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.

^{18}F-Fallypride PET and $D_{2/3}$ Receptors in PD

Stark et al. from Vanderbilt University/Vanderbilt University Medical Center (Nashville, TN) and the University of Alabama at Birmingham reported on February 10 in *NeuroImage. Clinical* (2018;18:433–442) on a study using ^{18}F-fallypride PET to characterize patterns of $D_{2/3}$ receptor binding in both striatal and extrastriatal regions in Parkinson disease (PD). The study included 35 patients with PD who were off medication and 31 age- and sex-matched healthy control subjects. Each participant underwent ^{18}F-fallypride PET imaging to assess striatal and extrastriatal $D_{2/3}$ nondisplaceable binding potential (BP_{ND}). The patient group also underwent concurrent motor assessment. Comparative results showed significant BP_{ND} reductions in striatal and several extrastriatal regions, including the locus coeruleus and mesotemporal cortex, in the patient group. In a region-of-interest–based approach, reduced BP_{ND} was seen in the globus pallidus, caudate, amygdala, hippocampus, ventral midbrain, and thalamus in PD patients. The researchers also found that severity of motor impairment in these patients correlated positively with $D_{2/3}$ receptor density in the putamen and globus pallidus. The authors concluded that "these findings support the hypothesis that abnormal $D_{2/3}$ expression occurs in regions related to both the motor and nonmotor symptoms of PD, including areas richly invested with noradrenergic neurons."

NeuroImage. Clinical

Dual-Tracer PET/CT in HCC Staging and Management

In an article e-published on March 5 ahead of print in the *Journal of Hepatology*, Chalaye et al. from Henri Mondor Hospital (Créteil), the CHU Côte de Nacre (Caen), the Hôpital Jean Verdier/Hôpitaux Universitaires Paris-Seine-Saint-Denis (Bondy), the Université of Paris, the Institut National de la Santé et de la Recherche Médicale (Paris), and the Avicenne Hospital (Bobigny; all in France) reported on a study designed to assess the effect of dual-tracer ^{18}F-fluorocholine and ^{18}F-FDG PET/CT on tumor staging and treatment management in hepatocellular carcinoma (HCC). The retrospective study included 177 patients (men, 87.5%; women 12.5%) with HCC who underwent a total of 192 dual-tracer PET/CT scans. Barcelona Clinic Liver Cancer (BCLC) staging data and initially proposed treatment were collected from the medical record, as well as post-PET/CT data on new lesions detected, changes in BCLC classification, or changes in treatment allocation. The primary cause of HCC was listed in the record as cirrhosis (71%), attributed to alcohol with or without nonalcoholic steatohepatitis (26%), viral infection (62%), or unknown causes (12%). For the 122 patients in whom PET/CT was performed for staging, BCLC stages based on conventional imaging were 0/A in 61 patients (50%), B in 32 patients (26%), and C in 29 patients (24%). With dual-tracer PET/CT, the researchers detected new lesions in 26 patients (21%), upgraded BCLC staging in 14 (11%), and changed treatment strategy in 17 (14%). PET/CT also changed the final treatment in 4 of 9 patients with unexplained elevation of α-fetoprotein (AFP), 10 of 25 with suspicious but unconfirmed lesions on conventional imaging, and 3 of 36 who were waiting for liver transplantation without active HCC after tumor response to bridging therapy. The authors concluded that "dual-tracer PET/CT might also be useful in specific situations," such as unexplained elevations in AFP, doubtful lesions, or pretransplant evaluation of patients without active HCC.

