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.

CFR, Triponin, and Cardiac Events

In an article e-published on December 5 ahead of print in *Circulation*, Taqueti et al. from the Brigham and Women's Hospital/Harvard Medical School (Boston, MA) reported on a study investigating correlations between low-level serum cardiac troponin elevation, impaired coronary flow reserve (CFR), and adverse outcomes in patients without overt coronary artery disease (CAD). The study included 761 patients evaluated for suspected CAD who underwent troponin level assessment and stress myocardial perfusion PET imaging before being followed for a median of 2.8 y. Patients with flow-limiting CAD, left ventricular ejection fraction <40%, and/or revascularization within 60 d after imaging were excluded from follow-up. Follow-up documentation of major adverse cardiovascular events included cardiovascular death, nonfatal myocardial infarction, and late revascularization. The authors found that patients ($n = 97$) with at least 1 elevated troponin result had higher pretest clinical scores, more renal dysfunction, and lower left ventricular ejection fraction and CFR than patients with negative troponin assessment.

Additional analysis showed that impaired CFR was independently associated with positive troponin and that both impaired CFR and positive troponin were independently associated with major adverse cardiovascular events. The combination of impaired CFR and positive troponin successfully identified patients at highest risk of major adverse cardiovascular events. The authors concluded that "in patients without overt CAD, impaired CFR independently associated with minimally elevated triponin and major adverse cardiovascular events," suggesting that impaired CFR (which reflects microvascular dysfunction) modifies the effect of a positive troponin assessment on adverse outcomes.

Circulation

Comparing PET Hypoxia Tracers

Peeters et al. from Maastricht University and VU University Medical Center Amsterdam (both in The Netherlands) reported ahead of print on December 6 in the *International Journal of Radiation Oncology, Biology, Physics* on a study comparing 3 clinically used PET hypoxia tracers, ^{18}F-FMISO, ^{18}F-FAZA, and ^{18}F-HX4, in a tumor model in rats. The study focused on tracer uptake assessment for information on optimal time of imaging, tumor-to-blood ratios, spatial reproducibility, and sensitivity to oxygen modification. Each of the tracers was injected into rhabdomyosarcoma R1-bearing rats, with serial PET/CT images acquired at multiple timepoints. The researchers found that tumor-to-blood ratios were stabilized and maximized at 2 h after injection for ^{18}F-FAZA and 3 h for ^{18}F-FAZA. ^{18}F-FMISO, however, showed a constant increasing tumor-to-blood ratio up to 6 h. High spatial reproducibility was found by voxel-to-voxel comparisons and Dice similarity coefficient calculations on the 30% highest uptake volume for ^{18}F-FMISO and ^{18}F-HX4, but ^{18}F-FAZA was less reproducible. Modification of the hypoxic fraction resulted in greater mean standardized uptake values for both ^{18}F-HX4 and ^{18}F-FAZA at 7% oxygen breathing. ^{18}F-FMISO uptake, alone among the tracers, was found to be reversible on exposure to nicotinamide and carbogen. The authors concluded that "this study indicates that each tracer has its own strengths and, depending on the question to be answered, a different tracer can be put forward."

International Journal of Radiation Oncology, Biology, Physics

PET/CT, Cardiac MR, and Isolated Cardiac Sarcoidosis

In an article e-published on December 12 ahead of print in the *Journal of Cardiac Failure*, Tezuka et al. from Tokyo Medical and Dental University and the University of Tokyo (Japan) described a study elucidating the clinical characteristics of isolated cardiac sarcoidosis, including imaging features on cardiac MR and ^{18}F-FDG PET/CT imaging. The study included 83 patients with suspected cardiac stenosis, in whom systemic sarcoidosis with cardiac stenosis was identified by clinical criteria in 30 and isolated cardiac sarcoidosis (sarcoidosis not detected in other organs) in 11. Left ventricular ejection fraction was somewhat lower in patients with isolated cardiac sarcoidosis; otherwise the clinical features of the 2 groups were not significantly different. Late gadolinium enhancement on MR imaging was seen in 9 systemic sarcoidosis and 4 isolated cardiac sarcoidosis patients. The coefficients of variance for myocardial standardized uptake values on PET/CT were higher in systemic sarcoidosis patients than in a set of control data. No differences in prognoses were identified in patients with systemic and isolated cardiac sarcoidosis. The authors concluded that "cardiac MRI and FDG PET, noninvasive imaging modalities, could be useful modalities to detect myocardial involvement in the cases with definite or suspected isolated cardiac sarcoidosis."

