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.

^{68}Ga-DOTATATE vs ^{18}F-FDG in Atherosclerotic Inflammation

In an article in the April issue of the *Journal of the American College of Cardiology* (2017;69:1774–1791), Tarkin et al. from the University of Cambridge (UK), the Rigshospitalet (Copenhagen, Denmark), Addenbrooke's Hospital (Cambridge, UK), National Health Service Blood and Transport (Cambridge, UK), Hammersmith Hospital (London, UK), University College London (UK), and the Wellcome Trust Sanger Institute (Hinxton, UK) reported on a study assessing the efficacy of the somatostatin receptor 2 (SSTR2)–binding PET tracer ^{68}Ga-DOTATATE for assessing atherosclerotic inflammation. The study included both in vitro and clinical elements. The authors first confirmed ^{68}Ga-DOTATATE binding in "proinflammatory" M1 macrophages and excised carotid plaques and characterized *SSTR2* gene expression using population-based RNA-sequenced data. ^{68}Ga-DOTATATE was then compared with ^{18}F-FDG PET in patients with wide-ranging severity of stable (n = 18) and unstable (n = 24) coronary vascular disease. Additional validation studies were performed in macrophages and postsurgical specimens from a subset of patients. Among the key findings were that ^{68}Ga-DOTATATE identified culprit acute coronary syndrome lesions in coronary arteries, high-risk stable lesions in coronary arteries, and culprit transient ischemic attack/stroke lesions in carotid arteries. In addition, aortic ^{68}Ga-DOTATATE signals were correlated with coronary ^{68}Ga-DOTATATE signals, and vascular ^{68}Ga-DOTATATE signals were correlated with clinical coronary vascular disease risk factors. Over all, ^{68}Ga-DOTATATE PET imaging produced higher tumor-to-background ratios and superior ability to discriminate high- from low-risk coronary atherosclerotic lesions than did ^{18}F-FDG, where results were often confounded by high myocardial spillover. The authors noted that their data supported the conclusion that "gene-, cell-, plaque-, and patient-level data demonstrating that SSTR2 PET imaging using ^{68}Ga-DOTATATE provides a quantifiable, cell-specific marker of atherosclerotic inflammation that outperforms ^{18}F-FDG in the coronary arteries." They added that "future research should explore the utility of ^{68}Ga-DOTATATE PET imaging of inflammation to classify patients for more aggressive therapeutic intervention and explore potential application to other inflammatory cardiovascular diseases."

Journal of the American College of Cardiology

^{18}F-FDG PET/CT and Adrenal Masses

Guerin et al. from the Centre Hospitalier Conception (Marseille), multiple Centres Hospitalier Universitaire (Lille, Nancy, Lyon, Nantes, and Pessac), and Aix-Marseille University (all in France) reported on April 20 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on the utility of ^{18}F-FDG PET/CT in characterizing adrenal masses. The study included 87 patients (56 with masses ≥40-mm diameter; 31 with masses <40-mm diameter) referred to endocrine surgeons. Masses were of "indeterminate" nature based on CT results. All patients underwent ^{18}F-FDG PET/CT, and results were compared with histology (n = 64) or, in the absence of clear pathology, with 12-mo post-surgical imaging (n = 23). Histology and follow-up classified 15 adrenal masses as malignant (including 11 adrenocortical carcinomas) and 72 as benign. On imaging, malignant lesions were larger, had higher unenhanced densities, lower relative washout values, and higher uptake parameters. With an optimal threshold value (tumor SUV_{max}/liver SUV_{max}) for malignancy of >1.5, the sensitivity, specificity, positive and negative predictive values, and accuracy of PET/CT were 86.7%, 86.1%, 56.5, 96.9, and 86.2%, respectively. The authors concluded that these results showed that "^{18}F-FDG PET/CT complements adrenal washout CT in the evaluation of adrenal masses and should be recommended in the evaluation of large and/or indeterminate adrenal masses."

