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.

Metabolic Correlates and Epilepsy Assessment

Struck et al. from the Massachusetts General Hospital (Boston, MA) and the University of Wisconsin (Madison) reported on May 11 ahead of print in *Neurocritical Care* on an investigation of ^{18}F-FDG PET imaging as a metabolic biomarker complementary to the use of ictal–interictal continuum (IIC) patterns identified in continuous electroencephalography (EEG) in assessing status epilepticus among patients with specific types of IIC patterns. The study included 18 individuals who underwent PET imaging while experiencing IIC patterns attributed to structural lesions (44%), neuroinflammatory/neuroinfectious disease (39%), or epilepsy (11%). Patients underwent MR imaging, and PET and MR images were coregistered. For comparison of regional SUV_{max} and EEG results, "electrographic" status epilepticus was defined as discrete seizures without interictal recovery or >3-Hz rhythmic IIC patterns. "Electroclinical" status epilepticus was defined as IIC patterns with EEG and clinical response to anticonvulsants, as clonic activity, or as persistent postictal encephalopathy. Sixty-one percent of participants were found to have regional PET hypermetabolism, which predicted electrographic or electroclinical status epilepticus (without differentiating between the 2) with a sensitivity of 79% and specificity of 100%. Hypermetabolism also predicted electroclinical status epilepticus alone with similar sensitivity and specificity. The authors concluded that "in hospitalized patients with IIC EEG patterns, FDG PET hypermetabolism is common and is a candidate metabolic biomarker of electrographic status epilepticus or electroclinical status epilepticus."

Neurocritical Care

Transdermal Hormone Therapy and AD Risk

In an article e-published on May 7 ahead of print in the *Journal of Alzheimer's Disease*, Kantarci et al. from the Mayo Clinic (Rochester, NY) and the University of Wisconsin (Madison) reported on a study designed to determine whether early postmenopausal transdermal 17β-estradiol therapy modifies the risk of Alzheimer disease (AD) by reducing rates of amyloid-β deposition. The study included 68 women who had participated in a larger study of early estrogen administration. Each joined the study within 5–36 mo after menopause and were randomized for 4 y to 0.45 mg/d of oral conjugated equine estrogens (CEE), 50 μg/d of transdermal 17β-estradiol; or placebo pills and patch. Oral progesterone (200 mg/d) was given to groups 1 and 2 for 12 d per month. At 7 y after randomization (3 y after end of randomized treatment), the participants underwent ^{11}C-Pittsburgh compound B PET imaging. SUV ratios were calculated. The authors found that the 21 women randomized to transdermal 17β-estradiol had lower SUV ratios than the 30 women on placebo (after adjusting for age). Among apolipoprotein-E ε4 (APOEε4) carriers, the 10 women treated with transdermal 17β-estradiol had lower SUV ratios than the 5 women on placebo or the 3 treated with oral CEEs (after adjusting for age). The use of hormone therapy was not correlated with SUV ratio changes in APOEε4 noncarriers. The authors concluded that the association of transdermal 17β-estradiol therapy with reduced amyloid-β deposition in recently postmenopausal women "may have important implications for the prevention of AD in postmenopausal women and needs to be confirmed in a larger sample."

Journal of Alzheimer's Disease

PET and MR in GBM Tumor Hypoxia

Gerstner, from the Massachusetts General Hospital (Boston, MA), and U.S. researchers participating in the American College of Radiology Imaging Network reported on May 16 ahead of print in *Clinical Cancer Research* on the results of a cooperative trial on the utility of ^{18}F-fluoromisonidazole (^{18}F-FMISO) PET and MR imaging in assessing tumor hypoxia in patients with newly diagnosed glioblastoma (GBM). The trial included 50 such patients, of whom 42 had complete imaging data for this analysis. Before treatment (chemotherapy + radiation), all 42 patients underwent MR imaging to assess tumor vascular permeability and tumor cerebral blood volume and flow and ^{18}F-FMISO PET to assess tumor hypoxia. This report included follow-up at 1 y. Shorter overall survival at this time point was associated with higher baseline SUV_{peak} and higher mean and median vascular permeability scores. Shorter progression-free survival was associated with higher pretreatment median vascular permeability scores, normalized regional cerebral blood volumes, and normalized cerebral blood flow. The authors concluded that "increased tumor perfusion, vascular volume, vascular permeability, and hypoxia are negative prognostic markers in newly diagnosed GBM patients, and these important physiological markers can be measured safely and reliably using MR imaging and ^{18}F-FMISO PET."

