2015 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 33 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. The 2015 Highlights Lectures were delivered on June 10 at the SNMMI Annual Meeting in Baltimore, MD. This is the fourth and last of the presentations (the previous 3 were serialized in the September, October, November, and December issues of Newsline). Janis O'Malley, MD, a professor in the Department of Radiology at the University of Alabama School of Medicine (Birmingham), spoke on general nuclear medicine highlights from the meeting's sessions. Note that in the following presentation summary, numerals in brackets represent abstract numbers as published in* The Journal of Nuclear Medicine *(2015;56[suppl 3]).*

It is truly my great honor to report once again on the General Nuclear Medicine highlights from this year's SNMMI Annual Meeting. A few days ago I was talking to James J. Conway, MD, who was SNM president in 1994 and 1995, about the history of the society. We talked about Henry N. Wagner, Jr., MD, and Jim gave me some advice for this presentation. He said, "What you have to remember is that when you are on that stage, Henry will be with you." So, I am hoping that the guiding spirit of Dr. Wagner will be whispering in my ear as I review only a small fraction of the interesting talks in the area of general nuclear medicine that were presented at this meeting.

SNMMI leadership has been working to increase participation from international investigators in our society and at this meeting. The results can be seen in the numbers of international presenters in 2015 (Table 1). Although North America still has a strong showing, it is not surprising that we are seeing rising levels of participation from around the world. International participation is especially important in those areas in which cutting-edge research in imaging and therapy in the United States is somewhat stymied by regulatory obstacles.

I have also been interested in the impact of hybrid imaging in our specialty as seen at this meeting. Investigators in the general nuclear medicine topic areas utilized hybrid imaging—PET/CT, SPECT/CT, PET/MR imaging, and other combinations—in more than half of the presentations (Table 2).

PET/MR imaging and its future direction are topics in which we are all interested. PET/MR is still in its infancy in the general nuclear medicine area, where practical and clinical studies tend to dominate. However, very interesting new approaches were shown this year, with some extraordinary images in settings in which soft tissue discrimination is critical but where PET can add something that MR cannot in terms of overall tissue function. One example is the study by Binzel et al. from The Ohio State University Wexner Medical Center (Columbus) and Pepperdine University (Malibu, CA). In this study, titled "Feasibility demonstration of dynamic FDG PET to assess ACL [anterior cruciate ligament] graft viability after reconstructive surgery" [547], PET was performed separately and fused subsequently, allowing evaluation of ACL viability following grafting (Fig. 1).

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Infection was also evaluated with PET/MR in a preliminary study looking at diabetes and osteomyelitis in a group of patients with a high degree of suspicion for osteomyelitis. Yaddanapudi et al. from Stony Brook University (Westbury and Stony Brook, NY) presented "PET-MRI in diagnosing pedal osteomyelitis in diabetic patients" [307]. Figure 2 includes a T1-weighted MR image of the foot, which clearly shows an extensive area of decreased signal in the soft tissues consistent with cellulitis. The patient had a large ulcer. The authors were fairly certain this was osteomyelitis. The MR image, however, is not perfect. In this case it does not show the classic areas of extensive decrease in intensity of signal one might expect to see in osteomyelitis. The PET image was definitive, showing intense uptake in the soft tissues as well as involvement in the bone. The MR image shows some diminished signal in the phalanx that was involved, but the PET image shows uptake in areas in the adjacent bone where MR signal remained normal.

