

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 and Mantle Cell Lymphoma

Mato et al. from Hackensack University Medical Center (NJ) reported on December 16 ahead of print in *Cancer* on a study of the prognostic utility of PET/CT in a group of patients with mantle cell lymphoma undergoing dose-intensive chemotherapy in the frontline setting. Key foci were the predictive abilities of imaging in progression-free and overall survival. The retrospective study included 53 patients with advanced mantle cell lymphoma who had both interim and posttreatment PET/CT results available. At a median follow-up of 32 mo, 3-y progression-free survival was estimated at 76% and overall survival at 84%. PET/CT findings during treatment were not found to be associated with either survival datapoint. PET/CT findings acquired after treatment were found to be significantly correlated with progression-free survival and trended toward significance for overall survival. The authors concluded that “these data do not support the prognostic utility of PET-CT in pretreatment and interim treatment settings” but that a “positive PET-CT after the

completion of therapy identifies a patient subset with an inferior progression-free survival and a trend toward inferior overall survival.”

Cancer

PET/CT and Infection Localization

In an article e-published on December 14 in the *Journal of Critical Care*, Kluge et al. from the University Medical Center Hamburg-Eppendorf (Germany) reported on the diagnostic value of PET/CT in assessing critically ill patients with septic shock of unknown origin. The retrospective study included 18 patients with severe sepsis or septic shock of unknown origin. All patients underwent ^{18}F -FDG PET/CT and had previously undergone chest radiography, transesophageal echocardiography, standalone CT imaging, and a series of lab analyses. Tracer accumulation was seen on PET in 14 of the 18 patients. Eleven of the studies were determined to be true-positive findings, 3 were false-positive, 4 were true-negative, and none were false-negative. PET/CT findings had direct effects on management in 6 patients (2 to surgery, 2 to pacemaker removal, 1 to initiation of antibiotics, and 1 to prolonged antibiotic therapy). Twelve of the 18 patients survived their infections. The authors concluded that ^{18}F -FDG PET/CT “is a valuable tool for the localization of infectious foci in critically ill patients with severe sepsis/septic shock in whom conventional diagnostic methods fail to detect these foci” and called for prospective studies with larger numbers of patients.

Journal of Critical Care

Thyroid Uptake and Breast Cancer Therapy

Kim et al. from the Pusan National University Hospital (Busan, Korea) reported on December 5 ahead of print in *Thyroid* on a study of the relationship between treatment of breast cancer and the development of new

diffuse thyroid ^{18}F -FDG uptake on PET. The retrospective study looked at a large PET/CT database to identify 290 women who had undergone PET/CT imaging before and after surgery for breast cancer. Those with histories of thyroid disorders and/or thyroid cancers were excluded, to yield a study group of 246 women, of whom 62 had available antithyroid antibody tests before surgery, of which 27 were positive. Data from these women were not excluded from the study. Analysis of results indicated that diffuse thyroidal uptake of tracer on PET/CT was seen to develop in 23 (9.3%) women over a median follow-up period of 21.1 mo. Factors found to be independently associated with increased uptake were age less than 55 y, bilateral breast cancer, and postsurgical radiation therapy. All patients with thyroid tracer uptake met at least 1 of several criteria related to chronic thyroiditis (positive for antithyroid antibodies, cytology findings or ultrasonography findings of Hashimoto's thyroiditis) and were statistically associated with development of hypothyroidism (52.2% and 4.5% in patients with and without uptake, respectively). The authors concluded that “radiotherapy in breast cancer may be an independent predictive factor for the development of new diffuse thyroidal uptake in PET-CT associated with thyroid dysfunction during follow-up” and that the development of diffuse ^{18}F -FDG uptake is a marker for thyroid abnormalities. They cautioned that “younger women who have radiotherapy after surgery for breast cancer, in particular, are candidates for close follow-up of their thyroid function.”