Journal of Hepatology

MR-Assisted PET Motion Correction in Dementia

Chen et al. from Massachusetts General Hospital and Harvard Medical School (Boston), the Massachusetts Institute of Technology (Cambridge), and Harvard University (Boston) reported on March 8 ahead of print in the *Journal of Magnetic Resonance Imaging* on the results of a study assessing the effects of realistic head motion and MR-based motion correction on static ^{18}F-FDG PET/MR imaging in patients with dementia. The study included 30 patients with diagnoses of dementia (mild cognitive impairment, 2; Alzheimer disease, 18; frontotemporal dementia, 10) who were imaged on a 3T hybrid MR scanner, with echo planar imaging and T1-weighted sequences acquired at the same time as PET data. Head motion parameters estimated from high-temporal resolution MR volumes were used for PET motion correction. The results were compared with PET frame-based motion correction methods using estimates derived from coregistering 5-min frames before and after accounting for attenuation–emission mismatch. Relative changes in SUV ratios were assessed with the motion correction methods. Motion correction was found to affect PET data quantification more in individuals with greater amplitude motion (>18% in the medial orbitofrontal cortex), and larger changes were observed for the MR-based motion correction method. The intraregion voxelwise variability of regional SUV

ratios was decreased using MR-based motion correction. The authors concluded that "incorporating temporally correlated MR data to account for intraframe motion has a positive impact on the FDG PET image quality and data quantification in dementia patients."

Journal of Magnetic Resonance Imaging

PET and SGLT2 Activity in High-Grade Astrocytomas

In an article e-published on March 10 ahead of print in the *Journal of Neuro-Oncology*, Kepe et al. from the Geffen School of Medicine at the University of California Los Angeles and the Cleveland Clinic (OH) reported on the use of α-methyl-4-^{18}F-fluoro-4-deoxy-D-glucopyaranoside (Me-4FDG), a PET probe targeting the sodium glucose cotransporter 2 (SGLT2) in evaluation of patients with high-grade astrocytic tumors. Four patients with World Health Organization grade III or IV astrocytomas and matched control subjects underwent PET imaging with the novel tracer, as well as standard ^{18}F-FDG PET and contrast-enhanced MR imaging. In grade IV resected tumors, immunocytochemistry was performed to determine the cellular location of SGLT proteins in the tumors. Uptake and retention of Me-4FDG was high in astrocytomas and absent in normal brain, resulting in high signal-to-noise ratios. Me-4FDG distribution within the tumors was congruent with that of ^{18}F-FDG and with tumor definition on MR imaging. The SGLT2 protein was expressed in neoplastic glioblastoma cells and endothelial cells of the proliferating microvasculature. The authors concluded that "this preliminary study shows that Me-4FDG is a highly sensitive probe for visualization of high-grade astrocytomas by PET." They pointed to the superior imaging sensitivity of Me-4FDG and suggested that "the presence of SGLT2 protein in astrocytoma cells and the proliferating microvasculature may offer a novel therapy using the SGLT2 inhibitors already approved by the FDA to treat type 2 diabetes mellitus."

Journal of Neuro-Oncology

^{18}F-FET PET/MR in Diagnosis of Progressive and Recurrent Glioma

Verger et al. from the Forschungszentrum Jülich (Germany), Lorraine University (Nancy, France), Aachen University Hospital (Germany), the University of Düsseldorf (Germany), the University of Cologne and Bonn (Germany), and the Jülich–Aachen Research Alliance (Jülich, Germany) reported on March 3 ahead of print in *World Neurosurgery* on a study designed to compare the performances of *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET) PET and perfusion-weighted MR imaging in the diagnosis of progressive or recurrent glioma. The study included 31 patients with 32 pretreated gliomas (25 progressive or recurrent, 7 with treatment-related changes). All underwent ^{18}F-FET PET and perfusion-weighted MR imaging on a hybrid scanner. Mean and maximum tumor-to-brain ratios and dynamic data on ^{18}F-FET uptake were calculated. ^{18}F-FET PET was found to have a significantly higher sensitivity than perfusion-weighted MR imaging (76% and 52%, respectively) in detecting abnormalities in pretreated gliomas. Maximum tumor-to-brain ratio on PET was the only parameter that successfully distinguished treatment-related changes from progressive or recurrent gliomas. Seventy-five percent of patients who had signal abnormalities on both imaging modalities had spatially incongruent local hot spots. The authors concluded that these results suggest that "^{18}F-FET PET is superior to perfusion-weighted MR to diagnose progressive or recurrent glioma."