As Vasken Dilsizian, MD, mentioned in his Highlights lecture on cardiovascular topics (*1*), hybrid imaging has also been used to evaluate infection associated with left ventricular assist devices (LVADs). Kim et al. from the University of Maryland School of Medicine (Baltimore) reported that "The presence and site of LVAD infection by FDG PET/CT bears important prognostic implications" [310]. Many patients encounter problems with infections several months after implantation of these devices, leading in some cases to significant complications: the device may have to be removed, the patient may be taken off the transplant list, and some evidence suggests decreased mortality in these patients. Impressive images were shown from these cases, with uptake

Table 1
General Nuclear Medicine Topics: Geographic Origins

Continent	Endocrine	Gastrointestinal	Infection	Musculoskeletal	Outcome	Peds	Pulmonary	Renal
N. America (U.S.)	17.5% (16.5%)	50% (46%)	25% (25%)	34.6% (34.6%)	43.75% (37.5%)	53.8% (34.6%)	30.8% (30.8%)	22% (22%)
Asia	26.7%	30.8%	58.3%	34.6%	43.75%	34.6%	26.9%	33.3%
Europe	52.6%	19.2%	8.3%	23.1%	12.5%	3.8%	38.5%	11.1%
Australia	1%	0	0	3.8%	0	7.6%	3.8%	0
Africa	2%	0	0	3.8%	0	0	0	33.3%
S. America	0	0	8.3%	0	0	0	0	0

consistent with infection around the devices, drive lines, and wires. The routine availability of a noninvasive method to identify central infections in these patients, particularly if these infections are predictive of further complications and outcomes, would be advantageous.

In the general nuclear medicine area, endocrinology topics are always a central focus. At the SNMMI meeting, endocrinology provides the most submissions in general nuclear medicine, with neuroendocrine tumor (NET) imaging leading these numbers. ^{68}Ga-DOTA is of particular interest to investigators. We are trying to expand the availability and utilization of ^{68}Ga-DOTA agents for neuroendocrine imaging in the United States. In 2012 ^{68}Ga-DOTA was available at 2 sites, Vanderbilt University and the University of Iowa; in 2014 it was available at 11 sites, with 7 pending. Papers at this meeting over the past several years have looked at comparisons among the various commonly available agents in terms of their affinity and ability to target different somatostatin receptor types that can be expressed to varying degrees in different tumors (*2,3*). These agents are quite useful in staging disease; identifying sites of disease not readily seen with other imaging modalities, including ^{111}In-octreotide SPECT; and in follow-up to assess response to therapy.

Menda et al. from the University of Iowa Carver College of Medicine (Iowa City) presented a study on the "Role of gallium-68 DOTATOC PET-CT in NETs with unknown primary site" [143]. Figure 3 is an example of the differences seen when comparing ^{68}Ga-DOTATOC PET/CT with ^{111}In-octreotide SPECT. Tumor-to-background ratios in the liver are lower in the SPECT scan, and margins are less sharp than in the PET/CT image. In addition, several lesions seen on the PET image are not visible on SPECT. An area of intense avidity on the pancreas in the PET image does not show any uptake on the SPECT image. In this project, ^{68}Ga-DOTATOC PET/CT was true-positive or unconfirmed positive for primary tumor in 17 of the 29 (59%) patients in whom primary lesions had not previously been identified. PET confirmed primary tumors in the small bowel in 7 patients and in the pancreas in 6 patients. PET also led to significant changes in management in 8 patients (28%), 7 of whom underwent resection of primary tumor based on positive ^{68}Ga-DOTATOC PET/CT and 1 of whom with prior equivocal findings underwent peptide receptor radionuclide therapy (PRRT).

My attention was also captured by other agents that may be on the horizon, including ^{44}Sc-DOTATOC for PET/CT. Singh et al. from the Zentralklinik Bad Berka GmbH (Germany) and the Paul Scherrer Institute (Villigen, Switzerland) reported on "Scandium-44 DOTATOC PET/CT: first-in-human molecular imaging of NETs and possible perspectives for theranostics" [267]. ^{44}Sc offers advantages, in that it can be

Table 2
General Nuclear Medicine Talks: Hybrid Imaging Impact (%)

