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.

PET-Negative Mass After HL Treatment

Adams et al. from University Medical Center Utrecht (The Netherlands) reported on November 11 ahead of print in *Pediatric Hematology and Oncology* on a review and meta-analysis of outcomes in patients with ^{18}F-FDG PET-negative residual masses after treatment for Hodgkin lymphoma. Study criteria allowed the inclusion of 5 reports with a total of 727 patients with PET-negative masses after first-line therapy. Between 0% and 13% of these patients were reported as experiencing disease relapse, with a calculated pooled overall disease relapse rate of 6.8%. On the basis of these data, the authors concluded that "considering the existing literature, the presence of a non-FDG–avid residual mass has not been proven yet to be associated with a worse outcome than a posttreatment FDG PET-based complete remission status without a residual mass."

Pediatric Hematology and Oncology

PET/CT and Smoldering Myeloma

In a study e-published on October 22 ahead of print in *Leukemia*, Zamagni, from the Bologna University School of Medicine (Italy), and a consortium of Italian and German investigators reported on the potential utility of ^{18}F-FDG PET/CT assessment of early skeletal involvement in predicting disease progression in patients with smoldering (indolent) multiple myeloma. The study included 120 patients with smoldering multiple myeloma who underwent PET/CT and were followed for a median of 2.2 y. Imaging was positive in 16% of patients (8 patients with 1 focal lesion, 3 with 2, 6 with >3, and 2 with diffuse bone marrow involvement). During follow-up, 38% of patients progressed to multiple myeloma, including 21% with skeletal involvement, and an overall median time to progression of 4 years. Patients with positive PET/CT findings had a calculated risk of progression of 3.00 and a median time to progression of 1.1 y, compared with 4.5 y for those with negative PET/CT findings. For these 2 groups the risks of progression within 2 years were 58% and 33%, respectively. The authors concluded that "PET/CT positivity significantly increased the risk of progression of smoldering multiple myeloma to multiple myeloma" and that "PET/CT could become a new tool to define high-risk smoldering multiple myeloma."

Leukemia

Imaging Tau in Early AD

Johnson et al. from the Massachusetts General Hospital, Brigham and Women's Hospital, Harvard Medical School, and Harvard School of Public Health (all in Boston, MA) reported on October 27 ahead of print in *Annals of Neurology* on a PET study of focal brain tau deposition and amyloid-β binding in patients with mild cognitive impairment (n = 13) or mild Alzheimer dementia (n = 6) and in older clinically normal individuals (n = 13). All patients underwent ^{18}F-T807 (AV1451) PET, ^{11}C-Pittsburgh compound B (^{11}C-PIB) PET, and MR imaging, as well as clinical assessment of cognitive status. Abnormally high cortical ^{18}F-T807 binding was identified in patients with mild cognitive impairment and Alzheimer dementia when compared with clinically normal controls. A stronger association was found between cognitive impairment and inferior temporal ^{18}F-T807 binding than with mean cortical ^{11}C-PIB binding. Regional ^{18}F-T807 correlated well with mean cortical ^{11}C-PiB in all participants. A subset of clinically normal participants with elevations in both temporal lobe ^{18}F-T807 binding and mean cortical ^{11}C-PiB estimates of amyloid-β were deemed to be "at elevated risk for imminent clinical and cognitive decline." The authors concluded that "these findings suggest that ^{18}F-T807 PET could have value as a biomarker that reflects both the progression of AD tauopathy and the emergence of clinical impairment."

Annals of Neurology

PET/CT, US, and Scintigraphy in Hyperparathyroidism

In a study e-published in the October issue of *Medicine (Baltimore)* (2015;94: e1701), Michaud et al. from the Hôpital Tenon (Paris, France) and Comenius University/St. Elisabeth Oncology Institute (Bratislava, Slovakia) reported on a pilot comparison of ^{18}F-fluorocholine (^{18}F-FCH) PET/CT in preoperative localization of hyperfunctioning parathyroid glands in patients with hyperparathyroidism and discordant or equivocal results on ultrasound and/or ^{123}I/^{99m}Tc-sestamibi dual-phase scintigraphy. The study included 17 patients with primary (n = 11), lithium-induced (n = 1), or secondary hyperparathyroidism (n = 5; 1 dialyzed, 4 renal transplanted), all of whom underwent ^{18}F-FCH PET/CT. Imaging results were compared with histopathology. In a preliminary analysis of image interpretation, equivocal images/foci were considered to be negative. Using this approach, per-patient sensitivity was 38% for ultrasound; 69% and 94% for open and masked reading, respectively, for scintigraphy; and 88% and 84% for open and masked reading, respectively, for ^{18}F-FCH PET/CT. Per-lesion sensitivity was 42% for ultrasound; 58% and 83% for open and