World Neurosurgery

^{68}Ga-PSMA PET Target Volume Definition and Current RT Guidelines

In an article e-published on March 1 in *Radiation Oncology* (2018;13:36), Schiller et al. from the Technische Universität Munich, Deutsches Konsortium für Translationale Krebsforschung Partner Site Munich (Heidelberg, Germany), and Helmoltz Zentrum (Munich) (all in Germany) asked whether standard clinical target volumes (CTVs) calculated under current radiation therapy guidelines cover the majority of ^{68}Ga-PSMA PET–detected lymph nodes in prostate cancer in the primary setting. The study included 25 high-risk patients with primary prostate cancer (total of 126 lymph nodes with positive ^{68}Ga-PSMA ligand uptake) who underwent ^{68}Ga-PSMA PET imaging. CTVs were delineated according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines, and lymph nodes were assessed as being in- or outside these volumes. The authors also determined whether Gleason score, prostate-specific antigen (PSA) value, or risk assessed by the Roach formula were correlated with higher probability of lymph node location outside of the CTVs in uncommon lymph node locations. The researchers found that 81 (64.3%) of the 126 lymph nodes were within the CTVs, with a complete coverage of all positive nodes inside the respective radiation volume in 11 of 25 patients (44%). Lymph nodes not within the CTVs were found in paraaortic, common iliac, presacral, obturatoric, pararectal, paravesical, and preacetabular locations. None of the additional parameters assessed (Gleason score, PSA, or calculated risk) were correlated with positive lymph node location in- or outside the CTV. The authors concluded that these results suggested that "trusting the RTOG consensus for CTV delineation would have led to up to 35.7% of all lymph nodes" being excluded from the clinical radiation volume, which might have resulted in insufficient radiation dose and coverage.

Radiation Oncology

PET + MARI in Node-Positive Breast Cancer

van der Noordaa et al. from The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital (Amsterdam) and the Haaglandend Medical Centre (The Hague, The Netherlands) reported on March 6 ahead of print in *Annals of Surgical Oncology* on a study assessing the effect of combining PET/CT before and the technique of marking axillary lymph nodes with radioactive iodine seeds (MARI) after

neoadjuvant systemic therapy as a possible approach for avoiding unnecessary lymph node dissections in patients with node-positive (cN+) breast cancer. The study included data from 159 patients who had undergone tailored axillary treatment in a protocol based on the results of PET/CT before and the MARI procedure after neoadjuvant systemic therapy. Patients with 1–3 ^{18}F-FDG–avid axillary lymph nodes on PET/CT and a tumor-negative MARI node did not undergo additional axillary treatment. Patients with <4 ^{18}F-FDG–positive nodes and a tumor-positive MARI underwent locoregional radiation therapy, as did patients with ≥4 ^{18}F-FDG–avid axillary lymph nodes and a tumor-negative MARI node after neoadjuvant systemic therapy. Axillary lymph node dissection was performed only for patients with ≥4 ^{18}F-FDG–avid axillary lymph nodes and a tumor-positive MARI node. PET/CT showed that 110 patients had 1–3 positive nodes and 49 patients had 4 or more before neoadjuvant therapy. Axillary lymph node dissection was avoided for 130 patients (82%) using this protocol. Ninety-one patients (57%) underwent locoregional radiotherapy, and 39 patients (25%) received no additional axillary treatment.