Section	PET/CT	SPECT/CT	PET/MR	Planar	SPECT	Other
Gastrointestinal	28.6%	14.3%	0	57.1%	0	0
Infection	62.5%	0	12.5%	12.5%	0	12.5%
Musculoskeletal	50%	11.1%	5.6%	0	11.1%	22.2%
Neuroendocrine	66.7%	22%	0	0	0	11%
Outcomes	42.9%	0	14.2%	0	0	42.9%
Parathyroid	14.3%	35.7%	0	28.6%	7.7%	14.3%
Pediatrics	50%	12.5%	25%	12.5%	0	0
Pulmonary	42.8%	28.6%	0	14.3%	14.3%	0
Renal	0	10%	0	40%	10	40%
Thyroid	18.2%	4.5%	0	40.9%	0	36.4%
Total	**35.3**%	**14.3**%	**4.2**%	**20.2**%	**4.0** %	**21.8**%

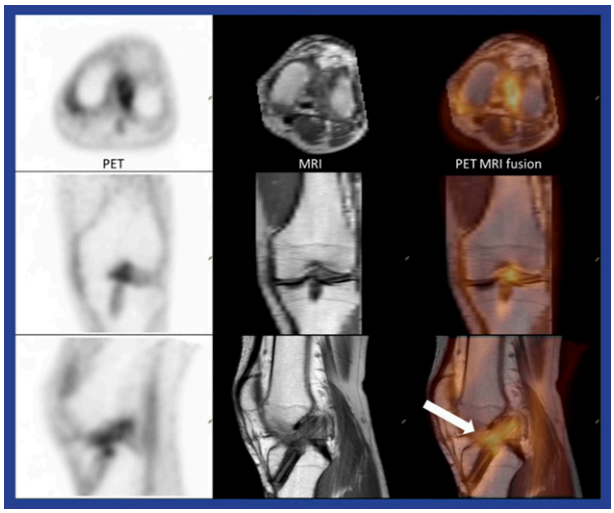

FIGURE 1. Dynamic ^{18}F-FDG PET in anterior cruciate ligament (ACL) graft viability. Static PET image (left) reconstructed from listmode data acquired 70–75 minutes after injection of 111 MBq (3 mCi) ^{18}F-FDG. Proton density and T1-weighted MR imaging sequences (middle) were acquired in all 3 planes with a 3D high-resolution series. Fusion of PET and MR images (right) for evaluation of ACL graft and bone tunnel uptake showed location of ACL graft (arrow), with marked uptake through the graft as well as the femoral and tibial bone tunnels.

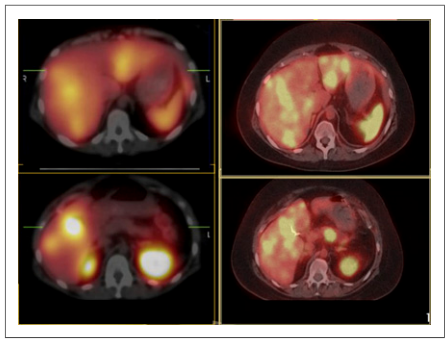

FIGURE 3. Comparative imaging in patient with neuroendocrine tumors associated with elevated cortisol and adrenocorticotropic hormone, Cushing syndrome, new onset diabetes, liver metastases; otherwise negative ^{111}In-octreotide SPECT (left). ^{68}Ga-DOTATOC PET/CT (right) had higher tumor-to-background ratios and sharper margins, with several lesions not visible on SPECT. An area of intense avidity on the pancreas in the PET/CT image showed no uptake on the SPECT image.

cyclotron-produced centrally and shipped to remote sites, thereby obviating the need for a dedicated and possibly expensive generator. This study's preliminary results in 2 patients found that ^{44}Sc-DOTATOC PET/CT imaging demonstrated high specific uptake in liver and lymph node metastases and no significant uptake in pituitary, salivary gland, or bowel, with no adverse effects noted. The authors concluded that this is a highly promising radiopharmaceutical for imaging somatostatin receptor–expressing tumors, that ^{44}Sc-DOTATOC appears highly sensitive compared to ^{68}Ga-DOTATOC, that both pretherapeutic imaging and dosimetry are feasible, and that imaging with ^{44}Sc-DOTATOC opens up the possibility for use with PRRT and the β-emitter ^{47}Sc. Figure 4 shows a comparison of ^{68}Ga-DOTATOC (left) and ^{44}Sc-DOTATOC imaging (middle). Background activity in the liver is diminished on the ^{44}Sc-DOTATOC image, with liver metastases appearing more conspicuous and more numerous than in the ^{68}Ga-DOTATOC image.