Clinical Cancer Research

^{90}Y-DOTATATE in Pancreatic and Small Bowel NETs

In an article e-published on May 9 in *Future Oncology*, Rogowski, from the Hospital Ministry of the Interior and Administration and Warmia & Mazury Oncology Centre (Olsztyn, Poland), and colleagues from Poland and the UK reported on a study designed to compare the long-term efficacy of ^{90}Y-DOTA^{0}, D-Phe^{1}, Tyr^{3}-octreotate (^{90}Y-DOTATATE) in patients with nonresectable pancreatic or small bowel neuroendocrine tumors (NETs). The study included 67 such patients, all of whom received ^{90}Y-DOTATATE therapy. The median progression-free survival for patients with pancreatic NETs was 25 mo; for those with small bowel NETs this figure was 28 mo. Median overall survival for patients with pancreatic NETs was 42 months and was 38.5 months for those with small bowel NETs. No significant differences were noted in overall or progression-free survival between the 2 groups when data were adjusted for tumor origin, secretory status, and sex. The authors concluded that "^{90}Y-DOTATATE may have similar efficacy in pancreatic and small bowel NETs," adding the observation that better World Health Organization performance status at baseline seems to be associated with more favorable outcomes.

Future Oncology

PET and Gastric Adenocarcinoma Staging

Serrano et al. from the Montefiore Einstein Medical Center (Bronx, NY) and the Albert Einstein College of Medicine (New York City, NY) reported in the May issue of the *Journal of Surgical Oncology* (2016;113:640–646) on a study focusing on the utility of ^{18}F-FDG PET in staging gastric adenocarcinoma. The study reviewed the results of CT and PET imaging in 166 patients with biopsy-proven gastric adenocarcinoma. CT imaging was successful in identifying primary tumor in 72.3% of patients, locoregional disease in 50.6%, distant lymph node disease in 15.1%, and metastasis in 19.3%. The corresponding percentages for PET were 75.3%, 47.0%, 24.7%, and 16.3%. PET provided significant changes in management, upstaging disease in 31 (18.7%) patients and downstaging disease in 17 (10.2%). Twenty (64.5%) of the patients who were upstaged went on to develop progressive disease. The authors concluded that their findings "support the use of FDG PET as a valuable adjunct to CT in the staging of gastric adenocarcinoma, as it changed the stage in 48 (28.9%) patients."

Journal of Surgical Oncology

^{18}F-AV-1451 and Neuromelanin in PD

In an article e-published on May 5 ahead of print in *Brain*, Hansen et al. from Aarhus University Hospital (Denmark), Imperial College London (UK), and Newcastle University (UK) reported on the ability of tau tangle ligand ^{18}F-AV-1451 PET imaging to visualize the concentration of nigral neuromelanin in Parkinson disease (PD) and compared their findings to dopamine transporter density as measured by ^{123}I-FP-CIT SPECT. The study included 17 individuals with idiopathic PD and 16 age- and sex-matched controls, all of whom underwent ^{18}F-AV-1451 PET imaging. Twelve of the individuals with PD also underwent standardized ^{123}I-FP-CIT SPECT imaging. Decreased ^{18}F-AV-1451 signal was visible in the midbrain in many members of the PD group. On analysis, the PD group had a 30% mean decrease in total nigral ^{18}F-AV-1451 volume of distribution compared with controls, although an overlap was noted in individual ranges. No significant correlation was noted between dominant clinical symptom side and distribution of nigral volume. Nor was there a correlation between nigral ^{18}F-AV-1451 volume of distribution and age or time since diagnosis. ^{123}I-FP-CIT SPECT showed that mean total striatal dopamine transporter signal was decreased by 45%. After median disease duration of 4.7 y (range, 0.5–12.4 y), the mean total ^{18}F-AV-1451 substantia nigra volume of distribution was decreased by 33%. The authors noted that "^{18}F-AV-1451 PET may be the first radiotracer to reflect the loss of pigmented neurons in the substantia nigra of parkinsonian patients" and that "the magnitude of the nigral signal loss was smaller than the decrease in striatal dopamine transporter signal measured by dopamine transporter SPECT." They concluded that these findings "suggest a more severe loss of striatal nerve terminal function compared with neuronal cell bodies, in accordance with the postmortem literature."