masked reading, respectively, for scintigraphy; and 88% and 96% for open and masked reading, respectively, for ^{18}F-FCH PET/CT. Classifying equivocal images/foci as positive increased the accuracy of open reading of both scintigraphy and PET/CT but not of ultrasound. PET/CT was significantly superior to ultrasound overall but was more sensitive than scintigraphy only for open reading when equivocal images/foci were classified as negative. The authors considered and discussed the potentially confounding effects of thyroid anomalies in these findings. They concluded that this pilot study confirmed that ^{18}F-FCH PET/CT "is an adequate imaging tool in patients with primary or secondary hyperparathyroidism, since both adenomas and hyperplastic parathyroid glands can be detected" and recommended that "further studies should evaluate whether FCH could replace Tc-sestamibi as the functional agent for parathyroid imaging," adding that "ultrasound would still be useful to identify thyroid lesions."

Medicine (Baltimore)

PET and Local–Regional Failure in NSCLC

Markovina and authors from the American College of Radiology Imaging Network 6668/Radiation Therapy Oncology Group 0235 trials reported in the November 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2015;93:597–605) on a secondary analysis of data to determine whether SUV of regional lymph nodes on posttreatment ^{18}F-FDG PET correlated with patient outcomes after definitive chemoradiation in non–small cell lung cancer. The study included patients treated with concurrent chemotherapy and radiation (doses ≥60 Gy) with identifiable ^{18}F-FDG–avid regional lymph nodes on pretreatment PET and available posttreatment imaging. Local–regional failure was defined as failure within the treated radiation therapy volume as reported by the treating institution. Maximum SUV was found to be greater for primary tumor than for regional lymph nodes before but not after treatment. Posttreatment SUV in regional lymph nodes was not associated with overall survival. Posttreatment elevation of SUV in regional lymph nodes (both absolute values and change in residual activity compared to pretreatment SUV) was found to be associated with inferior local–regional control. The authors concluded that "future trials evaluating a radiation therapy boost should consider inclusion of both primary tumor and FDG-avid regional lymph nodes in the boost volume to maximize local–regional control."

International Journal of Radiation Oncology, Biology, Physics

Second PET in Dementia Management

In an article e-published on October 15 ahead of print in the *Journal of Alzheimer's Disease*, Bergeron et al. from CHU de Québec, the Institut de Cardiologie et de Pneumologie de Québec, and Université Laval (all in Québec, Canada) reported on clinical outcomes associated with a repeat ^{18}F-FDG PET acquisition in patients with atypical/unclear dementia syndromes. The retrospective study included data on 59 such patients in whom initial PET was inconclusive and who underwent repeat PET imaging. The authors found that repeat imaging resulted in a reduction of unclear diagnoses from 80% to 34%, changed the diagnosis in 24%, and led to change in management in 22% of patients. On average, these changes were most marked in those cases in which the initial PET resulted in low diagnostic confidence and the second PET was not acquired until at least 12 months after the first. The authors concluded that "in tertiary care memory clinic settings, when diagnostic incertitude persists despite extensive evaluation and an equivocal FDG-PET, repeating the FDG-PET 12 months later can greatly clarify the diagnosis and improve the care management."

Journal of Alzheimer's Disease

Beam-On PET and Proton Therapy

Dendooven et al. from the University of Groningen (The Netherlands) reported in the November issue of *Physics in Medicine and Biology* (2015;60:8923–8947) on preliminary work aimed at developing practical in vivo dose delivery verification with PET during irradiation with proton beams. The authors initially assessed the suitability of short-lived nuclides (half-life <19 s, the half-life of ^{10}C) by measuring their production in the stopping of 55 MeV protons in water, carbon, phosphorus, and calcium. The most-produced short-lived nuclides and their production rates relative to the relevant long-lived nuclides were: ^{12}N (half-life = 11 ms) on carbon (9% of ^{11}C), ^{29}P (half-life = 4.1 s) on phosphorus (20% of ^{30}P), and ^{38m}K (half-life = 0.92 s) on calcium (113% of ^{38g}K). No short-lived nuclides are produced on oxygen. The authors discussed the practical implementation of ^{12}N PET beam-on imaging in proton therapy and concluded that "for any tissue, ^{12}N PET imaging potentially provides equal to superior proton range information compared to prompt gamma imaging with an optimized knife-edge slit camera."