Journal of Clinical Endocrinology and Metabolism

Grading Scheme for NET Imaging Prognosis

In a study published in the March 1 issue of *Theranostics* (2017;7:1149–1158), Chan et al. from Royal North Shore Hospital, the University of Sydney, and Sydney Vital Translational Cancer Research Centre (all in Australia) reported on the development of a grading scheme to assess the prognostic significance of staging dual somatostatin receptor (SSTR)/^{18}F-FDG PET/CT imaging in metastatic neuroendocrine tumors (NETs). The NETPET scoring process begins with identification of the single lesion that is most ^{18}F-FDG–avid relative to its SSTR agent uptake. This lesion provides the primary categorization for the patient, and secondary classification reflects subsequent assessment of burden of disease. The NETPET process uses a

0–5 categorical scale largely based on the characteristics of the initial lesion, with a grade of P1 indicating purely SSTR agent–avid disease without ^{18}F-FDG uptake in any lesions and P5 indicating the presence of significant ^{18}F-FDG–positive/and SSTR agent–negative disease (a very poor prognostic marker). A NETPET grade of P0 indicates a normal scan with both imaging agents (usually noted after early diagnosis and surgical resection). The authors also outlined subclassifications based on burden of disease and other characterizations. In a retrospective validation study, they looked at the records of 62 individuals with histologically proven metastatic NETs who underwent both ^{18}F-FDG and SSTR PET imaging within a period of 31 d. Grades assigned using the NETPET schema were compared with other data, including World Health Organization grades and overall survival. The NETPET grade proved to be significantly correlated with overall survival, whereas the WHO grade at the time of diagnosis did not correlate with survival. The authors concluded that the "NETPET grade has promise as a prognostic imaging biomarker in NETs. It permits the capturing of the complexity of dual radiotracer imaging in a single parameter which describes the subjects' disease and is readily amenable to use in patient management and further research."

Theranostics

Midlife Vascular Risk and Brain Amyloid

Gottesman et al. from Johns Hopkins University School of Medicine and Bloomberg School of Public Health (Baltimore, MD), the University of Mississippi Medical Center (Jackson), Hagerstown Imaging (MD), the Mayo Clinic (Rochester, MN), and the Wake Forest School of Medicine (Winston-Salem, NC) reported in the April 11 issue of the *Journal of the American Medical Association* (2017;317:1443–1450) on a study designed to determine whether midlife vascular risk factors are associated with late-life brain amyloid deposition as measured using ^{18}F-florbetapir PET. The study used data from the Atherosclerosis Risk in Communities–PET Amyloid Imaging Study, a prospective cohort investigation of 346 participants without dementia in 3 U.S. communities. Since 1987–1989, participants have been evaluated for vascular risk factors and markers and in 2011–2013 underwent ^{18}F-florbetapir PET imaging. Participants entered the study at 45–64 y old, and vascular risk factors were identified at entry as body mass index $\geq$30, current smoking, hypertension, diabetes, and total cholesterol $\geq$200 mg/dL. Additional variables assessed included age, sex, race, APOE genotype, and educational level. After PET imaging, SUV ratios were calculated, along with mean global cortical SUV ratios. Elevated tracer uptake (defined as an SUV ratio $>$ 1.2) was the dependent variable. The study results, which were widely covered in the scientific and popular media, included 322 participants with evaluable results (mean age at baseline, 52 y) with a mean entry-to-imaging time of 23.5 y. Elevated body mass index in midlife was directly associated with elevated SUV ratios. At baseline, 65 participants had no vascular risk factors, 123 had 1, and 134 had $\geq$2; a higher number of midlife risk factors was associated with elevated amyloid SUV ratio at follow-up. No significant associations between race and risk were identified. Late-life vascular risk factors were not found to be associated with late-life brain amyloid deposition. The authors concluded that these findings are consistent with our understanding of the role of vascular disease in the development of Alzheimer disease.