Brain

SPECT-Based Sjögren Syndrome Scoring

Chen et al. from the Huazhong University of Science and Technology (Hubei, China) reported on May 19 in *PLoS One* (2016;11:e0155666) on the development and evaluation of a quantified SPECT-based point-scoring diagnostic system for Sjögren syndrome (SS). The evaluation was conducted in a group of 213 patients with suspected SS. Patients and their accompanying data were clinically evaluated by specialists at initial visit and after treatment and categorized as SS (n = 149) and non-SS (n = 64). All patients had undergone SPECT imaging of the salivary gland. Using quantitative SPECT data, a point-scoring diagnostic system for SS was developed. The authors then evaluated the accuracy of the new system in this patient group and compared the results with 2002 American–European Consensus Group (AECG) and 2012 American College of Radiology (ACR) criteria. When 7.0 was used as a cut-off point, the sensitivity, specificity, positive and negative predictive values, and accuracy of the new system in diagnosing SS were 89.93%, 93.75%, 97.10%, 80.00%, and 91.08%, respectively. The authors concluded that "the new point-scoring diagnostic system for SS based on quantified SPECT imaging of salivary gland may be superior to 2002 AECG criteria and 2012 ACR criteria, with higher sensitivity and similar specificity in the diagnosis of SS." They added that the system is feasible in the clinical setting.

PLoS One

Differentiating DLB from AD

In an article e-published on May 3 ahead of print in *Geriatrics & Gerontology International*, Shimizu et al. from Tokyo Medical University (Japan) compared the diagnostic value of 4 neuroimaging techniques in differentiating dementia with Lewy bodies (DLB) from Alzheimer disease (AD): ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) dopamine transporter SPECT (DAT SPECT), MR imaging, perfusion SPECT, and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy. The study included 64 patients (32 with probable AD and 32 with probable DLB). Quantitative imaging data compared from the 4 techniques included specific binding ratio for ^{123}I-FP-CIT DAT SPECT, heart-to-mediastinum ratio in the delay phase for ^{123}I-MIBG myocardial scintigraphy, *z* scores in the medial occipital lobe for perfusion SPECT, and *z* scores of hippocampal atrophy using a voxel-based specific regional analysis system for AD for MR imaging. The authors found that ^{123}I-FP-CIT DAT SPECT provided more accurate differentiation of DLB from AD than the other methods and that ^{123}I-MIBG myocardial scintigraphy was more accurate in this differentiation than either MR imaging or perfusion SPECT. They noted that these results are in agreement with recent consensus clinical diagnostic criteria.