Journal of Cardiac Failure

^{18}F-FDG Uptake at the Gastroesophageal Junction

Stagg et al. from the University of Texas Southwestern Medical Center (Dallas, TX) reported on December 14 ahead of print in *Digestive Diseases and Sciences* on a study evaluating the significance of unexpected ^{18}F-FDG uptake on PET/CT at the gastroesophageal junction and comparing results with those from esophagogastroduodenoscopy (EGD). The retrospective study included the records of 219 patients who underwent EGD within 6 mo of PET/CT imaging. Patients were assigned to 1 of 5 groups based on the results of EGD: esophageal malignancy (n = 34), esophagitis (n = 21), Barrett esophagus (n = 8), other nonmalignant disorders (n = 5), and normal (n = 151). Maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}, respectively) were higher in patients with esophageal malignancy than in other groups. Mean SUV_{max} values for the 5 groups as listed above were 6.72, 2.47, 2.40, 3.48, and 2.06, respectively. SUVs for patients with high-grade esophagitis were greater than in those with low-grade esophagitis. These results yielded thresholds that might be useful in identifying the need for further endoscopic evaluation in patients with abnormal metabolic activity at the gastroesophageal junction: $SUV_{max} \geq 3.5$ predicted the need for EGD with a positive predictive value of 79%, whereas $SUV_{max} \leq 2.2$ had a negative predictive value of 86%. The authors concluded that "differentiation between benign and potentially significant disease at the gastroesophageal junction may be possible with quantification of incidental ^{18}F-FDG uptake at PET/CT."

Digestive Diseases and Sciences

^{11}C-PIB and Predictive Accuracy in MCI

In an article in the December issue of *Medicine (Baltimore)* (2014;93:e150), Ma et al. from Shengjing Hospital of China Medical University (Shenyang, China) reported on a systematic review and meta-analysis of published data on the performance of ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET in predicting conversion to Alzheimer disease in patients with mild cognitive impairment (MCI). The authors also looked at the question of whether long-term follow-up has a positive effect on predictive accuracy. After an extensive database search and a rigorous analysis for eligible studies, 11 studies with a total of 352 patients with MCI at baseline were included. In these studies, the sensitivity and specificity of ^{11}C-PIB PET for predicting conversion to AD ranged from 83.3% to 100% and 41.1% to 100%, respectively. Most diagnostic indicators assessed in a long-term follow-up subgroup were significantly superior to those in a short-term follow-up subgroup. The authors concluded that "current evidence suggests that prolongation of the follow-up duration tended to yield greater accuracy of ^{11}C-PiB PET for predicting the progression from MCI to Alzheimer disease." They noted that specificity, which reflects the exploratory nature of the use of amyloid imaging in neurodegeneration, was improved with longer follow-up. In addition to answering specific questions posed by the researchers, this study reveals the current challenges of systematic review and meta-analysis of studies that, although focusing on a single disease entity, come from a broad and disparate range of clinical practice and investigative standards.