Thyroid

False-Negative ^{123}I -MIBG SPECT

In an article e-published on December 14 ahead of print in *Endocrine-Related Cancer*, Fonte et al. from the National Institute of Child Health and Human Development

(Bethesda, MD) described the characteristics and outcomes of patients with proven pheochromocytoma or paraganglioma who had false-negative ^{123}I -MIBG SPECT findings. The study included 21 such patients (7 males, 14 females; ages 13–55 y, median age 41.4 y). Patients were classified as nonmetastatic or metastatic by disease stage at the time of false-negative SPECT imaging. Additional data considered included location and size of tumors, laboratory values, genetic mutations, and outcomes (occurrence and progression of metastasis and death). Thirteen patients were evaluated for metastatic tumors and 8 for nonmetastatic disease. SDHB gene mutations (associated with familial pheochromocytoma and paraganglioma) were present in 11 patients (52%), RET gain of function mutations (associated with a variety of human cancers, including pheochromocytoma) were present in 1 patient (4%), and the remaining cases were apparently sporadic. On initial presentation, only 5 patients (24%) had confirmed metastatic disease. Fourteen of the 21 patients were followed for a period of 3–7 y. Of these, 10 (71%) had metastatic disease and most had SDHB mutations. At the time of the report's preparation, 9 patients in the follow-up group were alive and 5 had died as the result of metastatic disease. The authors concluded that "false-negative ^{123}I -MIBG SPECT is frequently related to metastatic tumors and usually due to SDHB mutations with unfavorable prognosis" and recommended that patients with false-negative ^{123}I -MIBG SPECT findings "be tested for SDHB mutations and undergo more regular and close follow-up."

Endocrine-Related Cancer

SPECT/CT and Lymphatic Drainage

Uren et al. from the RPAH Medical Centre and the University of Sydney (both in Sydney, Australia) reported on December 5 ahead of print in *Breast* on a study using SPECT/CT to provide precise anatomical location of sentinel lymph nodes in breast cancer during preoperative lymphoscintigraphy and to

enhance understanding of lymphatic drainage of the breast. The report is derived from the authors' experience with SPECT/CT in a series of 741 patients in whom level 1 axillary nodes were defined as anterior, mid, or posterior and correlated with anatomical location of the primary cancers. A sentinel lymph node was found in the axilla in 97.8% of patients in the study. Slightly less than 50% of these sentinel nodes were in the mid or posterior group of level 1 axillary nodes. An SLN was identified in a single node field in 460 patients, 2 node fields in 261, 3 node fields in 6, and 4 node fields in 1 patient. The authors concluded that these data disprove the previously held view that axillary lymphatic drainage from the breast is exclusively to the anterior (or anteroposterior) group of level 1 nodes. Instead, SPECT/CT indicates that this drainage occurs "to the mid axilla and/or posterior group in about 50% of patients with breast cancer regardless of the location of the cancer in the breast."

Breast

PET/CT and Occult H&N Cancers

In an article e-published on December 17 ahead of print in *Clinical Oncology (Royal College of Radiologists)*, Wong et al. from the Mount Vernon Hospital (Northwood, UK) reported on a study designed to assess the value of ^{18}F -FDG PET/CT in patients with squamous cell and undifferentiated cancer neck nodes but with no primary site on conventional assessment. The study included 78 patients with neck nodal metastases from an unknown primary cancer, each of whom underwent PET/CT imaging. Tracer uptake indicating an occult primary cancer was identified in 46 (59%) patients. Primary sites were later confirmed in the base of the tongue in 14 patients, pharyngeal palatine tonsil in 14, postcricoid in 1, and lung in 1 patient. PET/CT correctly diagnosed primary cancers in 30 (38.5%) patients, with sensitivity, specificity, and positive and negative predictive values of 100%, 66.7%, 65.2%, and 100%, respectively. PET/CT also detected contralateral nodal disease in 2 patients, mediastinal

nodal disease in 1, and liver metastases in 1 patient. The authors concluded that although ^{18}F -FDG PET/CT has value in assessing patients with occult head and neck primary cancers, false-positive results are a limitation with this approach.