Geriatrics & Gerontology International

PET/MR and Tumor Heterogeneity

Pinker et al. from the Medical University of Vienna (Austria) and Florida State University (Tallahassee) reported in the May 11 issue of *PLoS One* (2016;11:e0155333) on a study designed to investigate multiparametric ^{18}F-FDG and ^{18}F-fluoromisonidazole (^{18}F-FMISO) PET/3T high-resolution, T2-weighted, contrast-enhanced, and diffusion-weighted MR imaging for noninvasive detection of tumor heterogeneity in locally advanced cervical cancer. The study included 16 patients, of whom 11 had complete fused ^{18}F-FDG/^{18}F-FMISO PET/MR imaging datasets available. Results were analyzed, with assessments of tracer avidity, tumor volume, enhancement kinetics, and diffusivity. Imaging characteristics in all tumors were consistent with cervical cancer (type II/III enhancement kinetics, restricted diffusivity, and SUV_{max} of 16.2 for ^{18}F-FDG and 3.1 for ^{18}F-FMISO). PET imaging identified hypoxic tumor subvolumes, which were independent of total tumor volumes. Additional image analyses showed only weak correlations between MR and PET parameters, which the authors noted was an indication "that each individual parameter yields independent information" and of the presence of tumor heterogeneity. They concluded that ^{18}F-FDG/^{18}F-FMISO PET/MR imaging in patients with cervical cancer "facilitates the acquisition of independent predictive and prognostic imaging parameters" and "enables insights into tumor biology on multiple levels and provides information on tumor heterogeneity, which has the potential to improve the planning of chemoradiation therapy."

PLoS One

PET/CT and Anti-EGFR Therapy in CRC

In an article in the May 19 issue of *PLoS One* (2016;11:e0155178) van Helden et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported on a study exploring intrapatient mixed metabolic response and strategies for early ^{18}F-FDG PET therapeutic evaluation in patients with advanced KRAS wild-type colorectal adenocarcinoma (mCRC) treated with cetuximab. The study focused on 9 patients with mCRC, who underwent ^{18}F-FDG PET imaging at baseline and after 2 cycles of cetuximab. PET Response Criteria in Solid Tumors–based thresholds were used to categorize metabolic response, and quantitative data were analyzed on all target lesions, on 5 or fewer lesions, and on the metabolically most active lesion. These were correlated with clinical benefit at 2 mo posttreatment according to Response Evaluation Criteria in Solid Tumors. A total of 34 target lesions were identified (1–8/patient). Using total lesion glycolysis (TLG), a mixed metabolic response was seen in 3 of the 7 patients with multiple target lesions. Metabolic data from either the sum of all or ≤5 lesions were concordant with a clinical benefit of 89% using maximum or peak SUV adjusted for lean body mass (SUL_{max} and SUL_{peak}, respectively) and 100% using TLG. For the metabolically most active lesion, concordance was 89% whether using TLG, SUL_{max}, or SUL_{peak}. Decreases in TLG were significantly associated with progression-free survival for all 3 quantification approaches. The authors concluded by noting that in this small study, mixed metabolic response was observed in nearly half of patients with advanced KRAS wild-type mCRC treated with cetuximab and that when ≤5 target lesions were evaluated using TLG, clinical benefit was predicted correctly for all patients. They called for validation of these findings in a larger study.

PLoS One

^{131}I Therapy and Atherosclerotic Burden

la Cour et al. from the Rigshospitalet/University of Copenhagen (Glostrup, Denmark), the Rigshospitalet/Gentofte University Hospital of Copenhagen (Hellerup, Denmark), and University Hospital of Herley (Denmark) reported on May 20 ahead of print in *Thyroid* on a study designed to determine whether radioiodine therapy of benign disease is associated with late or early development of atherosclerosis. The 2-part study included patients treated for benign thyroid disorders (nontoxic goiter, adenoma, and hyperthyroidism) who underwent ultrasound imaging to determine outcome, carotid intima media thickness, and presence of plaque. Thirty-nine patients were assessed for early radioiodine-associated damage using baseline ultrasound and repeat imaging at 1, 3, 6, and 12 mo after ^{131}I therapy. A longer-term cross-sectional case-control study included 193 radioiodine-treated patients and 95 surgically treated patients. Results were adjusted for age, sex, cholesterol levels, smoking status, known atherosclerotic

disease, and body mass index. For the first group, followed for 1 y, no changes in carotid intima media thickness were found to be associated with ^{131}I treatment for benign thyroid disease. In the longer term study on late effects, no differences in carotid intima media thickness or presence of plaques were identified between those with ^{131}I treatment and those treated surgically (after 8.8 and 5.6 y, respectively). Thyrotropin levels were not found to affect atherosclerosis markers. The authors concluded that "radiation to the carotid arteries by radioactive iodine therapy for benign thyroid disease may therefore have no or low effect on atherosclerotic burden of the carotid arteries in general."