Although useful, somatostatin agonists present some challenges for clinical imaging. In recent years, somatostatin antagonists have been the focus of much interest. These antagonists can bind to a larger number of receptors and thus may be superior to agonists in certain settings. Damian Wild, MD, PhD, and his group of researchers in Switzerland and

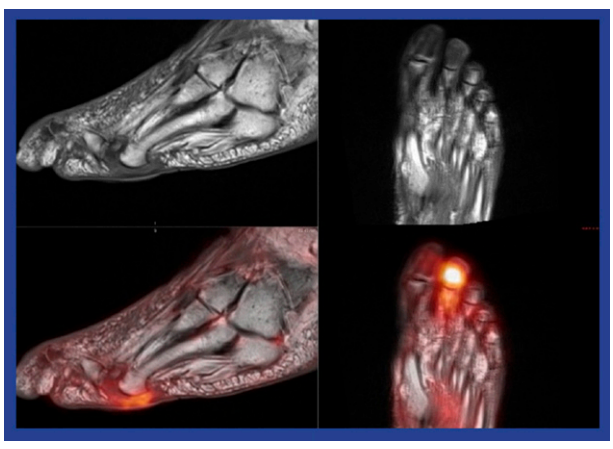

FIGURE 2. PET/MR and diagnosis of pedal osteomyelitis in diabetes. T1-weighted MR images of the foot (top) showed an extensive area of decreased signal in the soft tissues consistent with cellulitis but no classic areas of extensive decrease in signal intensity as seen in osteomyelitis. PET/MR imaging (bottom) was definitive, showing intense uptake in the soft tissues as well as involvement in the bone.

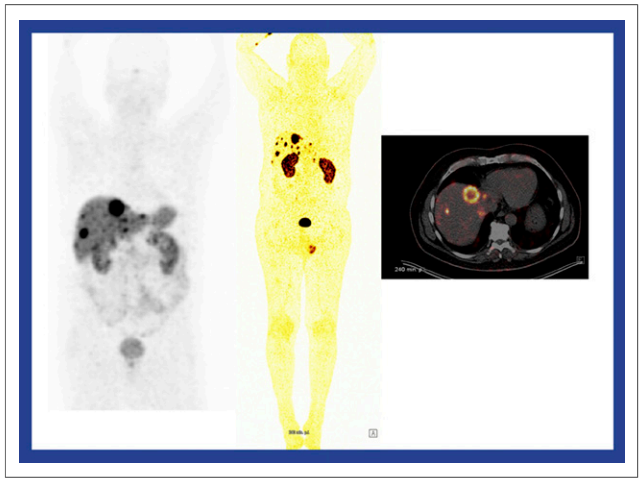

FIGURE 4. Restaging imaging in a patient with gastroenteropancreatic neuroendocrine tumors. Left: ^{68}Ga-DOTATOC PET at 1 h after injection. Middle and right: ^{44}Sc-DOTATOC PET/CT at 4 h after injection, with lower background activity and more conspicuous and numerous liver metastases. Optimal tumor-to-background ratio was achieved at 2–4 h after ^{44}Sc-DOTATOC injection.