Medicine (Baltimore)

^{18}F-FDG PET/CT in Posttherapy Breast Cancer

Chang et al. from Kaohsiung Veterans General Hospital and Taipei Veterans General Hospital (both in Taiwan) reported on December 17 in *PLoS One* (2014;9:e115127) on a study designed to evaluate the utility of ^{18}F-FDG PET/CT in early detection of breast cancer recurrence and to determine the corresponding utility in posttherapy monitoring. The study included 140 patients: patients with increased serum CA 15-3 levels (n = 31) or clinical/radiologic suspicion of recurrence (n = 40) and a group of asymptomatic patients in posttherapy follow-up (n = 69). All patients underwent ^{18}F-FDG PET/CT imaging, and analysis of results included data from histology, other imaging modalities, and clinical follow-up. In patients imaged for suspected recurrence, the sensitivity and specificity of PET/CT were 87.5% and 87.1%, respectively. In asymptomatic patients, the corresponding percentages were 77.8% and 91.7%. Recurrences were identified in 40 (56.3%) patients with suspected recurrence and 9 (13%) asymptomatic patients. The positive predictive value of PET/CT was higher in patients with suspected recurrence than in asymptomatic patients. The results of PET/CT imaging altered management in both groups. The authors concluded that ^{18}F-FDG PET/CT "should be used as a priority in patients with increased serum CA 15-3 levels, or with clinical/radiologic suspicion of recurrence, and might be useful for asymptomatic patients."

PLoS One

PET-Based Texture Features and Respiratory Motion

In an article in the December 17 issue of *PLoS One* (2014;9:e115510), Yip et al. from the Harvard Medical School (Boston, MA) and the University of Texas MD Anderson Cancer Center (Houston, TX) reported on a study using static (3D) and respiratory-gated (4D) PET imaging to explore the sensitivity of texture features to tumor motion in non–small cell lung cancer. The study included 26 patients (34 lesions) who underwent 3D and 4D ^{18}F-FDG PET imaging before chemoradiotherapy. Texture features analyzed within physician-defined tumor volumes included maximal correlation coefficient (MCC), long-run low-gray (LRLG), coarseness, contrast, and busyness. Relative differences between these features in 3D and 4D data were calculated. Increases in LRLG were seen in 4D PET, with decreases in busyness and MCC compared with 3D PET. No strong correlation was found between tumor volume and differences in 3D and 4D results for the texture features. Motion amplitude

had a moderate impact on the relative difference between the 2 techniques for MCC and busyness but no impact for LRLG, coarseness, or contrast. The authors concluded that "texture features, blurred out by respiratory motion during 3D PET acquisition, can be better resolved by 4D PET imaging" and that "4D PET textures may have better prognostic value as they are less susceptible to tumor motion."

PLoS One

High-Res PET and MR in Cushing Disease

Chittiboina et al. from the National Institute of Neurological Disorders and Stroke (Bethesda, MD) reported on December 5 ahead of print in the *Journal of Neurosurgery* on a study comparing high-resolution ^{18}F-FDG PET with MR imaging in the detection of pituitary adenomas in Cushing disease. The study included 10 patients (7 females and 3 males; age range, 11–59 y) with Cushing disease, each of whom underwent preoperative ^{18}F-FDG high-resolution PET and MR (spin-echo [SE] and spoiled gradient–recalled [SPGR] sequences) imaging. Surgical and histology findings were correlated with imaging data. SE MR imaging identified a pituitary adenoma in 4 (40%) patients, and SPGR MR did so in 7 (70%) patients. Tracer uptake on PET was consistent with an adenoma in 4 patients (40%). Maximum standardized uptake values were significantly higher for ^{18}F-FDG PET-positive tumors than for PET-negative tumors, and PET positivity was not associated with tumor volume or dural invasion. All PET-positive adenomas had a <180% adrenocorticotropic hormone (ACTH) increase, and all ^{18}F-FDG PET-negative adenomas had a >180% ACTH increase after corticotropin-releasing hormone stimulation The authors concluded that although ^{18}F-FDG high-resolution PET imaging can detect small functioning corticotroph adenomas and is more sensitive than SE MR imaging, "SPGR MRI is more sensitive than ^{18}F-FDG high-resolution PET and SE MRI in the detection of Cushing disease–associated pituitary adenomas" and that "response to corticotropin-releasing hormone stimulation can predict ^{18}F-FDG high-resolution PET-positive adenomas in Cushing disease."

