

Each month the editor of *Newsline* selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.

SPECT/CT and Diabetic Osteomyelitis

In an article e-published on March 20 ahead of print in *Diabetes Care*, Aslangul et al. from the Université Paris Descartes (France) reported on a study combining ^{67}Ga SPECT/CT and bedside percutaneous bone puncture in diagnosis of diabetic foot osteomyelitis in patients without signs of soft tissue infection. The study included 55 patients with clinically suspected osteomyelitis but without soft tissue infection. All participants underwent ^{67}Ga SPECT/CT imaging, with 42 positive and 13 negative findings, and were followed for at least 1 y. The patients with negative results did not receive antibiotic therapy, and all of their foot ulcers were resolved. Forty of the patients with positive findings (2 were excluded from analysis because of recent antibiotic administration) proceeded to bedside percutaneous bone puncture, and the 24 patients with gram-positive cocci proceeded to antibiotic therapy. At ~1-y follow-up, 47 patients were infection free, 3 had undergone amputation, and 3 had died. The combined imaging/bone puncture approach yielded sensitivity and specificity of

88.0% and 93.6%, respectively, with positive and negative predictive values of 91.7% and 90.7%, respectively. The authors concluded that the “coupling of ^{67}Ga SPECT/CT imaging and bedside percutaneous bone puncture appears to be accurate and safe for diagnosing diabetic foot osteomyelitis in patients without signs of soft tissue infection, obviating the need for antibiotic treatment in 55% of suspected cases.”

Diabetes Care

^{11}C -Met PET/CT and Parathyroid Adenoma Localization

Weber et al. from the University Medical Center (Ulm, Germany) reported on March 8 ahead of print in *Annals of Surgery* on the utility of ^{11}C -methionine (^{11}C -met) PET/CT in preoperative localization of parathyroid adenomas. The study included 102 patients scheduled for parathyroidectomy for primary hyperparathyroidism. All underwent preoperative ^{11}C -met PET/CT imaging of the neck and mediastinum. The imaging results/reports were compared with the surgical and histopathologic findings. Primary hyperparathyroidism was found to be caused by a single-gland adenoma in 97 patients, in whom PET/CT accurately localized the adenoma in 83 (86%; sensitivity, 91%; positive predictive value, 93%). In the 5 patients found to have multiglandular disease, PET/CT identified 2 hyperfunctioning parathyroid glands in 1 patient, 1 gland in 3 individuals, and was negative in the remaining patient (sensitivity, 80%). True-positive findings were significantly correlated with the size of parathyroid adenomas. The authors summarized their findings: “the high accuracy of Met PET/CT in the preoperative localization of parathyroid adenomas in a large series of patients with primary hyperparathyroidism.”

Annals of Surgery

Preoperative SPECT/CT and SN Retrieval

In an article e-published on February 21 ahead of print in *Gynecologic Oncology*, Hoogendam et al. from the University Medical Center Utrecht (The Netherlands) compared the preoperative sentinel node mapping abilities of planar lymphoscintigraphy with those of $^{99\text{m}}\text{Tc}$ -nanocolloid SPECT/CT in patients scheduled for robot-assisted laparoscopic cervical cancer surgery. The study included 62 women, 33 of whom underwent planar lymphoscintigraphy and 29 of whom underwent SPECT/CT before sentinel node resection by 4-arm robot-assisted laparoscopy, followed by pelvic lymph node resection. Uni- and bilateral sentinel node visualization rates were 15.2% and 75.8% for lymphoscintigraphy. The corresponding percentages for PET/CT were 6.9% and 86.2%. The correlation in sentinel node location between mapping and surgery was low for lymphoscintigraphy and high for SPECT/CT. Time required for bilateral intraoperative sentinel node retrieval was 75.4 ± 33.5 min for planar lymphoscintigraphy and 50.1 ± 15.6 min for SPECT/CT (average difference of 25.4 min). The authors concluded that “SPECT/CT significantly reduces intraoperative sentinel node retrieval with a clinically relevant time compared to [planar] lymphoscintigraphy.”

Gynecologic Oncology

SPECT/CT in Breast Radiation Treatment Planning

Cheville et al. from the Mayo Clinic (Rochester, MN) reported in the March 15 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2013;85:971–977) on a study to determine whether the addition of SPECT/CT lymphoscintigraphy to radiation treatment planning for breast cancer results in reduction of radiation delivered to nonpathologic lymph nodes that

drain the arm. The study included 28 patients with stage I or II breast cancer. All underwent SPECT/CT imaging, and results were fused with routine radiation therapy planning CT images. Two treatment fields were generated for each patient: 1 using the institution's standard practice and the other with treatment fields modified to minimize radiation dose to the arm-draining lymph nodes identified on SPECT/CT while not modifying the dose to target tissues. All patients were treated using the modified approach, and arm volumes were measured before radiation and serially over at least 1.5 y. Of the 68 level I–III arm-draining lymph nodes identified, 39 (57%) were inside the standard planning field but could be effectively blocked in the modified plan. Sixty-five percent of arm-draining lymph nodes in the standard plan fields and 16% of those in the modified plan fields received a mean of ≥ 10 Gy; 26% in the standard and 4% in the modified plans received a mean of ≥ 40 Gy. For the standard plans, mean lymph node radiation exposure was 23.6 Gy (SD = 18.2), compared with only 7.7 Gy (SD = 11.3) for the modified plans. Using the modified plans, no patients developed lymphedema. The authors concluded that “The integration of SPECT/CT scans into breast cancer radiation treatment planning reduces unnecessary arm-draining lymph node radiation exposure and may lessen the risk of lymphedema.”

International Journal of Radiation Oncology, Biology, Physics

¹⁸F-FDG PET and Cardiac Metabolic Monitoring

In an article published in the February issue of the *Annals of the American Thoracic Society* (2013;10:1–9) Lundgrin et al. from the Cleveland Clinic Lerner College of Medicine (OH) reported on the use of fasting ¹⁸F-FDG PET in monitoring metabolic changes in pulmonary arterial hypertension over the course of a year's treatment. The study included 14 patients with pulmonary arterial hypertension and 6 healthy volunteers, all of whom underwent fasting ¹⁸F-FDG PET imaging and echocardiography, as well as

assessments of proangiogenic progenitor (CD34⁺CD133⁺) cells and erythropoietin as indicators of transcription factor hypoxia-inducible factor (HIF)-1 α activation. Twelve individuals from the patient group also underwent repeat ¹⁸F-FDG PET 1 y later to determine whether changes in tracer uptake were related to echocardiographic parameter changes or to measures of HIF-1 α activation. Uptake of ¹⁸F-FDG in the right ventricle was higher in patients than in healthy individuals, and this difference correlated with echocardiographic assessments of cardiac dysfunction and with circulating proangiogenic progenitor cells but not with erythropoietin. Tracer uptake was lower in patients receiving β -adrenergic receptor blockers. In the patient group, changes in tracer uptake at the 1-y mark were correlated with changes in echocardiographic parameters and CD34⁺CD133⁺ cell numbers. In corollary immunohistochemistry examination of explanted hearts from patients with pulmonary arterial hypertension undergoing transplantation, the authors found that HIF-1 α was present in myocyte nuclei but was only weakly detectable in control hearts. The authors concluded that the hearts of patients with pulmonary arterial hypertension are characterized by “pathologic glycolytic metabolism that is quantitatively related to cardiac dysfunction over time, suggesting that metabolic imaging may be useful in therapeutic monitoring of patients.”

Annals of the American Thoracic Society

Prolonged Preclinical Phase for AD

In a study published on March 7 ahead of print in *Lancet Neurology* that received wide media coverage, Villemagne and the members of the Australian Imaging Biomarkers and Lifestyle Research Group reported on the results of a longitudinal study on rates of amyloid- β deposition, neurodegeneration, and cognitive decline associated with Alzheimer disease (AD). The study included 145 healthy volunteers, 36 individuals with mild cognitive impairment (MCI), and 19 individuals

with AD. Participants underwent neuropsychologic examination and both MR and ¹¹C-Pittsburgh compound (¹¹C-PiB) PET imaging at baseline and every 1.5 y for 3–5 y thereafter. Amyloid- β burden was expressed as ¹¹C-PiB standardized uptake value ratio (SUVR), with the cerebellar cortex as reference region. An SUVR of 1.5 differentiated high from low amyloid- β burden. Changes in amyloid- β deposition, MR volumetrics, and cognition were calculated over time. At enrollment, patients with AD and MCI showed significantly higher amyloid- β burdens than healthy volunteers. At follow-up, 163 (82%) of all participants showed positive rates of amyloid- β accumulation. To go from the lowest threshold of ¹¹C-PiB positivity to the levels observed in AD a calculated 19.2 y of increasing amyloid- β deposition would be required, and this accretion was posited to be in an almost linear fashion, with mean annual SUVR increases of 0.043. The estimated time to proceed from levels observed in healthy controls with low levels of amyloid- β deposition to the lowest threshold of ¹¹C-PiB positivity was 12.0 y. As has been noted elsewhere, as full AD progressed, the rate of amyloid β deposition slowed toward a plateau. The authors summarized their findings by noting that these projections suggest a prolonged preclinical phase of AD in which amyloid- β deposition reaches a threshold of positivity at 17.0 y, hippocampal atrophy at 4.2 y, and memory impairment at 3.3 y before the clinical onset of dementia. They concluded that amyloid- β deposition is slow and protracted and likely to extend for more than 2 decades. They added that these and similar findings on the rate of preclinical changes and the onset of the clinical phase of AD “will facilitate the design and timing of therapeutic interventions aimed at modifying the course of this illness.”

Lancet Neurology

MPI in Renal Transplant Evaluation

Chew et al. from the Royal Adelaide Hospital (Australia) reported on March 12 ahead of print in *Nephrology*

(Carlton) on a study designed to assess the prognostic value of myocardial perfusion imaging (MPI) in renal transplant evaluation. The retrospective study included the records of 387 patients who had undergone 393 pretransplant MPIs at 3 hospitals. Variables, including cardiac events, imaging results (any reversible defect was classified as positive; fixed defects and normal results were classified as negative), clinical follow-up results, and comorbidities (diabetes and hypertension), were mined from a large database of patients' medical records. Study endpoint events were "soft" (admission with angina, percutaneous intervention, or bypass) or "hard" (myocardial infarction or cardiac death). Age (\geq or $<$ 60 y), sex, diabetes, and hypertension were considered in multivariate analyses. For patients with negative MPI results, event rates in dipyridamole stress were compared with tachycardic stress. At 5-y follow-up, MPI-negative patients had significantly lower soft event rates (3.9%) than MPI-positive patients (20.8%). Although MPI-negative patients had a lower rate of hard events than MPI-positive patients, this difference was not statistically significant. Age, sex, diabetes, and hypertension were not significant variables. For patients with negative MPIs, soft and hard event rates were similar for dipyridamole and tachycardic stress. The authors concluded that "MPI is a good modality of prognosticating cardiac events in renal failure patients being considered for transplantation" and that "the value of a negative MPI is similar for dipyridamole and tachycardic stress."

Nephrology (Carlton)

¹¹¹In-Girentuximab SPECT in CCRCC

In an article e-published on February 21 ahead of print in *European Urology*, Muselaers et al. from Radboud University Nijmegen Medical Center (The Netherlands) reported on their experience with immunoSPECT imaging with the ¹¹¹In-labeled anti-carbonic anhydrase IX (anti-CAIX) antibody girentuximab in patients presenting with either a primary renal tu-

mor or a history of clear cell renal cell carcinoma (CCRCC) and lesions suspect for metastases detected at follow-up. The study included 29 patients, all of whom underwent SPECT imaging with ¹¹¹In-girentuximab. Tracer uptake was seen in 16 of the 22 patients found to have renal masses. At surgical resection, 15 of these were determined to be CCRCC. In 6 patients with suspect lesions, no tracer uptake was observed, no CCRCC was found, and no progression occurred. Seven patients who had histories of CCRCC and possible metastatic lesions on follow-up CT were imaged with ¹¹¹In-girentuximab SPECT. In 4 of these patients, lesions showed preferential uptake of ¹¹¹In-girentuximab, and local or systemic treatment was initiated. In the 3 remaining patients, no ¹¹¹In-girentuximab uptake was seen. During follow-up, 1 of these 3 showed progression, for which systemic treatment was started, and no progression was seen in the remaining 2. The authors concluded that "¹¹¹In-girentuximab immunoSPECT can be used to detect CCRCC lesions in patients with a primary renal mass and to clarify the nature of lesions suspect for metastases in patients with a history of CCRCC."

European Urology

PET/CT in Polymyositis/Dermatomyositis

Tanaka et al. from Chiba University and Sannoh Medical Center (both in Chiba, Japan) reported on March 11 ahead of print in *Rheumatology (Oxford)* on a study designed to determine whether ¹⁸F-FDG PET/CT can differentiate polymyositis/dermatomyositis (PM/DM) from nonmuscular diseases and also whether ¹⁸F-FDG uptake in proximal muscles reflects the activity and severity of muscular inflammation in PM/DM. The study included the records of 20 previously untreated patients with PM/DM patients and 20 age- and sex-matched control patients with nonmuscular diseases, all of whom had undergone ¹⁸F-FDG PET/CT imaging. Standardized uptake values (SUVs) were calculated for each of the 7 proximal muscles, and patient-based assessments for these muscles were calculated. The

mean proximal muscle SUVs were found to be significantly greater in PM/DM patients than in patients with nonmuscular diseases. Mean proximal muscle SUVs were significantly correlated with mean proximal manual muscle test scores and serum levels of creatine kinase and aldolase in the PM/DM patient. In those instances where biopsy specimens were obtained, SUVs in proximal muscles were significantly correlated with histologic grade for inflammatory cell infiltration. The authors concluded that these results suggest that "¹⁸F-FDG PET/CT is useful in the diagnosis of PM/DM when inflammation in proximal muscles is globally assessed with quantitative measurements" and that "local FDG uptake in a proximal muscle reflects the activity of inflammation in the same muscle and provides useful information in determining the region for muscle biopsy."

Rheumatology (Oxford)

¹⁸F-DOPA PET in Glioma Treatment Planning

In an article e-published on March 3 ahead of print in *Neuro-oncology*, Pafundi et al. from the Mayo Clinic (Rochester, MN, and Scottsdale, AZ) reported on the results of a prospective pilot comparing ¹⁸F-DOPA PET and MR imaging for neurosurgical biopsy targeting, resection planning, and radiotherapy target volume planning in patients with suspected malignant brain tumors. The study included 10 such patients, all of whom underwent both conventional MR and ¹⁸F-DOPA PET/CT imaging. In each patient, 1 to 3 biopsy locations were chosen in regions of concordant and discordant ¹⁸F-DOPA uptake and MR contrast enhancement. ¹⁸F-DOPA PET was quantified using standardized uptake values (SUVs) and tumor-to-normal hemispheric tissue (T/N) ratios, and 23 biopsied lesions underwent histopathologic examination, which confirmed glioma in 22 specimens. Of the 16 high-grade biopsy specimens, 13 were obtained from regions of elevated ¹⁸F-DOPA uptake, whereas MR T1-CE was present in only 6 of those

16 samples. Optimal ^{18}F -DOPA PET thresholds corresponding to high-grade disease based on histopathology were calculated as $T/N > 2.0$. In every patient, tracer uptake regions with $T/N > 2.0$ extended beyond T1-CE up to a maximum of 3.5 cm, and SUV was found to correlate with grade and cellularity. The authors concluded that “ ^{18}F -DOPA PET SUV_{max} may more accurately identify regions of higher grade/higher density disease in patients with astrocytomas and will have utility in guiding stereotactic biopsy selection” and that “using SUV-based thresholds to define high-grade portions of disease may be valuable in delineating radiotherapy boost volumes.”

Neuro-oncology

^{68}Ga -DOTATOC PET/CT and Partial Volume Effects

Ruf et al. from the Universitätsklinikum Magdeburg (Germany) reported on March 9 ahead of print in *Neuroendocrinology* on a study designed to determine the lesion cut-off size for the occurrence of partial volume effects in clinical use of ^{68}Ga -DOTATOC PET/CT in neuroendocrine neoplasms. The investigation included retrospective evaluation of 51 PET/CT studies in 45 patients for malignant PET foci. Maximum standardized uptake values (SUV_{max}) and maximum lesion diameter on CT were recorded. Of 413 PET foci identified, 313 were malignant, measurable on CT,

and with roughly spherical geometry (SUV_{max} , 2.45–103.27 mm; CT diameter, 5.3–103.3). The cutoff lesional size for the occurrence of partial volume effects was found to be 20.4 mm by mathematical and 25 mm by visual assessment. The authors concluded that “In ^{68}Ga -DOTATOC imaging, the clinical lesional size-threshold is far larger than expected from systemic resolution only” and that “tracer uptake quantification is only acceptable in sufficiently large lesions.”

Neuroendocrinology

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in March and April. In an article published in the March 5 issue of *Neurology* (2013;80:952–956), Portnow et al. from the University of Florida (Gainesville) provided an overview of “The history of cerebral PET scanning: from physiology to cutting-edge technology.” Skali et al. from Brigham and Women’s Hospital (Boston, MA) reviewed “ ^{18}F -FDG PET/CT for the assessment of myocardial sarcoidosis” in the May issue of *Current Cardiology Reports* (2013;14:352). In the March issue of *Expert Review of Anticancer Therapy* (2013;13:359–373),

Goldstein et al. from the University College London Cancer Institute (UK) summarized “Developments in single photon emission computed tomography and PET-based HER2 molecular imaging for breast cancer.” Henry and Juhász from the University of Minnesota Medical School (Minneapolis) and Wayne State University School of Medicine (Detroit, MI) described “Serotonergic PET in temporal lobe epilepsy: biomarking or etiologic mapping?” on March 20 ahead of print in *Neurology*. On March 21, ahead of print in the *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, Conway et al. from the University of Southampton (UK) described “The co-imaging of gamma camera measurements of aerosol deposition and respiratory anatomy.” Jasinska et al. from the National Institute on Drug Abuse (Baltimore, MD) provided an overview of the “Dual role of nicotine in addiction and cognition: a review of neuroimaging studies in humans,” on March 6 ahead of print in *Neuropharmacology*. In an article e-published on March 6 ahead of print in *Current Radiopharmaceuticals*, Cucurullo et al. from Second University of Naples (Italy) reported on “Bone metastases radiopharmaceuticals: an overview.” O’Farrell et al. from the University of Bradford (UK) summarized “Noninvasive molecular imaging for preclinical cancer therapeutic development” on March 12 ahead of print in the *British Journal of Pharmacology*.