Germany have investigated therapeutic effects using the antagonist agent ^{177}Lu-DOTA-JR11 (*4*). This agent showed superior tumor-to-kidney and tumor-to-bone marrow activity and longer tumor residence times compared to the agonist agents, which would suggest that this agent might produce superior results in terms of therapy. At this meeting. Nicolas and colleagues with Wild's laboratory at University Hospital Basel (Switzerland) and from Octreopharm Sciences GmbH (Berlin, Germany) presented "First clinical data on ^{68}Ga-labeled somatostatin receptor antagonists: a phase I/II study comparing ^{68}Ga-OPS202 with ^{68}Ga-DOTATOC PET/CT" [266]. The study looked at safety and biodistribution in 12 patients with metastatic gastroenteropancreatic NETS and at least 1 ^{68}Ga-DOTATOC PET/CT-positive lesion. Somatostatin receptor analogs were stopped at 4 weeks before imaging. Patients received 2 sequential doses (15 and 50 μg, 3–4 weeks apart) and were imaged 1 h after injection. Patients tolerated the agent well, with no serious adverse effects. One patient did develop eosiniphilia of unknown origin. Figure 5 compares biodistribution of the 2 agents at 1 hour after injection, with the ^{68}Ga-DOTATOC on the left and the ^{68}Ga-OPS202 antagonist agent on the right. Diminished activity is seen in the bowel, liver, and spleen with the antagonist. Figure 6 compares tumor-to-background ratios with the 2 agents. At 15 μg, lesions in the liver are more conspicuous on the ^{68}Ga-OPS202 image, showing up to a 2-fold increase in activity over ^{68}Ga-DOTATOC imaging. Figure 7 compares uptake ratios with 15 and 50 μg ^{68}Ga-OPS202. No serious adverse effects were noted with the escalated dose, and some additional lesions were visible.

Insulinomas remain a problem for somatostatin receptor imaging. Sensitivity for imaging insulinomas has been estimated at 25%–60% for ^{111}In-octreotide and at 75% for enhanced CT and ultrasound (*5*). Even with ^{68}Ga-DOTANOC PET/CT, success has been limited (*6,7*). Investigators at this meeting reported on ^{68}Ga-NOTA-exendin-4 PET/CT as a promising approach for evaluation of insulinomas. This and similar agents target the glucagon-like peptide 1 receptors, which are overexpressed significantly over pancreas background in insulinomas, yielding a 90% sensitivity, and are underexpressed in other NETs, lymphomas, and carcinomas,

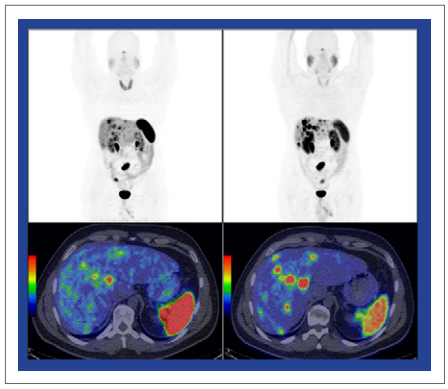

FIGURE 6. Tumor-to-background uptake of 15 μg ^{68}Ga-OPS202 (right) and comparison with ^{68}Ga-DOTATOC (left). Lesions in the liver were more conspicuous on the ^{68}Ga-OPS202 images, showing up to a 2-fold increase in activity over ^{68}Ga-DOTATOC imaging.

which should improve specificity. Luo et al. from Peking Union Medical College Hospital (Beijing, China) reported that "^{68}Ga-exendin-4 PET/CT is highly effective in localizing insulinomas" [146]. Figure 8 is an example from a case in which the primary tumor shows high avidity and where it is possible to detect quite small metastases with this agent, with results superior to other modalities assessed, including perfusion CT, MR, endoscopic ultrasound, and ^{99m}Tc-labeled SPECT/CT. Results presented by investigators with this agent suggest exciting possibilities for the future.

Another area of interest at the meeting was in imaging of adrenocortical carcinoma with the chemokine receptor CXCR4. Bluemel et al. from University Hospital Würzburg (Germany), Technische Universität München (Germany), and Scintomics GmbH (Furstenfeldbruck, Germany) reported on "A theranostic approach for adrenocortical neoplasia based on high adrenal CXCR4 expression" [145]. CXCR4 is in the G protein–coupled receptor family; is overexpressed in a number of solid tumors; and is involved in cellular proliferation, invasion, and metastasis. ^{68}Ga-pentixafor has been developed as a PET tracer to target CXCR4 and for use in theranostic applications with PRRT. Bluemel et al. looked at 22 patients (12 men, 10 women) with ^{68}Ga-pentixafor PET. The patients had known metastatic adrenocortical carcinomas and extensive histories of prior therapy. Each patient received a routine ^{18}F-FDG PET/CT in addition to the ^{68}Ga-pentixathor study, which was performed within a few days of the ^{18}F-FDG scan. They received 124 MBq of the ^{68}Ga agent and were imaged