Annals of Surgical Oncology

Regional Cerebral Glucose Consumption After Antihistamines

In an article e-published on March 13 ahead of print in *Human Psychopharmacology*, Kikuchi et al. from Tohuku University and Graduate School of Medicine (Sendai, Japan), the National Institutes of Biomedical Innovation, Health, and Nutrition (Osaka, Japan), and the Charité-Universitätsmedizin Berlin (Germany) reported on a study incorporating ^{18}F-FDG PET in multiparameter measurement of regional cerebral glucose consumption and hemodynamic responses in young adults after antihistamine administration. The study included 18 healthy young men who received single doses of levocetirizine (5 mg) and diphenhydramine (50 mg) at intervals of at least 6 d. Subjects underwent serial cognitive testing, ^{18}F-FDG PET imaging to assess cerebral glucose consumption changes, and near-infrared spectroscopy to assess regional hemodynamic responses. The test was double blinded and placebo controlled. The researchers found that energy consumption in prefrontal regions was significantly increased after antihistamine administration, more notably with diphenhydramine. Prefrontal hemodynamic responses (evaluated by oxygenated hemoglobin levels) were significantly lower with diphenhydramine. Accuracy on one of the cognitive tests was significantly worse with diphenhydramine, an effect not noted with levocetirizine. No difference was noted in reported drowsiness. The authors concluded that "physiological 'coupling' between metabolism and perfusion in the healthy human brain may not be maintained under pharmacological influence due to antihistamines." They suggested that this uncoupling "may be caused by a combination of increased energy demands in the prefrontal regions and suppression of vascular permeability in brain capillaries after antihistamine treatment."

Human Psychopharmacology

^{11}C-DPV PET and Hepatobiliary Transport

In an article e-published on March 19 ahead of print in *Drug Metabolism and Disposition*, Kaneko et al. from RIKEN (Institute of Physical and Chemical Research) (Wakō), Osaka City University Graduate School of Medicine, and the University of Tokyo (all in Japan) reported on a new PET probe, ^{11}C-dehydropravastatin (^{11}C-DPV), and its utility for quantitative investigation of Oatps/SLCO (organic anion transporting polypeptides) and Mrp2/ABCC2 (multidrug resistance-associated protein 2) in hepatobiliary transport in rats. Additional pharmacokinetic parameters were assessed with serial ^{11}C-DPV PET imaging of the abdomen in 6 healthy humans with and without an OATP1Bs and with an MRP2 inhibitor (rifampicin). In humans, ^{11}C-DPV was distributed rapidly to the liver and kidneys, followed by elimination via bile and urine. Rifampicin resulted in a 3-fold reduction in liver distribution of the tracer, with a 7.5-fold reduction in excretion into bile and a delayed elimination of ^{11}C-DPV from circulation. Hepatic uptake clearance and canalicular efflux clearance of the tracer was lower in humans than in reported data from rats. Rifampicin treatment in humans reduced these clearances by 58% and 44%, respectively. The authors concluded that their results suggested "that PET imaging with ^{11}C-DPV is an effective tool for quantitatively characterizing the OATP1Bs and MRP2 functions in the human hepatobiliary transport system."

Drug Metabolism and Disposition

^{18}F-FDOPA PET/CT and MAX-Related Pheochromocytoma

In an article e-published on March 8 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Taïeb et al. from the Thomas Jefferson University Hospital reported on experience with contrast-enhanced CT and ^{18}F-FDOPA PET/CT imaging in MYC-associated factor X (MAX)–related pheochromocytoma. The study included 6 patients (4 at initial diagnosis and 2 at follow-up evaluation) with this rare pheochromocytoma who underwent ^{18}F-FDOPA PET/CT and CT/MR imaging. The patients had 4 different MAX gene disruptions causing disruption of Max/Myc interaction and/or eliminating interactions with DNA (based on in silico analyses). In 5 patients, ^{18}F-FDOPA PET/CT results were compared with those from other radiopharmaceuticals. Five patients developed bilateral pheochromocytomas during their lifetimes. In all 6 subjects, ^{18}F-FDOPA PET/CT accurately visualized pheochromocytomas (often as multiples within the same gland or bilateral) and detected more adrenal and extraadrenal lesions than CT (per lesion sensitivity of 90.5% for PET/CT and 52.4% for CT/MR imaging). ^{18}F-FDOPA PET/CT missed 2 pheochromocytomas that were <1 cm, corresponding to nodular adrenomedullary hyperplasia. ^{68}Ga-DOTATATE PET/CT detected fewer lesions than ^{18}F-FDOPA in 2 patients, whereas ^{18}F-FDG PET/CT was only

faintly positive in half the patients imaged with this agent and produced an underestimation of extraadrenal lesions in 1 of these patients. The authors concluded that MAX-related pheochromocytomas exhibit "marked ^{18}F-FDOPA uptake, a finding that illustrates the common well-differentiated chromaffin pattern of pheochromocytomas associated with activation of kinase signaling pathways" and that this technique "should be considered as the first-line functional imaging modality for diagnostic or follow-up evaluation in these patients."