Thyroid

PET/CT in Paraneoplastic Neurological Syndrome

In an article e-published on May 2 ahead of print in *Clinical & Translational Oncology*, Pena Pardo et al. from the University General Hospital (Ciudad Real), Castilla La Mancha University (Ciudad Real), Virgen de la Salud Hospital (Toledo), University Hospital (Albacete), Mancha Centro Hospital (Ciudad Real), and Puertollano Hospital (Ciudad Real), all in Spain, reported on a pretest risk classification approach in patients with suspected paraneoplastic neurological syndrome (PNS) and the diagnostic impact of ^{18}F-FDG-PET/CT imaging in this risk assessment setting. The authors described the development of a 7-point scoring system using clinical syndrome characteristics, location (central, peripheral, in the neuromuscular junction, or combined), onconeural antibodies, and tumor markers. With these data points and the devised system, patients were classified as at low, intermediate, or high pretest risk of PNS. A total of 73 patients were included and, in addition to pretest risk stratification, all underwent ^{18}F-FDG PET/CT, with results categorized as positive or negative. Patients were followed for 33 mo. Final diagnoses were made as definite, possible, or no PNS according to Graus criteria. Eleven (15%) patients were ultimately diagnosed with neoplasms. PET/CT diagnosed 6 (75%) of the 8 cancers that were invasive. PET/CT findings were significantly correlated with the final diagnosis of neoplasm and the diagnosis of PNS by Graus criteria. The authors' pretest risk assessment showed significant association with the final diagnosis of neoplasm and PET/CT results. Ten of the 11 patients diagnosed with a neoplasm had been assessed as at intermediate-to-high risk. The authors concluded that their assessment tool "seems to be a valid tool to select candidates for PET/CT imaging in this setting."

Clinical & Translational Oncology

Updated AACE/ACE/AME Thyroid Nodule Guidelines

Gharib and members of the American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Task Force on Thyroid Nodules released an update to their joint guidelines for diagnosis and management of thyroid nodules in the May issue of *Endocrine Practice* (2016;22:622–639). This publication updated previous guidelines released by the 3 professional societies in 2006 and 2010 and addressed challenges in work-up approaches to thyroid nodules, which can be detected in 50%–60% of healthy individuals. Key issues addressed in the guidelines included: (1) ultrasound (US)-based categorization of malignancy risk and indications for US-guided fine-needle aspiration (FNA); (2) cytologic classification of FNA samples; (3) roles of immunocytochemistry and molecular testing in thyroid FNA; (4) therapeutic options; and (5) follow-up strategies. Topics on thyroid nodule management during pregnancy and in children were also addressed. Risk stratification, based on US features, was recommended, categorizing thyroid nodules into low-, intermediate-, and high-malignancy risk, with guidelines for specific follow-up, including follow-up categorization of cytologic report results. The authors cautioned, as in previous versions of the guidelines, that "at present, no single cytochemical or genetic marker can definitely rule out malignancy in indeterminate nodules," adding that these markers should be considered together with clinical data, US signs, elastographic patterns, and/or results of other imaging techniques. Although surgery remains the treatment of choice for malignant or suspicious lesions, the guidelines emphasized that most thyroid nodules do not require any treatment and that levothyroxine suppressive therapy is not recommended. In addition, percutaneous ethanol injection was recommended as a first-line treatment option for relapsing, benign cystic lesions, and US-guided thermal ablation treatment was listed as an option for solid or mixed symptomatic benign thyroid nodules.