Clinical Oncology (Royal College of Radiologists)

Exposure in Low-Dose PET/CT

Willowson et al. from the University of Sydney (Australia) reported on December 10 ahead of print in *Australasian Physical & Engineering Sciences in Medicine* on a retrospective evaluation of radiation dose associated with low-dose ^{18}F -FDG protocols in whole-body PET/CT. The records of 483 patient studies performed on a Siemens Biograph mCT were reviewed. The CT dose-length product was used to estimate radiation dose to each patient from the whole-body CT component of the hybrid study. The net injected tracer dose was used to calculate the whole-body effective dose by International Commission on Radiological Protection (ICRP) standards. Patient body weights were also used in calculations for individual dose. The calculated PET and CT exposures were combined to yield a total effective dose. For a CT protocol of 120 kVp and effective tube current-time product of 80 mAs with automatic exposure control, the mean effective dose was calculated to be 8.2 mSv (range, 3.4–23.4 mSv). For an average injected ^{18}F -FDG activity of 304 MBq, the mean PET effective dose was calculated to be 6.3 mSv when using the ICRP standard models, but was reduced to 6.0 mSv when effective doses were scaled to individual patient weights or patient blood volumes. The average total effective dose of the combined PET/CT scan across all patients was ~14.5 mSv (9.6–29.8 mSv). The authors concluded that if, as these data indicate, low-dose protocols for whole-body PET/CT scanning result in an effective radiation dose to the patient of approximately 14.5 mSv, then "additional reductions through the use of

iterative CT reconstruction and optimized low-dose FDG protocols could see total effective doses for whole-body PET/CT fall to below 10 mSv.”

Australasian Physical & Engineering Sciences in Medicine

SPECT and Multivessel CAD

In an article e-published on December 15 ahead of print in *Circulation Journal*, Hida et al. from Tokyo Medical University (Japan) compared the diagnostic significance of post-stress myocardial stunning with that of transient ischemic dilation (TID) of the left ventricle for detection of multivessel coronary artery disease. The study included 271 patients with suspected or known coronary artery disease, each of whom underwent adenosine triphosphate (ATP) loading and at-rest gated SPECT imaging. Myocardial perfusion was evaluated with a 20-segment model, and changes in left ventricular volume induced by ATP and an automatically derived TID ratio were analyzed. The incidence of multiterritorial ischemia was higher and post-ATP increases in end-systolic volume were greater in the 147 patients with multivessel coronary artery disease than in the 124 patients with insignificant or single-vessel disease. Analysis of receiver operating characteristic curves indicated cutoff values for end-systolic volumes of 5 mL and a TID ratio of 1.11. Additional statistical analyses showed that a combination of a poststress increase in end-systolic volume of ≥ 5 mL and multiterritorial ischemia best identified multivessel coronary artery disease, with a sensitivity of 78% and a specificity of 84%. The TID ratio did not prove to be an independent predictor. The authors concluded that “post-ATP stress myocardial stunning is superior to the TID ratio for detecting multivessel CAD.”

Circulation Journal

ApoE and Effects of A β on Cognition

Kantarci et al. from the Mayo Clinic (Rochester, MN) reported on

December 21 ahead of print in *Neurology* on a study designed to determine the relationship between β -amyloid (A β) load as measured by ^{11}C -Pittsburgh compound B (PiB) PET and cognitive function in cognitively normal older adults. The study included 408 such adults who underwent PiB PET and neuropsychometric testing within a 6-mo period. Higher PiB retention was found to be negatively associated with cognitive performance, specifically with memory, language, attention/executive function, and visual-spatial processing domains across the entire group of participants. Linear regression analyses showed that the association between PiB retention and cognition was modified by apolipoprotein E (ApoE) status, even after controlling for differences in the distribution of PiB values among ApoE $\epsilon 4$ allele carriers and noncarriers. Decrements in cognitive performance were associated with A β deposition in the frontal, temporal, and parietal lobe association cortices in ApoE $\epsilon 4$ carriers. These results suggested a modest association between tracer retention and cognitive function in cognitively normal older adults and that this relationship between A β load and cognitive function is modified by ApoE status. The authors concluded that “whereas A β load is associated with greater cognitive impairment in ApoE $\epsilon 4$ carriers, the cognitive function in ApoE $\epsilon 4$ noncarriers is influenced less by the A β load, suggesting that ApoE isoforms modulate the harmful effects of A β on cognitive function.”

