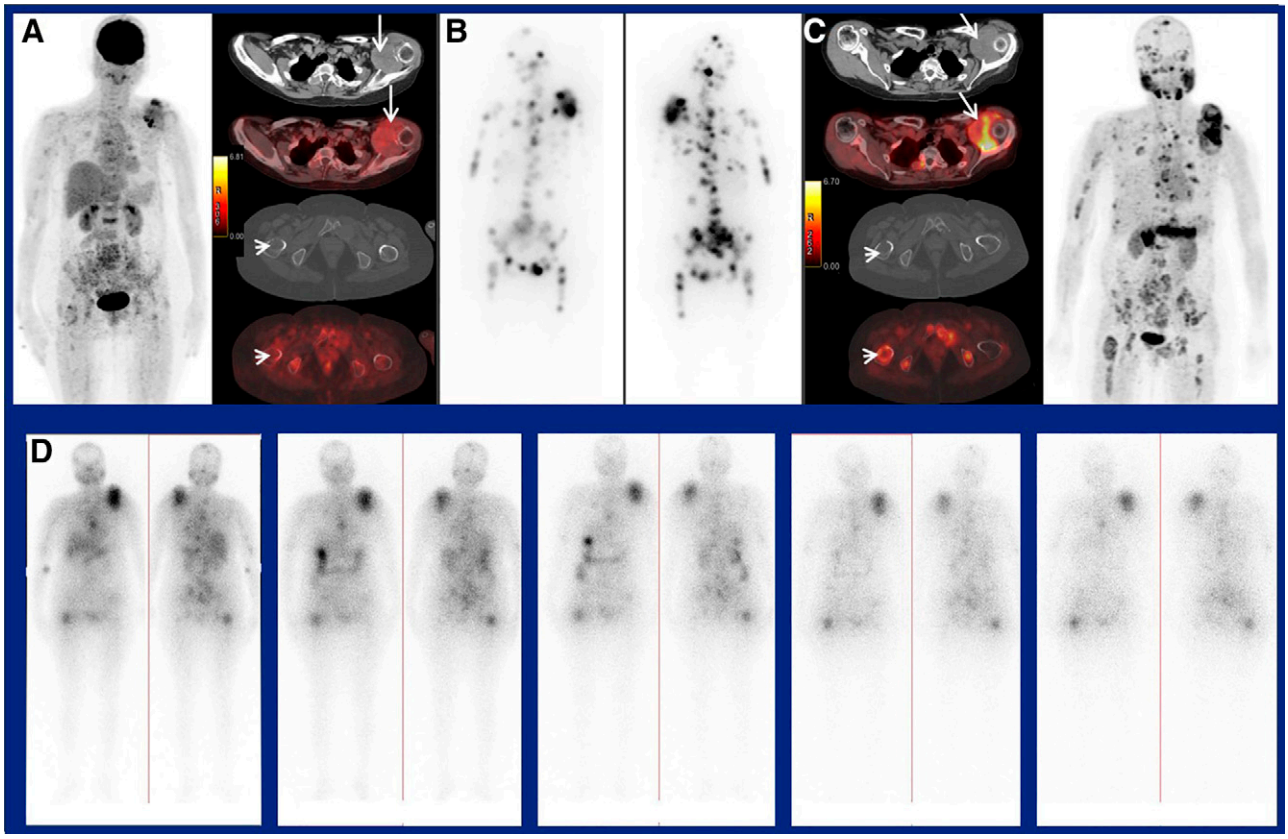

FIGURE 10. ^{177}Lu-DOTAGA (SA FAPi)$_2$ therapy as a salvage treatment option in end-stage differentiated thyroid cancer. A. Pretreatment ^{18}F-FDG PET/CT. B. Post-^{131}I therapy whole-body scans. C. ^{68}Ga-DOTA (SA FAPi) PET/CT. D. ^{177}Lu-DOTAGA (SA FAPi)$_2$ serial whole-body PET acquired at 1, 24, 48, 96, and 168 h after treatment. Rapid accumulation of radiotracer is seen in the 2-h image with long retention.

Conclusion

I would like to acknowledge Umar Mahmood, MD, PhD, and Heather Jacene, MD, for entrusting me with this presentation, as well as time spent advising on preparation.

I will end by circling back to Sam Gambhir, who received numerous awards and was especially proud of the ones from SNMMI. I remember vividly the plenary talk he gave at the SNMMI Annual Meeting in 2018 in Philadelphia. He included a very personal and touching story, and, at the conclusion of the lecture, was met with a standing ovation. Despite his exceptional scientific, academic, and professional achievements, as well as innumerable awards and honors, he remained humble, approachable, kind, and generous—simply an amazing human being and I hope a role model for everyone in our field, especially for those riding the wave of successes during this renaissance time for nuclear medicine. He was particularly proud of the achievements of others working with him. During his tenure at Stanford, his faculty and collaborators received the SNMMI Image of the Year award 3 times, in 2005, 2009, and 2011.

In 2018, as the first in a series of discussions with leaders in *The Journal of Nuclear Medicine* (2018;59:1783–1785), Johannes Czernin, MD, talked with Sam. In discussing the practice of nuclear and molecular medicine, Sam said, "We shouldn't be celebrating how full our hospitals are. We should celebrate when our hospitals are empty." This far-sighted goal should be inspiring to us all. Over his career, Sam migrated his research from early cancer detection to a more overarching focus on precision health. I hope that in the coming years our nuclear medicine community will remain focused on early cancer detection, expand our contributions to precision health, and honor Sam by continuing his groundbreaking work. Perhaps one year soon, the Image of the Year will highlight both early cancer detection and precision health.