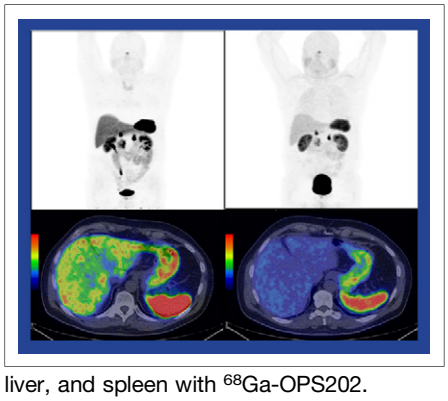

FIGURE 5. Biodistribution of 15 μg ^{68}Ga-OPS202 (right) at 1 h after injection and comparison with ^{68}Ga-DOTATOC (left) in PET/CT in a patient with gastroenteropancreatic neuroendocrine tumors. Diminished activity was seen in the bowel, liver, and spleen with ^{68}Ga-OPS202.

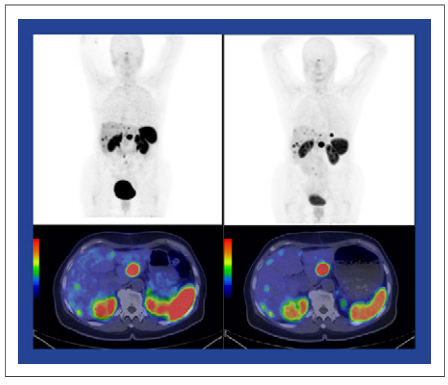

FIGURE 7. Tumor-to-background uptake ratios with 15 and 50 μg ^{68}Ga-OPS202 on PET/CT. No serious adverse effects were noted with the escalated dose, and some additional lesions were visible.

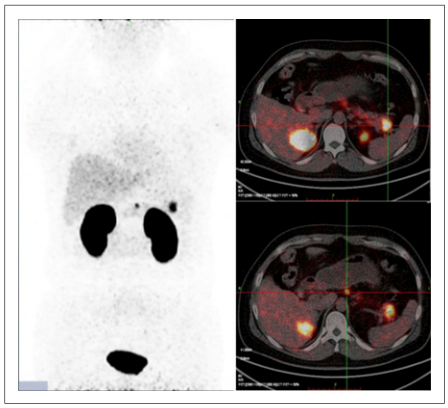

FIGURE 8. ^{68}Ga-exendin-4 PET/CT localization of insulinomas in a 37-y-old man with a 6-mo history of neuroglycopenia. Somatostatin receptor scintigraphy (left) was positive in the pancreatic tail but negative in the body. A 30-min ^{68}Ga-exendin-4 PET/CT scan (right) localized 2 G1 insulinomas (SUV_{max} 10.2 and 17.3).

60 minutes later. Comparison of results with the 2 agents shows an interesting mix of findings. In 1 example (Fig. 9), the ^{68}Ga image (left) shows lower levels of liver activity with more conspicuous metastatic lesions than the ^{18}F-FDG image (right). However, ^{18}F-FDG PET is not always a loser in these comparisons, because its results can be complementary or contradictory depending on the grade of tumor and other factors. Even within a single patient some tumors may be seen better with 1 agent and some with the other. In Figure 10, definite uptake is seen in a tumor (red arrow) with ^{68}Ga-pentixafor PET/CT with no significant corresponding ^{18}F-FDG uptake (right). In the same patient, significant abnormal hypermetabolic adenopathy was visualized in the mediastinum (red arrow) with ^{18}F-FDG but was barely perceptible on the ^{68}Ga image. ^{68}Ga-pentixafor clearly does not replace ^{18}F-FDG PET/CT, but it appears to be complementary and could help identify patients as potential candidates for therapy, such as with the ^{177}Lu-labeled versions of these agents.