Journal of the American Medical Association

Visual/Semiquantitative Assessment of ^{123}I-FP-CIT SPECT

In an article e-published on April 7 ahead of print in *Neurological Sciences*, Ueda et al. from Kobe City Medical Center General Hospital (Japan) reported on combined visual and semiquantitative assessment of ^{123}I-FP-CIT SPECT in the diagnosis of dopaminergic neurodegenerative diseases (dNDDs) and in differentiation of dNDDs from non-dNDDs. The study included data on 114 patients with newly diagnosed possible parkinsonian syndrome of $<$7 y duration who had undergone ^{123}I-FP-CIT SPECT and who had been assigned a diagnosis of dNDD or non-dNDD according to established criteria and/or clinical judgment. Clinical characteristics and visual and semiquantitative (striatal binding ratios) assessments of SPECT imaging results were evaluated. Sensitivity and specificity of visual assessment alone, semiquantitative assessment alone, and combined visual and semiquantitative assessment were calculated for the diagnosis of dNDD. Striatal binding ratios were found to be correlated with visual assessments, although some dNDD patients with normal visual assessments had an abnormal striatal binding ratio and vice versa. No statistically significant difference was identified between the sensitivity of diagnoses with visual assessment alone and semiquantitative assessment alone (91.2% vs. 86.8%, respectively). Combined visual and semiquantitative assessment, however, was superior in sensitivity (96.7%) to either approach alone, with equal specificity.

Neurological Sciences

False-Negative PET and Multiple Myeloma

Rasche et al. from the University of Arkansas for Medical Sciences (Little Rock), the Institute of Cancer Research (London, UK), Avera Cancer Institute (Sioux Falls, SD), the University of Heidelberg (Germany), and the German Cancer Research Center (Heidelberg, Germany) reported on April 21 ahead of print in *Blood* on a study designed to assess the proportion of ^{18}F-FDG PET false-negatives in a cohort of patients with multiple myeloma and to identify associated tumor-intrinsic features on both PET and MR diffusion-weighted imaging with background signal suppression (DWIBS). The study included 227 transplant-eligible patients with newly diagnosed multiple myeloma who underwent simultaneous PET/MR. Gene expression

profiling and fluorescent in situ hybridization markers were also analyzed. Imaging results categorized 186 patients as positive on both MR DWIBS and PET. Fifteen patients were categorized as negative on both modalities. Twenty-six patients (11%) were positive on MR and negative (false-negative) on PET. Of these, 5 had focal lesions only, 13 had focal lesions and diffuse involvement, and 13 had extensive diffuse involvement. In assessing the genetic data, the researchers found that gene coding for Hexokinase-2 was significantly lower in patients with PET false-negatives, "a finding which may also be relevant for clinical imaging of other hematological cancers."

Blood

PET/CT-Surveilled Watch-and-Wait in HNSCC

In an article in the April issue of *Health Technology Assessment* (2017; 21:1–122) Mehanna et al. from the University of Birmingham (UK), University of Warwick (Coventry, UK), Mount Vernon Hospital (Northwood, UK), University of Leeds (UK), Royal Marsden Hospital (London, UK), Federal University of Espírito Santo (Vitória, Brazil), Newcastle University (Newcastle upon Tyne, UK), and University Hospitals Coventry and Warwickshire (Coventry, UK) reported on a study intended to determine the efficacy and cost effectiveness of PET/CT-guided surveillance, rather than planned neck dissection, in management of locally advanced (N2/N3) nodal metastases in patients with squamous cell head and neck cancer (HNSCC). In this large, randomized, controlled trial, 564 eligible patients had histologically confirmed diagnoses of SCC of the oropharynx, hypopharynx, larynx, oral cavity, or an unknown primary site in the head or neck, with clinical and radiologic stage N2 or N3 nodal metastases, and were deemed to be suitable for chemoradiotherapy (CRT) with curative intent. Patients were randomly assigned to undergo either a planned neck dissection (control group) before or after CRT or PET/CT imaging 12 weeks after completion of CRT (surveillance group); neck dissection was performed in the latter group only when PET/CT showed incomplete or equivocal response of nodal disease (intervention subgroup). Primary outcomes were overall survival and cost effectiveness (estimated as incremental cost per incremental quality-adjusted life-year [QALY]). Secondary outcomes were recurrence in the neck, complication rates, and quality of life. After analyzing results from the 221 neck dissections performed in the control group and the 54 neck dissections performed in the surveillance arm, no inferior results were found to be associated with imaging surveillance. Quality-of-life scores were slightly better in the surveillance arm, and PET/CT surveillance produced an incremental net health benefit of 0.16 QALYs over the trial period and 0.21 QALYs over a modeled lifetime horizon. The authors concluded that PET/CT-guided active surveillance "showed similar survival outcomes to neck dissection but resulted in considerably fewer neck dissections, fewer complications, and lower costs, supporting its use in routine practice."