Journal of Clinical Endocrinology and Metabolism

PET/CT and Tumor Margins in SCCHN

Zrnc et al. from the Medical University of Graz (Austria), the University Medical Center Hamburg Eppendorf (Hamburg, Germany), and the University of Virginia Health System (Charlottesville) reported on February 19 ahead of print in the *Journal of Cranio-Maxillo-Facial Surgery* on a study comparing histopathologic findings from image-guided needle biopsies taken from metabolically different regions within tumors as assessed by ^{18}F-FDG PET/CT in patients after surgical treatment of primary squamous cell head and neck cancer (SCCHN). The study included 12 patients (8 men, 4 women) who underwent surgical treatment for primary SCCHN (stages III and IV) as well as ^{18}F-FDG PET/CT imaging, with fusion performed on a 3D navigation system workstation. Image-guided needle biopsies were performed in 4 metabolic areas (identified by PET/CT and assessed on the workstation for metabolic activity) within their tumors. The results indicated that 81.3% of needle biopsies from the central tumor area were positive and that specimens taken from the outer metabolic zone of the tumor were positive in 66.7% of patients. The highest numbers of positive biopsies was found in the zone adjacent to the outermost area. A statistically significant difference in positive tumor histopathology was identified in comparing the different metabolic zones. The authors concluded that although many approaches to precisely determining tumor extent remain controversial, "the results of this study suggest that in some cases PET scans may overestimate tumor extension."

Journal of Cranio-Maxillo-Facial Surgery

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 systematic and general reviews accessioned into the PubMed database in late February and March. Langston et al. from the Parkinson's Institute (Sunnyvale, CA) published "Optimizing Parkinson's disease diagnosis: The role of a dual nuclear imaging algorithm" on February 23 in *NPJ Parkinson's Disease* (2018;4:5). In an article e-published on February 27 ahead of print in the *Journal of Thoracic Imaging*, Lau et al. from the National Heart Centre Singapore, Washington University School of Medicine (St. Louis, MO), and University Hospital Essen (Germany) provided an overview of "Cardiac positron emission tomography–magnetic resonance imaging: Current status and future directions." Lauri et al. from the "Sapienza" University of Rome (Italy) and the University of Groningen/University Medical Center Groningen (The Netherlands) reviewed "Leukocyte imaging of the diabetic foot" on February 26 ahead of print in *Current Pharmaceutical Design*. In the March 8 issue of the *AAPS Journal*, Burvenich et al. from the Olivia Newton-John Cancer Research Institute (Melbourne and Heidelberg), La Trobe University (Melbourne), Austin Health (Melbourne), and the University of Melbourne (all in Australia) reported on "Receptor occupancy imaging studies in oncology drug development." Mikail et al. from the Centre Hospitalier Universitaire Bichat and the Université Paris Diderot (both in Paris, France) summarized "^{18}F-FDG PET/CT imaging to diagnose septic emboli and mycotic aneurysms in patients with endocarditis and cardiac device infections" in the March 6 issue of *Current Cardiology Reports* (2018;20:14). In the February issue of *Quantitative Imaging in Medicine and Surgery* (2018;8:47–59), Blake et al. from King's College London (UK) and the Royal Marsden Hospital (Sutton, UK) reviewed "Site specific measurements of bone formation using ^{18}F-sodium fluoride PET/CT." Pell et al. from King's College London (UK) reported on "PET imaging of cardiac hypoxia: Hitting hypoxia where it hurts" on February 23 in *Current Cardiovascular Imaging Reports* (2017;11:7). On March 12 ahead of print in *Medicinal Research Reviews*, Rybczynska et al. from the University of Groningen/University Medical Center Groningen (The Netherlands) and Ghent University (Belgium) described "Avenues to molecular imaging of dying cells: Focus on cancer."