Several leaders in the field of renal nuclear medicine referred me to an outstanding presentation by Palestro et al. from North Shore–Long Island Jewish Health System (New Hyde Park, NY), asking "Can ^{18}F-FDG replace ^{67}Ga for differentiating acute interstitial nephritis [AIN] from acute tubular necrosis [ATN]?" [88] in patients with renal failure. AIN is an inflammation of the renal interstitium, sparing vessels and glomeruli, and can be found in up to 15% of patients with acute renal failure. Clinical presentation is highly variable, including but not limited to fevers, rash, arthralgias, and a range of findings in urinalysis. Ultrasound findings are also variable and may include enlargement of the kidneys as well as some echogenicity, but biopsies remain the gold standard. ^{67}Ga has been available for decades for tumor and infection imaging and has been used in this particular indication with definite success. Marked uptake of ^{67}Ga may be seen in AIN and is usually not anticipated in ATN. Variable accuracy has been reported in the literature in differentiating ATN and AIN, which may be in part attributed to factors that can alter ^{67}Ga distribution, including iron overload and chronic renal disease. The study by Palestro et al. included 50 rats in 2 imaging groups (^{67}Ga and ^{18}F-FDG) of 25 each. Each group included 5 controls, 10 rats in which ATN was induced, and 10 rats in which AIN was induced. In example images (Fig. 11) ^{67}Ga showed intense uptake in the kidneys bilaterally in AIN. This uptake was significantly higher than background activity noted in controls and significantly higher than uptake seen in ATN. ^{18}F-FDG was not as successful. Although increased bilateral activity was visualized in the kidneys in ATN and AIN, ^{18}F-FDG was not able to discriminate between the 2. ^{18}F-FDG PET, then, does not appear to be an appropriate replacement for gallium as a differentiator in this setting.

Over the past several years, gastric emptying has undergone a process of standardization, involving determination of normal values and standardization of the gastric emptying meal. Recommendations have been published as consensus papers and SNMMI guidelines (*8,9*). Under these guidelines, imaging is performed each hour for up to 4 hours until retained activity calculated in the stomach falls below 10%. The patient is considered abnormal when gastric retention is >90% at 1 hour, >60% at 2 hours, >30% at 3 hours, or >10% at 4 hours. The recommendations cited the 4-hour study as the optimal discriminator between abnormal and

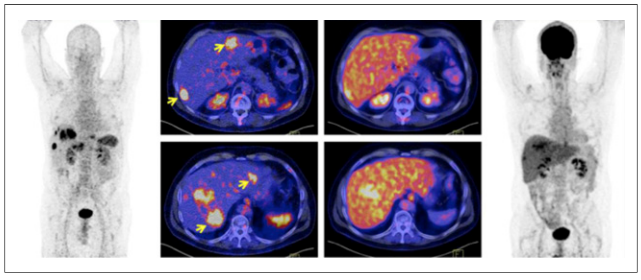

FIGURE 9. Comparison of CXCR4-targeting ^{68}Ga-pentixafor (left) and ^{18}F-FDG (right) in PET/CT imaging in a patient with histopathology-proven metastatic adrenocortical carcinoma. The ^{68}Ga images showed lower levels of liver activity with more conspicuous metastatic lesions than the ^{18}F-FDG images.

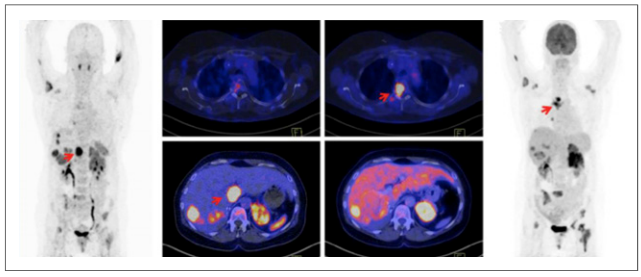

FIGURE 10. Comparison of CXCR4-targeting ^{68}Ga-pentixafor (left) and ^{18}F-FDG (right) in PET/CT imaging in a patient with histopathology-proven metastatic adrenocortical carcinoma. Uptake is seen in a tumor (red arrow) with ^{68}Ga-pentixafor PET/CT with no significant corresponding ^{18}F-FDG uptake. In the same patient, significant abnormal hypermetabolic adenopathy was visualized in the mediastinum (red arrow) with ^{18}F-FDG but was barely perceptible on the ^{68}Ga image.