Journal of Neurosurgery

Kidney Function and ^{90}Y-DOTATOC Therapy

In an article e-published on December 15 in *Current Radiopharmaceuticals*, Arveschoug et al. from Aarhus University Hospital (Denmark) reported on a study assessing monitoring methods for kidney function in patients treated with ^{90}Y-DOTATOC as well as the protective effects of 4-h and 24-h amino acid infusion protocols with that treatment. The study included 28 patients with neuroendocrine tumors in whom glomerular filtration rate (GFR; assessed as both ^{51}Cr-ethylenediaminetetraacetic acid [^{51}Cr-EDTA] plasma clearance and estimated GFR [eGFR]) was monitored before and 3, 6, 12, and 18 mo after ^{90}Y-DOTATOC treatment. GFRs were also assessed in 15 patients treated with a 4-h amino acid infusion protocol and 13 patients with a 24-h infusion. The majority of patients (82%) in the study had preexisting risk factors associated with kidney failure. A significant reduction in GFR (mean loss, 32%) as assessed by ^{51}Cr-EDTA plasma clearance was seen up to 12 mo after therapy, with eGFR overestimating this loss. Although no statistically significant differences were noted in renal protection between the 2 amino acid infusion protocols, the 24-h protocol showed a tendency to reduce mean GFR loss at 12 mo after therapy. The authors concluded that "peptide receptor radionuclide therapy treatment is best monitored by ^{51}Cr-EDTA plasma clearance" and that resulting data suggest that the use of a 24-h amino acid kidney protection protocol "may reduce the loss of kidney function in these patients."

Current Radiopharmaceuticals

^{18}F-FDG PET in Aortic Graft Infection

Saleem et al. from the University of Groningen and the University Medical Center Utrecht (both in The Netherlands) reported on December 9 ahead of print in the *Journal of Vascular Surgery* on the use of ^{18}F-FDG PET in assessment of suspected aortic prosthetic graft infection, using 2 semiquantitative parameters (maximum standardized uptake value [SUV_{max}] and tissue-to-background ratio [TBR]) and 2 visual parameters (^{18}F-FDG distribution patterns and a visual grading scale). The analysis included 37 patients with symptoms clinically suggestive of aortic graft infection who underwent ^{18}F-FDG PET, imaging and from whom perigraft material for culturing was obtained (positive cultures were used as the standard of proof for infection). Tissue culture was positive in 21 (56.7%) patients. In these patients, mean plus standard $SUV_{max} = 8.1 \pm 3.7$ (range, 3.6–18.5) and TBR = 5.9 ± 2.7 (range, 1.7–13.0). An SUV_{max} cutoff value of 8 yielded positive and negative predictive values of 80% and 54%, respectively. A TBR cutoff value of 6 yielded positive and negative predictive values of 73% and 52%, respectively. Positive predictive values for the visual grading scale and ^{18}F-FDG distribution patterns were 75% and 61%, respectively, and corresponding negative predictive values were 77% and 67%. The authors concluded that these results in a small patient sample "showed that the diagnostic abilities of quantitative and visual ^{18}F-FDG PET parameters are modest."

Journal of Vascular Surgery

Partial Volume Correction in Amyloid Imaging

In an article e-published on December 5 ahead of print in *Neuroimage*, Su, from Washington University School of Medicine (St. Louis, MO), and researchers from Columbia University Medical Center (New York, NY), the University of Pittsburgh School of Medicine (PA), University of Southern California Los Angeles, Indiana University School of Medicine (Indianapolis), Massachusetts General Hospital/Harvard Medical School (Boston), and the University of New South Wales (Sydney, Australia) reported on evaluation of a 2-component partial volume

correction technique and a regional spread function technique in detecting changes in amyloid deposition in both simulated and human ^{11}C-Pittsburgh compound B (^{11}C-PiB) PET imaging data. Both techniques compensated for partial volume effects and resulted in improved detection of subtle changes in tracer retention. The regional spread function technique was more accurate in the simulated data. The authors noted that partial volume correction has sometimes been avoided in this imaging setting "because it increases the sensitivity to inaccuracy in image registration and segmentation." Their results in this study suggest that the right partial volume correction techniques may enhance the ability to detect changes in amyloid deposition.