Health Technology Assessment

MicroRNA Signatures and PET in Abdominal Aortic Aneurysm

Courtois et al. from the University of Liège, the Centre Hospitalier Universitaire Liège, and the Centre Hospitalier Chrétien St. Joseph (all in Liège, Belgium) reported on April 18 ahead of print in the *Journal of Vascular Surgery* on a study building on previous work correlating circulating microRNAs with positive ^{18}F-FDG PET findings in patients with abdominal aortic aneurysms (AAAs). This study was designed to characterize circulating microRNAs associated with positive PET findings that could serve as biomarkers in identifying patients at high risk of rupture. The study included 57 patients with AAAs classified as negative (A0; $n = 35$) and positive (A+; $n = 22$) for uptake on ^{18}F-FDG PET. Levels of 372 microRNAs were evaluated in plasma from both groups and validated in aneurysm tissues from a subset. Six circulating microRNAs were found be significantly modulated in the A+ group and were also significantly correlated with the intensity of ^{18}F-FDG uptake. Two correlated with AAA diameter. Three downregulated circulating microRNAs were also significantly reduced in the analyzed aneurysm tissue at the specific sites of ^{18}F-FDG uptake. They were also significantly inversely correlated at uptake sites with expression of some of their potential gene targets, notably matrix metalloproteinase-13.

Journal of Vascular Surgery

Pretreatment PET SUV as a Predictor in Gastric Cancer

In an article in the April 17 issue of *BMC Cancer* (2017;17:275), Wu et al. from the First Affiliated Hospital of China Medical University (Shenyang, People's Republic of China) reported on a meta-analysis assessing the prognostic value of pretreatment ^{18}F-FDG PET SUVs in patients with gastric cancer. After searching the major literature databases, 8 studies including 1,080 patients met the analytic criteria. The pooled hazard ratio for overall survival for 6 studies including 672 patients was 1.72, with data suggesting that high SUVs may indicate poor prognoses. Subsequent subgroup analyses indicated that the receiver operating characteristic method can better define a cutoff value for SUVs in this setting. Other subgroup analyses based on outcomes indicated the significant prognostic value of SUV. The meta-analysis indicated that "pretreatment SUV in primary lesions can be an important prognostic factor for overall survival and recurrence-free survival in patients with gastric cancer."

BMC Cancer

SPECT and Histopathology in Condylar Hyperplasia

Martín-Granizo et al. from the Hospital Clínico San Carlos (Madrid, Spain) reported on March 24 ahead of print in the *Journal of Cranio-Maxillo-Facial Surgery* on a study analyzing

correlations between SPECT and pathology findings in patients with condylar hyperplasia of the temporomandibular joint. The study included 28 patients (20 women, 8 men; mean age, 24.4 y at time of diagnosis) with diagnoses of condylar hyperplasia with SPECT-identified evidence of activity who had undergone surgery. Sixteen patients (57.1%) were classified as showing high activity on SPECT, and 12 (42.9%) were classified as showing low activity. Thirteen patients (6 in the low- and 7 in the high-activity group) presented with islands of cartilage. Histopathology showed that these islands were larger (more than double in size) and more frequent in the high-activity group than in the low activity group. The authors concluded that "Radioisotope tests are the best indicator of the level of activity in condylar hyperplasia, which seems to be directly related to the intensity signal collection."