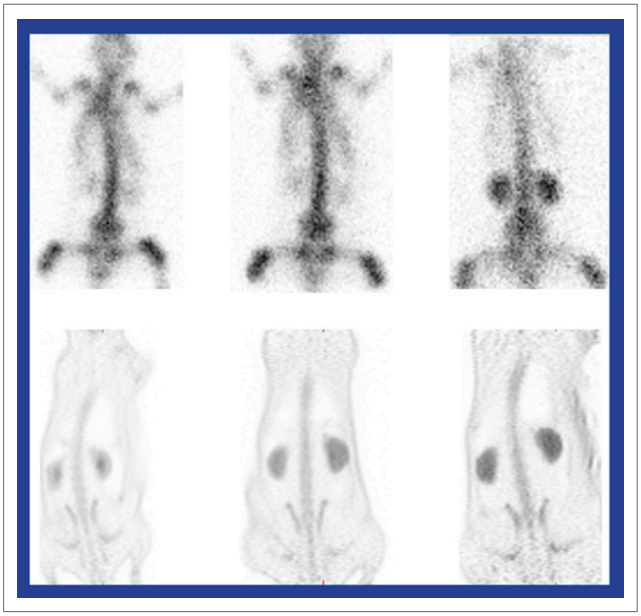

FIGURE 11. Comparison of ^{67}Ga (top) and ^{18}F-FDG (bottom) imaging for differentiation of acute interstitial nephritis (AIN, right images) from acute tubular necrosis (ATN, middle images) in rats. Control animals are at left. In animals with AIN, ^{67}Ga showed intense uptake in the kidneys bilaterally that was significantly higher than uptake seen in animals with ATN. ^{18}F-FDG was not a clear differentiator.

normal status. Once the guidelines were published, investigators began to try to optimize protocols to reduce the 4-hour time period, which is challenging in the clinical setting (*10*). At the SNMMI meeting last year, Sogbein et al. from the University of Ottawa (Canada) reported on a study with 102 patients, in which imaging time was cut to 2 hours using the Bonta criteria (*11*). That work was expanded into a 4-center trial involving 431 patients. Pelletier-Galarneau et al. from the Ottawa Hospital (Canada), the University of Vermont Medical Center (Burlington), and Montefiore Medical Center (Bronx, NY) reported on "Multicenter validation of a shortened gastric-emptying protocol" [53]. Using the Bonta criteria, they considered any patient at 2 hours in whom gastric retention was >65% as abnormal and anyone with retention <45% as normal. About 75% of patients were in 1 of these groups (60.6% normal, 14% abnormal), and their imaging studies could be ended at 2 hours. Of the 25% of patients who had indeterminate findings at 2 hours, continued imaging up to the 4-hour point was advised. At 4 hours, 8 patients were identified as borderline positive with 11%–14% retention. Although results of >10% retention are generally regarded as abnormal, the authors identified these low percentages as of "doubtful significance" and noted that if the cutoff for normal value were extended to 12%, the sensitivity of the shortened gastric emptying protocol would be 96%. Results from these data were published recently in *The Journal of Nuclear Medicine* (*12*).

I would like to personally thank, on behalf of all the speakers, our fearless leader, Satoshi Minoshima, MD, PhD, Scientific Program Committee Chair, a man who does everything and makes it seem effortless. I would like to thank Alan Packard, PhD, General Program Committee Chair, and the rest of the SNMMI program committee members for putting on a great meeting.

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