Neuroimage

PET Prediction in Hypopharyngeal Cancer

Oh et al. from the University of Ulsan College of Medicine (Seoul, Republic of Korea) reported on December 9 ahead of print in *Annals of Surgical Oncology* on a study designed to determine whether intratumor textural heterogeneity on pretreatment ^{18}F-FDG PET imaging predicts response and survival after chemoradiotherapy for hypopharyngeal squamous cell carcinoma (HPSCC). The study included 70 patients with HPSCC who underwent ^{18}F-FDG PET imaging before cisplatin-based induction chemotherapy followed by definitive chemoradiation. Variables assessed included standardized uptake value (SUV), metabolic tumor volume (MTV), and textural features (coarseness, busyness, complexity, and contrast) of primary tumors. Patients were classified as nonresponders or responders using the Response Evaluation Criteria in Solid Tumors. A total of 58 (83%) patients showed a complete or partial response after chemoradiation. These responders had lower maximum SUVs, lower MTVs, and lower coarseness and busyness than nonresponders. Additional analyses indicated that high coarseness and busyness were independently associated with poor disease-free survival and that high coarseness was independently associated with poor overall survival. The authors concluded that "intratumoral heterogeneity characterized by textural features extracted from pretreatment ^{18}F-FDG PET images" may identify patients at risk for low response rates and poor outcomes. The abnormal textural feature of tumor coarseness also may be useful in predicting response and survival after chemoradiation for HPSCC, with potential advantages in pretreatment management decisions.

Annals of Surgical Oncology

PET, MR, and RITL Studies

In an article e-published on December 3 ahead of print in *Molecular Oncology*, Hasegawa et al. from the National Institute of Radiological Sciences (Chiba, Japan) reported on development of PET and MR imaging methods for quantifying critical sequential events in fractionated whole-body X-ray–induced thymic lymphoma (RITL). The RITL mouse model is useful in investigating radiation carcinogenesis, particularly in studies in which bone marrow transplantation blocks RITL. The authors also looked at the ability of the imaging techniques to monitor cellular processes after bone marrow transplantation. Diffusion-weighted MR imaging was used to evaluate changes in bone marrow in mice receiving radiation. Apparent diffusion coefficients changed significantly in the irradiated marrow, corresponding to findings on pathology, and returned to normal levels sooner than recovery from irradiation without bone marrow transplant. ^{11}C-thiothymidine PET, a novel tracer for cell proliferation, showed significantly higher uptake in the irradiated thymus at 1 wk than in unirradiated thymus. This increased uptake was entirely eliminated by bone marrow transplantation, even with very few donor-derived cells in the thymus. After 1 wk, however, the thymus receiving bone marrow transplantation had significantly increased tracer uptake. The authors concluded that these findings suggest that bone marrow transplantation "first suppresses [radiation]-induced aberrant thymocyte proliferation and then accelerates thymic regeneration." The study successfully showed the feasibility of PET and MR imaging for "noninvasive monitoring of tumorigenic cellular processes in an animal model of radiation-induced cancer."

Molecular Oncology

Aβ and Cognitive Decline

Lim et al. from the University of Melbourne (Australia) and a consortium of Australian and U.S. researchers reported on December 2 ahead of print in *Archives of Clinical Neuropsychology* on a study investigating the extent to which decline in cognition and working memory in β-amyloid (Aβ)–positive nondemented individuals is related to hippocampal atrophy and Aβ accumulation. The study included 227 individuals (178 cognitively normal adults and 49 adults with mild cognitive impairment [MCI]) who underwent PET and MR imaging as well as cognitive assessments at baseline and at 18 and 36 mo. Regardless of cognitive status, those who were Aβ-positive showed greater rates of cognitive decline, Aβ accumulation, and hippocampal atrophy. In these patients, the rate of Aβ accumulation was directly associated with the rate of hippocampal atrophy, which was associated independently with rate of decline in memory. The authors noted that this suggests that "Aβ accumulation precedes any neurodegeneration or clinical symptoms, and that the relationship between Aβ and cognitive decline is mediated by hippocampal atrophy."