Endocrine Practice

Calculating TLG in NSCLC Treatment

In an article e-published on May 10 ahead of print in *Radiotherapy and Oncology*, Grootjans et al. from the Radboud University Medical Center (Nijmegen, The Netherlands), Leiden University Medical Center (The Netherlands), the Royal Marsden NHS Foundation Trust (London, UK), INSERM (Brest, France), and the University of Twente (Enschede, The Netherlands) reported on the use of total lesion glycolysis (TLG) as determined by different automatic segmentation algorithms for early response monitoring during chemoradiation in patients with non–small cell lung cancer (NSCLC). The study included 27 patients with locally advanced NSCLC treated with concomitant chemoradiation who underwent ^{18}F-FDG PET/CT imaging before and during week 2 after initiation of treatment. Segmentation of the primary tumors and lymph nodes was performed using fixed threshold segmentation as 40% SUV_{max} (T40), 50% SUV_{max}, relative-threshold level, signal-to-background ratio, and fuzzy locally adaptive Bayesian segmentation. Primary tumor TLG, lymph node TLG, summed TLG (primary tumor TLG + lymph node TLG), and relative TLG decrease were compared with overall and progression-free survival.

Regardless of the segmentation method used, pretreatment total primary tumor TLG was predictive of overall and progression-free survival. Early response assessment was improved by the inclusion of lymph node TLG, with summed pretreatment TLG more strongly associated with survival than primary tumor TLG. Relative TLG decrease was also significantly associated with overall and progression-free survival, with the exception of relative threshold level and T40. The authors concluded that the inclusion of lymph node TLG "improves early treatment response monitoring during concomitant chemoradiotherapy with FDG PET."

Radiotherapy and Oncology

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 May. Hagens et al. from the VU University Medical Center (Amsterdam, The Netherlands) summarized current research in "Novel MRI and PET markers of neuroinflammation in multiple sclerosis" in the June issue of *Current Opinion in Neurology* (2016;29:229–236). In an article e-published on May 4 ahead of print in *Alzheimer's & Dementia*, Holtzman, from Washington University (St. Louis, MO), and a consortium of researchers from the United States, Germany, the UK, and Switzerland reviewed "Tau: from research to clinical development." In the June issue of *Current Atherosclerosis Reports* (2016;18:30), Evans et al. from the University of Cambridge Biomedical Campus (UK) provided an overview of "PET imaging of atherosclerotic disease: advancing plaque assessment from anatomy to pathophysiology." Calsolaro and Edison, from Imperial College London (UK), presented "Neuroinflammation in Alzheimer's disease: current evidence and future directions" on May 11 ahead of print in *Alzheimer's & Dementia*. In the June 1 issue of *Frontiers in Bioscience* (2016;21:1187–1193), Wang et al. from the Shanxi Tumor Hospital and the First Hospital of Shanxi Medical University (both in China) summarized issues in "Radionuclide imaging and treatment of thyroid cancer." In an article e-published on May 16 ahead of print in *Cancer Letters*, Pantel and Mankoff from the University of Pennsylvania Perelman School of Medicine published "Molecular imaging to guide systemic cancer therapy: illustrative examples of PET imaging cancer biomarkers." Papadimitriou et al. from Stony Brook University (NY), Emory University (Atlanta, GA), and Northwestern University (Chicago, IL) reported on the "Utility of positron emission tomography for drug development for heart failure" in the May issue of the *American Heart Journal* (2016;175:145–152). A review on "Neuroimaging the effectiveness of substance use disorder treatments" was published by Cabrera et al. from the National Institute on Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse (both in Bethesda, MD) on May 16 ahead of print in the *Journal of Neuroimmune Pharmacology*. Delgado-Alvarado, from the Biodonostia Health Research Institute (San Sebastián, Spain) and researchers from several centers in Spain provided an overview of "Biomarkers for dementia and mild cognitive impairment in Parkinson's disease" on May 19 ahead of print in *Movement Disorders*.