Physics in Medicine and Biology

PET and PTLD

In an article e-published on October 30 in *Pediatric Transplantation*, Vali et al. from the University of Toronto (Canada) described the results of a retrospective study assessing the value of initial ^{18}F-FDG PET added to CT in pediatric patients with posttransplant lymphoproliferative disorder (PTLD). The study included 34 patients (20 boys, 14 girls), aged 3.5–17.0 y (mean age, 9.9 y), each of whom had undergone PET/CT at initial diagnosis of PTLD after heart (n = 13), lung (n = 8), kidney (n = 4), liver (n = 3), liver and bowel (n = 3), or bone marrow (n = 3) transplantation. In all except 1 patient, PTLD was confirmed by histopathology; in the remaining patient, the diagnosis was made with clinical findings and imaging. On a per-lesion basis, PET identified 168 lesions and CT identified 134; however, CT identified 22 lesions that were not detected on PET. On a per-patient basis, PET detected more lesions in 13 patients, CT identified more in 7, and the 2 modalities identified the same number in 14 patients. The addition of ^{18} F-FDG PET to CT scans

upstaged the diagnosis in 7 patients, and PET/CT proved to be useful in guiding biopsy. The authors concluded that "^{18}F-FDG PET and CT are complementary at initial staging of pediatric PTLD and that ^{18}F-FDG PET/CT scanning can guide biopsies."

Pediatric Transplantation

Amyloid PET and Cutpoints for CSF Markers

Zwan, from the VU University Medical Center (Amsterdam, The Netherlands), and a consortium of researchers from Finland, Denmark, Sweden, Spain, the UK, and The Netherlands reported on October 14 ahead of print in *Neurology* on a study to identify cerebrospinal fluid (CSF) amyloid-β 1-42 ($A\beta_{42}$) cutpoints for cortical amyloid deposition as assessed by ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET imaging and to determine whether these cutpoints correlate with those used in current clinical practice. The study included data from 5 European centers on 433 individuals (195 with Alzheimer disease [AD], 99 with mild cognitive impairment, and 57 nonsymptomatic controls). Each participant had undergone ^{11}C-PiB PET imaging, and CSF $A\beta_{42}$ and $A\beta_{42}$/tau ratio cutpoints for cortical amyloid deposition were calculated based on visual interpretation of these images. These CSF $A\beta_{42}$ cutpoints ranged from 521 to 616 pg/mL, compared with existing clinical-based cutpoints of 400–550 pg/mL. With a cutpoint of 557 pg/mL calculated from the overall results, the agreement between CSF $A\beta_{42}$ and ^{11}C-PiB PET was 84%. Individuals with positive ^{11}C-PiB PET imaging and normal CSF $A\beta_{42}$ levels had higher CSF tau and phosphorylated tau levels and more often had mild cognitive impairment or AD dementia than those with negative ^{11}C-PiB PET and abnormal CSF $A\beta_{42}$ levels. In summarizing the evidence provided by these findings, the authors noted that "an amyloid-PET-based CSF $A\beta_{42}$ cutpoint identifies individuals with amyloid deposition with a sensitivity of 87% and specificity of 80%."