Archives of Clinical Neuropsychology

PET/CT and Outcomes in MDR TB

In an article in the December issue of *Science Translational Medicine* (2014; 6:265ra166), Chen, from the National Institute of Allergy and Infectious Diseases (Bethesda, MD), and colleagues from the International Tuberculosis Research Center (Changwon, South Korea), NET

Esolutions Corporation (McLean, VA), the National Institutes of Health Clinical Center (Bethesda, MD), the University of Pittsburgh (PA), National Masan Hospital (Changwon, South Korea),· Yonsei University College of Medicine (Seoul, South Korea), and Pusan National University School of Medicine (Busan, South Korea) looked at the potential utility of ^{18}F-FDG PET/CT in providing surrogate imaging endpoints relative to treatment failure and relapse in patients with multidrug-resistant tuberculosis (MDR TB). The study included 28 individuals with pulmonary MDR TB, who were treated with second-line TB therapy for 2 y and then followed for an additional 6 mo after the end of therapy for final treatment outcomes. All participants underwent PET/CT at 2 mo and CT only at 6 mo after initiation of therapy. CT imaging at 6 mo (but not 2 mo) was predictive of outcomes, and changes in computed volumes for TB-associated abnormalities were predictive of drug response at both timepoints. Quantitative changes in ^{18}F-FDG on PET at 2 mo after starting treatment were associated with long-term outcomes. The authors concluded that "these preliminary data constitute a proof of concept of the possibility of using imaging early in the course of treatment to predict final TB treatment outcome in the context of clinical trials of new TB drugs and regimens."

Science Translational Medicine

Reviews

Review articles offer 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 November, December, and January. In an article e-published on December 16 ahead of print in the *British Journal of Cancer,* Fleming, from the Aberdeen Biomedical Imaging Centre (UK), and a consortium of UK researchers reviewed the current status of "Imaging tumour hypoxia with positron emission tomography." Villemagne et al. from the University of Melbourne (Australia) reported on "Tau imaging: early progress and future directions" in the January issue of *The Lancet. Neurology* (2015;14:114–124). Ahmadi et al. from the University of Ottawa Heart Institute (Canada) provided an overview of "FDG PET imaging for identifying pulmonary hypertension and right heart failure" in the January issue of *Current Cardiology Reports* (2015;17:555). In an article e-published on November 24 ahead of print in *Alzheimer's & Dementia*, Schmidt, from Janssen Pharmaceutica (Beerse, Belgium), and researchers from the United States and Sweden described "The influence of biological and technical factors on quantitative analysis of amyloid PET: points to consider and recommendations for controlling variability in longitudinal data." Nagai from the National Hospital Organization Nagoya Medical Center (Japan) offered a summary of "Recent advances in Hodgkin lymphoma: interim PET and molecular-targeted therapy" in an article e-published on December 8 ahead of print in the *Japanese Journal of Clinical Oncology.* Su and colleagues from the Medical School of Nanjing University (Nangjing, China) reviewed "PET and MR imaging of neuroinflammation in hepatic encephalopathy" on December 17 ahead of print in *Metabolic Brain Disease*. In the November 20 issue of *Parkinsonism & Related Disorders* Ba and Martin, from the University of Alberta (Edmonton, Canada), provided an overview of "Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice." Johnbeck et al. from the Rigshospitalet and University of Copenhagen (Denmark) summarized "PET tracers for somatostatin receptor imaging of neuroendocrine tumors: current status and review of the literature" in *Future Oncology* (2014;10:2259–2277). In an article in the December 7 issue of the *World Journal of Gastroenterology* (2014;20:16964–16975), Kijima et al. from Jichi Medical University (Tochiga, Japan) reviewed the literature on "Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT."