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. We have added articles outside of radionuclide-based procedures in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress across the spectrum of molecular imaging. 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.

PET Dementia Differentiation

In an article e-published on January 17 ahead of print in *Neurodegenerative Diseases*, Villemagne et al. from the University of Melbourne (Australia) reported on a study evaluating the diagnostic potential for PET imaging of striatal monoaminergic terminal integrity with the novel vesicular monoamine transporter type 2 (VMAT2) radioligand ^{18}F-AV-133 as a way of differentiating dementia with Lewy bodies from Alzheimer disease. The study included 50 participants (9 with dementia with Lewy bodies, 11 with Alzheimer disease, 20 with Parkinson disease, and 10 age-matched, healthy volunteers). All underwent ^{18}F-AV-133 PET imaging, and 20 selected participants also underwent PET amyloid imaging with either ^{11}C-PiB or ^{18}F-florbetaben. VMAT2 density was calculated by normalized tissue uptake value ratios at 120–140 min after injection, with the primary visual or cerebellar cortex as reference region, and resulting ratios were compared among the participant groups. Participants with dementia with Lewy bodies and Parkinson disease showed significantly lower striatal VMAT2 densities, especially in the posterior putamen, than did those with Alzheimer disease and healthy controls. Neither the Alzheimer group nor the healthy volunteers showed reductions in striatal VMAT2 density. The authors concluded that ^{18}F-AV-133 "allows assessment of nigrostriatal degeneration in Lewy body disease" and, in contrast to amyloid imaging, "can robustly detect reductions of dopaminergic nigrostriatal afferents in dementia with Lewy bodies patients, assisting in the differential diagnosis from Alzheimer disease."

Neurodegenerative Diseases

^{18}F-FDOPA PET and VHL Syndrome

Weisbrod et al. from the National Institutes of Health (Bethesda, MD) reported on January 18 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a study of the clinical value of functional imaging with ^{18}F-FDOPA in patients with Von Hippel–Lindau syndrome–related tumors. The prospective study included 52 patients with Von Hippel–Lindau syndrome. All patients underwent imaging with ^{18}F-FDOPA PET, and these results were compared with data from clinical, laboratory, and pathology assessments, as well as other imaging approaches (CT, MR, and ^{18}F-FDG PET). Imaging identified an aggregate total of 390 lesions in these patients, with CT identifying the greatest number (139), followed by MR imaging (117), ^{18}F-FDG PET (94), and ^{18}F-FDOPA PET (40). ^{18}F-FDOPA PET detected 20 pancreatic and 20 extrapancreatic tumors, including lesions in the adrenal gland (11), kidney (3), liver (4), lung (1), and cervical paraganglioma (1). These were not seen by other imaging studies in 9.6% of patients (4.4% of lesions). Eighty-four percent of patients who underwent resection on the basis of ^{18}F-FDOPA PET-positive lesions were found to have neuroendocrine tumors. The authors concluded that "^{18}F-FDOPA PET is a useful complementary imaging study to detect neuroendocrine tumors in patients with VHL undergoing surveillance, especially in those suspected to have adrenal pheochromocytoma or unusual ectopic locations."

Journal of Clinical Endocrinology and Metabolism

^{11}C-Methionine PET and Glioma Immunotherapy

In an article e-published on January 13 ahead of print in the *Journal of Neurosurgery*, Chiba et al. from Osaka University Graduate School of Medicine (Japan) and Yokohama City University Graduate School of Medicine (Japan) reported on the use of ^{11}C-methionine PET parametric mapping for monitoring response to Wilms tumor 1 immunotherapy. The study included 14 patients with recurrent malignant glioma. Overall survival after initiation of immunotherapy was assessed in relation to: (1) serial changes in tumor area on gadolinium-enhanced MR imaging; (2) serial changes in maximum uptake on ^{11}C-methionine PET; and (3) detailed voxel-wise parametric response mapping of changes in ^{11}C-methionine PET images. The mapping technique differentiated 3 types of areas within tumor cores, including those with no change in uptake before and after treatment, increased uptake after treatment, and decreased uptake after treatment. Although the results of MR imaging and conventional ^{11}C-methionine PET were not correlated with overall survival, the percentage of increased uptake after treatment as indicated by the mapping technique was highly correlated with overall survival after initiation of Wilms tumor 1

immunotherapy. The authors concluded that these results pointed to "the limited value of gadolinium-enhanced MR imaging" in this setting and highlighted "the potential of voxel-wise parametric response mapping analysis of ^{11}C-methionine PET for monitoring treatment response in immunotherapy for malignant gliomas."