Neurology

Multimodality GTV Delineation

In an article appearing on November 4 in *BMC Cancer* (2015;15:844) Bird et al. from St. James' University Hospital/Leeds Teaching Hospitals NHS Trust (UK) reported on a multimodality imaging approach for target volume delineation in radiation therapy of oropharyngeal squamous cell carcinoma. The study included 11 patients with locally advanced disease who underwent pretreatment contrast-enhanced ^{18}F-FDG PET/CT and MR imaging while wearing radiation therapy treatment masks. Gross tumor volumes (GTVs) were contoured separately for CT, MR, and CT/MR by 2 radiologists and 3 radiation oncologists. PET GTVs were contoured using a semiautomated segmentation algorithm. After additional analyses, significant differences in mean GTVs were found between CT and CT/MR, CT/MR and PET, and MR and PET. Significant differences in GTV positions were found between all modalities, with the exception of CT/MR and MR. The CT, MR, and CT/MR GTVs contained a mean of 64%, 74%, and 77%, respectively, of the PET GTVs. A mean of 57% of the MR GTVs were included within the CT GTVs, and a mean of 63% of the CT GTVs were included within the MR GTVs. CT interobserver variability was higher (for position and/or volume) than either MR or CT/MR. Contoured volumes differed significantly between radiologists and radiation oncologists for all modalities. The authors concluded that because no single imaging technique encompassed all potential GTV regions, "these data suggest delineation based on multimodality imaging has the potential to improve accuracy of GTV definition."

BMC Cancer

PET and Brain Changes After Bariatric Surgery

Karlsson et al. from the University of Turku/Turku University Hospital (Finland), Medical Imaging Center of Southwest Finland (Turku), and Aalto University (Espoo, Finland) reported on October 13 ahead of print in *Molecular Psychiatry* on a PET study of opioidergic and dopaminergic systems in patients before and after bariatric surgery. The study included 16 morbidly obese women who underwent brain μ-opioid receptor and dopamine D_2 receptor availability assessment with ^{11}C-carfentanil and ^{11}C-raclopride, respectively, twice before and 6 months after bariatric surgery. Receptor binding potentials in the study group were compared before and after surgery and with control data from 14 lean individuals. Brain μ-opioid receptor availability was 23% higher after bariatric surgery and subsequent weight loss than before, with changes seen in areas associated with reward processing, including the ventral striatum, insula, amygdala, and thalamus. Change in dopamine D_2 receptor availability was not associated in any brain region with weight loss. The authors concluded that because bariatric surgery and concomitant weight loss recover downregulated μ-opioid receptor availability, "lowered μ-opioid receptor availability is associated with an obese phenotype and may mediate excessive energy uptake." They added that a more complete understanding of the opioidergic contribution to overeating is "critical for developing new treatments for obesity."

Molecular Psychiatry

PET and SPECT in Cardiac Sarcoidosis

In an article e-published on October 19 ahead of print in *Circulation Journal*, Momose et al. from Tokyo Women's Medical University (Japan) reported on a study assessing the degree to which ^{18}F-FDG uptake on PET as a measure of active inflammation in patients with cardiac sarcoidosis is correlated with ^{123}I-radioiodinated 15-(p-iodophenyl)-3 (R,S)-methylpentadecanoic acid (BMIPP) and ^{201}Tl SPECT findings. The study included 52 patients with suspected cardiac sarcoidosis who underwent both ^{18}F-FDG PET and dual-tracer SPECT imaging. Both segmented and total defect scores, as well as mismatch scores, were calculated for the SPECT tracers, and SUV_{max} was recorded for the entire myocardium. SUV_{max}, BMIPP defect scores, and summed mismatch scores

were all higher in patients with cardiac sarcoidosis. Mismatch scores had diagnostic sensitivity and specificity of 74% and 80%, respectively. ^{18}F-FDG SUV_{max} was not associated with either BMIPP defect scores or mismatch scores. After additional analysis, the combined mismatch score and SUV_{max} had greater prognostic significance than either assessment alone. The authors concluded that BMIPP and ^{201}Tl dual-tracer mismatch is a useful finding in the diagnosis of cardiac sarcoidosis and that it adds "greater diagnostic value" to SUV_{max} on ^{18}F-FDG PET/CT.

Circulation Journal

^{90}Y-Daclizumab RIT in Relapsed HL

Janik et al. from the National Institutes of Health (Bethesda, MD) and the Roger Williams Medical Center (Providence, RI) reported in the October 20 issue of the *Proceedings of the National Academy of Sciences of the United States of America* (2015;112:13045–13050) on a study evaluating the effects of multiple infusions of the anti-CD25 antibody ^{90}Y-daclizumab in patients with refractory and relapsed Hodgkin lymphoma (HL). The study included 46 patients treated with 7 intravenous infusions. Fourteen complete responses were noted, along with 9 partial responses, 14 patients with stable disease, and 9 whose disease progressed. The authors focused on the effects of the radioimmunotherapy (RIT) on Reed–Sternberg cells, some of which express CD25 and around which T cells that express CD25 cluster. Complete and partial responses were observed both in patients in whom Reed–Sternberg cells expressed CD25 and in whom those cells did not express CD25, as long as the associated clustering T cells expressed CD25. Toxicities associated with the RIT included transient bone marrow suppression and myelodysplastic syndrome in 6 patients. The authors concluded that "repeated ^{90}Y-daclizumab infusions directed predominantly toward nonmalignant T cells rosetting around Reed–Sternberg cells provided meaningful therapy for select HL patients."

Proceedings of the National Academy of Sciences of the United States of America

Imaging Cancer Aggressiveness

In an article in the September 13 issue of *Theranostics* (2015;5:1303–1316) Persson et al. from the Rigshospitalet and University of Copenhagen (Denmark) described the results of a first-in-human clinical trial of PET imaging of the urokinase-type plasminogen activator receptor (uPAR) in patients with breast, prostate, and bladder cancer. uPAR expression is associated with and predictive for cell invasion and metastasis. The researchers conjugated a uPAR-specific peptide to the macrocyclic chelator DOTA and labeled the agent with ^{64}Cu for PET imaging. The agent, ^{64}Cu-DOTA-AE105, was assessed for safety, pharmacokinetics, and dosimetry after a single intravenous dose in 10 patients with cancer (4 prostate, 3 breast, and 3 bladder). No adverse effects were noted in these and other safety and stability assessments. The agent showed both fast clearance by renal excretion and high uptake in primary tumor lesions and lymph node metastases, findings that were confirmed in histopathology. The authors concluded that "overall, this first-in-human study therefore provides promising evidence for safe use of ^{64}Cu-DOTA-AE105 for uPAR PET imaging in cancer patients."

Theranostics

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 September, October, and November. Tao et al. from the Zhejiang Cancer Hospital, (Hangzhou, China) published "Predicting the response of neoadjuvant therapy for patients with esophageal carcinoma: an in-depth literature review" in the September 15 issue of the *Journal of Cancer* (2015;6:1179–1186). On October 27, ahead of print in *Current Pharmaceutical Design*, Qiao et al. from the Chinese Academy of Sciences (Beijing, China) reviewed "Imaging tumor metastases with molecular probes." Bjurlin et al. from New York Langone Medical Center (NY) provided an overview of "Imaging and evaluation of patients with high-risk prostate cancer," in the November issue of *Nature Reviews. Urology* (2015;12:617–628). In an article e-published on November 9 ahead of print in *Nucleus (Austin, TX)*, Babu and Fullwood from the National University of Signapore described "3D genome organization in health and disease: emerging opportunities in cancer translational medicine." "A perspective on the future role of brain PET imaging in exercise sciences" was offered by Boecker and Drzezga from the German Center for Neurodegenerative Diseases (Bonn and Cologne, Germany) on October 22 ahead of print in *Neuroimage*. Nekolla and Rischpler from the Deutsches Zentrum für Herz-Kreislauf-Forschung e.V. (Munich, Germany) published "Assessing myocardial metabolism with hybrid PET imaging: instrumentation, concepts, and workflows" on November 8 ahead of print in *Current Pharmaceutical Design*. In an article e-published on October 28 ahead of print in *Alcoholism, Clinical and Experimental Research*, Hillmer et al. from Yale University School of Medicine (New Haven, CT) described "How imaging glutamate, γ-aminobutyric acid, and dopamine can inform the clinical treatment of alcohol dependence and withdrawal." Purohit et al. from Geneva University Hospital and the University of Geneva (Switzerland) published "Orbital tumours and tumour-like lesions: exploring the armamentarium of multiparametric imaging" on October 31 ahead of print in *Insights into Imaging*. In an article in the December issue of *Current Oncology Reports* (2015;17:56), Koo et al. from the University of Colorado School of Medicine (Aurora) and the National Cancer Institute (Bethesda, MD) reviewed "Novel imaging of prostate cancer with MRI, MRI/US, and PET." Gunn et al. from Imperial College London (UK), Hammersmith Hospital (London, UK), and University of Oxford (UK) provided an overview of "Quantitative imaging of protein targets in the human brain with PET" in the November 21 issue of *Physics in Medicine and Biology* (2015;60: R363–R411).