Journal of Cranio-Maxillo-Facial Surgery

Amyloid Burden and Longitudinal Cognitive Decline

In an article e-published on May 30 ahead of print in the *Journal of the American Medical Association Neurology*, Farrell et al. from the University of Texas at Dallas, University Hospital Cologne (Germany), the Cognitive Neuroscience Research Center (Jülich, Germany), Baycrest Health Sciences (Toronto, Canada), Avid Radiopharmaceuticals (Philadelphia, PA), and the University of Texas Southwestern Medical Center (Dallas) reported on a 4-year study of the magnitude of amyloid burden in middle-aged and older adults and whether observed metrics could offer information about rates of future cognitive decline. The investigation took as its starting point the hypothesis that magnitude of amyloid burden at baseline may provide more useful information about future cognitive decline than the current PET reporting standard of amyloid-positive or -negative status. The study included 174 participants (mean age at study initiation, 66.44 y; range, 40–89 y; 109 women, 65 men). All participants were cognitively normal at baseline, with no history of neurologic or psychiatric illness. Each participant underwent ^{18}F-florbetapir PET imaging to assess amyloid burden (as mean cortical SUV ratio) at study initiation, with additional cognitive assessments at baseline and 4 years later. SUV ratios and elapsed time in the study proved to be highly correlated with episodic memory, processing speed, vocabulary, and Mini-Mental State Examination performance but not reasoning performance. A higher baseline SUV ratio was associated with greater cognitive decline over 4 years. Higher baseline amyloid burden among middle-aged adults was also related to changes in vocabulary, which was, in turn, related to apolipoprotein ε4 homozygotes. When the original PET results were recorded as simply amyloid-positive or –negative, these correlations were neither as numerous nor as strong. The authors concluded that not only is the magnitude of amyloid burden at baseline associated with the rate of cognitive decline over 4 years but that measuring amyloid burden "potentially provides important information about the rate of future cognitive decline that is not available from a dichotomous positive/negative categorization."

Journal of the American Medical Association Neurology

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 April and May. Guldbrandsen et al. from the Department Nordsjællands Hospital Hillerød (Denmark), the Herlev and Gentofte Hospital (Herley, Denmark), and the Rigshospitalet (Copenhagen, Denmark) summarized "Nuclear molecular imaging strategies in immune checkpoint inhibitor therapy" on April 21 ahead of print in *Diagnostics (Basel).* In an article in the May issue of *Neuroimaging Clinics of North America* (2017;27:343–356), Moccia and Ciccarelli from University College London (UK) reviewed the current status of "Molecular and metabolic imaging in multiple sclerosis." Prior et al. from Lausanne University Hospital (Switzerland), Kantonsspital (St. Gallen, Switzerland), University Hospital Carl Gustav Carus (Dresden, Germany), the University of Chicago (IL), the Clinique de Genolier (Geneva, Switzerland), and the Royal Marsden Hospital (London, UK) published "Radiopharmaceuticals in the elderly cancer patient: practical considerations, with a focus on prostate cancer therapy: a position paper from the International Society of Geriatric Oncology Task Force" in the April 6 issue of the *European Journal of Cancer* (2017;77:127–139). In an article in the May issue of *Critical Reviews in Oncology/Hematology* (2017;113:28–42), Ferrari et al. from the European Institute of Oncology (Milan, Italy), Mount Vernon Hospital (Northwood, UK), and the University of Milan (Italy) discussed the utility of "Interim ^{18}FDG PET/CT during radiochemotherapy in the management of pelvic malignancies: a systematic review." Violet and Hofman from the Peter MacCallum Cancer Centre (Melbourne, Australia) reported on April 5 ahead of print in *BJU International* on "Prostate specific membrane antigen (PSMA) from diagnostic to therapeutic target: radionuclide therapy comes of age in prostate cancer."