Journal of Neurosurgery

Accuracy and PET Spine Studies

Al-Beyatti et al. from King's College London (UK) reported on January 12 ahead of print in *Osteoporosis International* on a study evaluating the precision of ^{18}F-fluoride PET lumbar spine measurements in assessing regional bone turnover. The study included 58 scans performed in 20 osteoporotic postmenopausal women who underwent ^{18}F-fluoride PET immediately after stopping long-term biphosphonate treatment and at 6 and 12 mo thereafter. No significant changes in PET measurements were seen over the 12-month period, and the data were determined to be suitable for a precision study. Precision errors were calculated for standardized uptake values (SUVs) and for fluoride plasma clearance to bone mineral (determined using both the Patlak and 3-compartment Hawkins methods). Precision errors were expressed as percentage coefficients of variation for the mean L1–L4 region and for individual vertebrae. For the L1–L4 region, the percentage coefficients of variation were 9.2% (range, 7.5%–11.8%) for SUV, 11.7% (range, 9.5%–14.9%) for plasma clearance to bone mineral using the Patlak method, and 14.5% (range, 11.7%–18.5%) for clearance to bone mineral measured using the Hawkins method. No significant differences were seen in precision errors for the L1–L4 region and those for single vertebrae. The authors concluded that SUV measurements seemed to produce the greatest precision (smallest precision error) and that the fact that measurement of a smaller region of interest did not increase the precision error suggested that scanner calibration may be the determining factor in such errors.

Osteoporosis International

Dual-Tracer H&N Sentinel Node Biopsy

In an article e-published on December 30 ahead of print in the *Annals of Surgical Oncology*, Brouwer et al. from The Netherlands Cancer Institute (Amsterdam) reported on a study investigating the feasibility of combining lymphoscintigraphy and intraoperative sentinel node detection, using a radioactive and fluorescent hybrid protein colloid, in head and neck melanoma. The study included 11 patients scheduled for sentinel node biopsy in the head and neck. The ^{99m}Tc- and indocyanine green–labeled nanocolloid was injected intradermally at 4 sites around the scar of the primary melanoma excision approximately 5 h before the scheduled biopsy. Each patient then underwent lymphoscintigraphy and SPECT/CT to identify sentinel nodes. Patent blue dye was injected in 7 of 11 patients in the surgical suite. Sentinel nodes were localized intraoperatively with a gamma probe and visualized with fluorescence-based near-infrared light and an associated camera, and a portable gamma camera confirmed excision of all sentinel nodes. Twenty-seven sentinel nodes were preoperatively identified on lymphoscintigraphy and SPECT/CT images, and all were localized during surgery. In the 7 patients in whom blue dye was used, only 43% of the sentinel nodes stained blue, but all were fluorescent. The portable gamma camera identified additional sentinel nodes in 2 patients. All resected radioactive lymph nodes were fluorescent, and all fluorescent nodes were radioactive. The authors concluded that the dual-labeled nanocolloid "allows for preoperative sentinel node visualization and concomitant intraoperative radio- and fluorescence guidance to the same sentinel nodes in head and neck melanoma patients."

Annals of Surgical Oncology

PET/CT in Presurgical Thyroid Nodules

Deandreis et al. from the Institut Gustav Roussy (Villejuif, France) reported on January 18 ahead of print in *Thyroid* on a study designed to evaluate the role of ^{18}F-FDG PET/CT in predicting malignancy of thyroid nodules with indeterminate fine-needle aspiration cytology (FNAC) results and to correlate tracer uptake with pathologic and ultrasound results. The study included 55 patients (42 women, 13 men; mean age, 50 y) scheduled for surgery for 56 thyroid nodules with indeterminate FNAC. All patients underwent presurgical ^{18}F-FDG PET/CT and neck ultrasound. Pathology indicated after surgery that 34 nodules were benign, 10 were malignant (7 papillary carcinomas, 3 follicular carcinomas), and 12 were "tumors of uncertain malignant potential" (TUMP). The sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) of ^{18}F-FDG PET in detecting cancer or TUMP were 77%, 62%, 57%, and 81%, respectively. Cellular atypia proved after additional analyses to be the only factor predictive of tracer uptake. Hurthle cells and poorly differentiated components were independent predictive factors of high maximum standardized uptake values. The sensitivity, specificity, PPV, and NPV of ultrasound in detecting cancer or TUMP were 82%, 47%, 50%, and 80%, respectively. Additional analyses showed that hypervascularization was correlated with malignancy and TUMP and cystic features were correlated with benign status. The authors summarized their findings by noting that adding ^{18}F-FDG PET findings to neck ultrasound provided no benefit and concluded that "the sensitivity and specificity of ^{18}F-FDG PET in the presurgical evaluation of indeterminate thyroid nodules are too low to recommend FDG-PET routinely."

Thyroid

Interim PET in Hodgkin Disease

In an article e-published on January 19 ahead of print in *Radiation Oncology*, Tseng et al. from Stanford University (CA) and the Johns Hopkins Medical Institute (Baltimore, MD) reported on the ability of interim-treatment quantitative PET to predict progression and survival in patients with Hodgkin disease. The study included 30 such patients (53% with stage III–IV disease; 67% with International Prognosis Scores [IPS] ≥2) in treatment at first presentation or after relapse. All participants underwent staging and interim PET/CT (at an ~55-d interval after initiation of 1 of 4 chemotherapeutic regimens). Data points from the serial imaging included metabolic tumor volume, mean standardized uptake value, maximum SUV (SUV_{max}), and integrated SUV. The authors looked at the predictive and comparative values of IPS, absolute value PET parameters, and calculated ratios of interim- to pretreatment PET parameters for progression-free and overall survival. Patients were followed for a median of 50 mo, during which 6 patients progressed clinically. None of the initial absolute value PET parameters was found to be predictive. Absolute value SUV_{max} from interim-treatment scans was correlated with overall survival and progression-free survival. All 4 calculated PET parameter data points (both pre- and during treatment) were associated with overall survival, and 3 were associated with progression-free survival. IPS was associated with both progression-free and overall survival. The authors concluded that "calculated PET metrics may provide predictive information beyond that of traditional clinical factors and may identify patients at high risk of treatment failure early for treatment intensification."

Radiation Oncology

Patterns of Spinal Cord FDG Uptake

Amin et al. from Cairo University (Giza, Egypt) reported on January 17 ahead of print in the *Journal of Neuro-oncology* on a study designed to evaluate the characteristics and normal patterns of ^{18}F-FDG uptake by the spinal cord in cancer patients. The study included 101 cancer patients who underwent ^{18}F-FDG PET/CT in which the spinal cord was visually assessed for tracer uptake, using a maximum standardized uptake value of ≥1 as a cutoff. Forty-nine (48.5%) patients were found to have positive tracer uptake in the spinal cord and were followed up with additional MR and PET/CT imaging. Uptake was seen most frequently on initial imaging in the 11th and 12th dorsal vertebrae (36/49; 73.5%), all cervical levels (24/49; 49%), and the first lumbar segments (19/49; 38.7%). Uptake was seen >3 times more frequently in winter than in summer. MR imaging results were available for 25 of the patients with positive tracer uptake in the spinal cord and showed no abnormalities. Follow-up ^{18}F-FDG PET/CT studies at 3–6 mo showed that uptake had faded completely in 41 of 49 (83.7%) patients, with stationary or reduced uptake in the remaining 8 (16.3%). The authors concluded that it is important to note that "FDG uptake in multiple consecutive segments of the spinal cord is not uncommon in cancer patients" and should not be mistaken for malignant involvement. They added that such physiological uptake is seen most often in the cervical, last 2 dorsal, and first lumbar levels and is also seen more often in winter.

Journal of Neuro-oncology

FDG and Organ Radiation Dose

In an article e-published on January 14 ahead of publication in *Radiation Protection Dosimetry*, Staaf et al. from Stockholm University (Sweden) reported on a revision to absorbed organ radiation doses from intravenous bolus administration of ^{18}F-FDG with reference to the presence or absence of tumors. Absorbed doses were calculated using the Medical Internal Radiation Dose standard from experimental activity–time curves. The calculation study group included 30 patients (22 with macroscopic lung tumors and 8 with no observable disease) who were investigated using a state-of-the-art combined PET/CT system. Each patient underwent a series of 10 consecutive whole-body PET scans during the first 60-min after tracer administration. Organ radiation dose results were compared with those reported in International Commission for Radiation Protection (ICRP) Publication 106 (Radiation Dose to Patients from Radiopharmaceuticals). The presence or absence of tumor did not affect FDG biodistribution. Larger interindividual variations in organ-absorbed doses were observed than anticipated with the ICRP reports. The authors concluded that "this, in combination with the lack of a model for bladder voiding suitable for all patients, suggests the need for a more precise estimate of normal-organ radiation doses," which would be beneficial in optimizing FDG administration in routine clinical practice.

Radiation Protection Dosimetry

Optical Imaging and Treatment Response

Van den Ven et al. from the University Medical Center Utrecht (The Netherlands) and Stanford University (CA) reported on January 10 ahead of print in *Clinical Cancer Research* on a study designed to determine whether optical imaging can be used for in vivo therapy response monitoring as an alternative to radionuclide techniques. The researchers looked at HER2-targeted affibody molecules to monitor Hsp90 (17-DMAG) treatment response in breast cancer xenografts in mice. After establishment of tumors, 14 mice were treated over 2 d with 17-DMAG, and 9 mice served as controls. All mice underwent optical imaging before treatment and at d 3, 6, and 9, with each imaging session preceded by injection of the anti-HER2 affibody. Imaging signal was reduced by 22.5% in tumors at d 3 but recovered by d 6–9. No signal reduction was seen in the control group. Ex vivo HER2 levels correlated

with in vivo optical imaging results. The authors concluded that "optical imaging with an affibody can be used to noninvasively monitor changes in HER2 expression in vivo as a response to treatment with an Hsp90 inhibitor, with results similar to response measurements in PET imaging studies."

Clinical Cancer Research

Interim PET and DLBCL Treatment

In an article e-published on January 10 ahead of print in *Blood*, Pregno et al. from the San Giovanni Battista Hospital and University (Turin, Italy) reported on a study designed to assess the predictive value of interim PET in patients with diffuse large B-cell lymphoma treated at diagnosis with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. The study included 88 such patients, who underwent PET/CT imaging at diagnosis, after 2–4 courses of therapy, and at the end of therapy. Interim PET results were negative in 72% of patients and positive in 28%. Final PET results were negative in 88% of patients and positive in 12% (2 were false-positive), and clinical results indicated a complete response in 90%. Over a median follow-up of more than 2 y, overall and progression-free survival were 91% and 77%, respectively. For interim PET, 2-y progression free survival rates were 85% for negative studies and 72% for positive studies. For final PET, these figures were 83% and 64%. The authors concluded that positive interim PET "is not predictive of a worse outcome in diffuse large B-cell lymphoma patients treated with rituximab–CHOP" and called for larger prospective studies to standardize interim PET reading criteria.

Blood

PET and Photodynamic Therapy

Cauchon et al. from the Université de Sherbrooke (Canada) reported on January 3 ahead of print in *Photochemical and Photobiological Sciences* on a study of the utility of ^{18}F-FDG PET and a constant infusion technique in predicting the efficacy of photodynamic therapy in a mouse tumor model. The researchers looked at the effects of photodynamic therapy on tracer uptake rates in tumors, using 4 different sulfonated phthalocyanine analogs as photosensitizers in combination with either continuous or fractionated illumination protocols. Mice with EMT-6 tumors were infused with tracer 30 min before therapy, with dynamic PET images acquired to measure uptake for these tumors and for a group of mice with untreated tumors. Almost all of the therapy protocols induced reductions in tracer uptake rates in treated tumors, with a rebound in uptake after therapy. A sequence of a sharp drop in ^{18}F-FDG tumor uptake rates during photodynamic therapy, followed by a strong rebound and accompanied by short delay-to-response times, was correlated with optimal long-term tumor response outcomes. The authors concluded that "this dynamic FDG PET protocol provides real-time observations to predict long-term photodynamic therapy efficacy, while using fewer animals than conventional methods, thus making possible the rapid optimization of treatment parameters."

Photochemical and Photobiological Sciences

PET and Restless Leg Syndrome

In an article e-published on January 11 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism*, Oboshi et al. from the Hamamatsu University School of Medicine (Japan) reported on a study designed to clarify the contribution of $D_{2/3}$ receptor function to the clinical symptoms of idiopathic restless leg syndrome by comparing the binding potential of ^{11}C-raclopride with clinical improvements after $D_{2/3}$ stimulation with pramipexole. The study included 8 previously untreated patients with idiopathic restless leg syndrome and 8 age-matched healthy volunteers, each of whom underwent ^{11}C-raclopride PET imaging before oral pramipexole administration over 2 wk. Binding potential values were compared using regions of interest and voxel-based methods and were found to be significantly lower in the mesolimbic dopamine region (nucleus accumbens and caudate) in the restless leg patients than in controls. No significant differences were noted in the putamen in the 2 groups. Binding potential levels in the nucleus accumbens in the patient group correlated negatively with clinical severity scores and positively with the degree of posttreatment improvement in symptoms. The authors concluded that these results "suggest that alterations in mesolimbic $D_{2/3}$ receptor function reflect the pathophysiology of idiopathic restless leg syndrome, and the baseline availability of $D_{2/3}$ receptors may predict the clinical outcome after $D_{2/3}$ agonist treatment."

Journal of Cerebral Blood Flow and Metabolism

PET/MR in MI Inflammation

Lee et al. from the Harvard Medical School (Boston, MA) and the Seoul National University College of Medicine (Korea) reported in the January 10 issue of the *Journal of the American College of Cardiology* (2012;59:153–163) on a study using both PET and MR imaging to explore myocardial inflammation occurring after myocardial infarction (MI). The study was performed in mice with acute myocardial inflammation after coronary ligation–induced MI, and assessments were made with ^{18}F-FDG PET, gadolinium-DTPA MR imaging, fluorescence-activated cell sorting, polymerase chain reaction (PCR), and histology. Among the findings were the fact that CD11b+ cells had 4-fold higher PET tracer uptake than the infarct tissue from which they were isolated. In addition, the researchers identified significant monocyte recruitment in remote myocardium, consistent with observed macrophage infiltration in the remote myocardium of patients after acute MI. Quantitative

PCR showed a strong increase of recruiting adhesion molecules and chemokines in the remote myocardium, although these levels were always lower than in the infarct. Matrix metalloproteinase activity was also significantly increased in noninfarcted myocardium, which suggested to the authors that monocyte recruitment to the remote zone may contribute to post-MI dilation.

Journal of the American College of Cardiology

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 late December and January. In an article in the January issue of *Kidney International* (2012;81:129–131), Kobayashi and Choyke from the National Institutes of Health (Bethesda, MD) provided a "Recipe for a new imaging biomarker: carefully combine target, reagent, and technology." Palm et al. from the Istituto Oncologico Veneto (Padua, Italy) reported online on January 12 ahead of print in *Critical Reviews in Oncology/Hematology* on "PET/CT imaging in gynecologic malignancies: a critical overview of its clinical impact and our retrospective single center analysis." The January 2 online-before-print issue of *Current Pharmaceutical Biotechnology* contained several reviews related to molecular imaging. Among these were De Saint-Hubert et al. from the Universitätklinikum de RWTH Aachen (Germany), with "Apoptosis imaging to monitor cancer therapy: the road to fast treatment evaluation," and Bäuerle et al. from the German Cancer Research Center (Heidelberg, Germany), with "Monitoring molecular, functional, and morphologic aspects of bone metastases using noninvasive imaging." Silindir et al. from Hacettepe University (Ankara, Turkey), reviewed "The use and importance of liposomes in positron emission tomography" in the January issue of *Drug Delivery* (2012;19:68–80). In an article e-published on December 29 ahead of print in the *European Journal of Cancer*, Soloviev et al. from the Cambridge Research Institute (UK) offered perspective on "^{18}F-FLT: an imaging biomarker of tumour proliferation for assessment of tumour response to treatment."