Neurology

PET/CT vs CT in Lung Cancer

In an article e-published on December 17 ahead of print in *Clinical Lung Cancer*, Peng et al. from Shandong University (Jinan, China) reported on a study comparing the diagnostic abilities of integrated ^{11}C -choline PET/CT and contrast-enhanced helical CT in pulmonary lesions and locoregional lymph node metastases in patients with lung cancer. The study included 108 patients with proven or suspected lung cancer, each of whom underwent both

^{11}C -choline PET/CT and contrast-enhanced CT, followed by surgery and nodal staging. Pathologic analyses showed benign lesions in 26 patients and lung cancers in 82 patients (39 with adenocarcinoma, 23 with squamous cell carcinoma, 7 with carcinoid, 5 with small-cell lung cancer, 5 with adenosquamous carcinoma, and 3 with large-cell lung cancer). The accuracy, sensitivity, and specificity of PET/CT for diagnosing lung cancer were 82.4%, 85.4%, and 73.1%, respectively, whereas comparable figures for CT were 73.1%, 76.8%, and 61.5%, respectively. Additional analyses led to the conclusion that despite an advantage for PET/CT, differences between ^{11}C -choline PET/CT and CT in diagnosing lung cancer were not statistically significant. However, when preoperative nodal staging was compared with postoperative histopathologic staging, PET/CT correctly staged 80.5% of patients, 12.2% were overstaged, and 7.3% were understaged. Corresponding values for CT were 58.5%, 24.4%, and 17.1%, respectively. The accuracy, sensitivity, specificity, and positive and negative predictive values for PET/CT in lymph nodes were 83.8%, 82.4%, 84.1%, 50.3%, and 96.1%, respectively. Comparable figures for CT were 69.3%, 63.7%, 71.2%, 30.2%, and 91.0%, respectively. These differences were statistically significant and suggest an advantage for ^{11}C -choline PET/CT over enhanced CT in evaluation of locoregional lymph nodes.

Clinical Lung Cancer

ApoE $\epsilon 4$ and the Reserve Hypothesis

Garibotto et al. from San Raffaele Scientific Institute (Milan, Italy) reported on December 16 ahead of print in *Neurological Sciences* on a study of the relationship between the apolipoprotein E (ApoE) $\epsilon 4$ allele and the “reserve hypothesis,” which holds that high educational/occupational attainment can modulate Alzheimer disease clinical status. This multicenter study looked at the metabolic correlates of reserve and ApoE genotype in 51 individuals with early

probable Alzheimer disease (27 ϵ 4 carriers, 24 noncarriers). All participants underwent PET brain imaging. Brain glucose metabolism results were correlated with both educational and occupational levels, controlling for age and gender and for cognitive performance. The authors found an inverse correlation between education/occupational levels and metabolism in the posterior cingulate cortex and precuneus in both ApoE ϵ 4 carriers and noncarriers, with no significant differences between the groups. The authors concluded that “education and occupation act as proxies for reserve in ϵ 4 carriers, compensating for an unfavorable genetic background” and that “the degree of compensation does not differ significantly by ApoE ϵ 4 status.”

Neurological Sciences

^{18}F -FLT PET and Proliferating Cells

Zhang and a consortium of researchers from Pfizer, Inc. laboratories and academic centers reported on December 14 ahead of print in *Clinical Cancer Research* on a study designed to validate the use of ^{18}F -FLT-PET imaging for measuring xenograft proliferation and subsequent monitoring of targeted therapy. The authors evaluated factors, including nucleoside transporters, thymidine kinase 1, the relative contribution of DNA salvage pathways, and the ratio of FLT to thymidine, that could affect results of ^{18}F -FLT PET imaging in a panel of proliferating xenografts. In exponentially growing xenografts, neither ^{18}F -FLT nor ^3H -thymidine uptake reflected tumor growth rate across different tumor types, despite high expressions of Ki67 (a nuclear protein marker for proliferation) and thymidine kinase 1. Thymidine levels in different tumor types appeared to be variable and showed an inverse rela-

tionship with FLT tracer avidity. In FLT tracer-avid models, results indicated that ^{18}F -FLT PET imaging can be a surrogate biomarker predicting the therapeutic response of CDK4/6 inhibitor PD-0332991. The authors concluded that “tumor thymidine level is one of the factors that impact the correlation between ^{18}F -FLT uptake and tumor cell proliferation” and that “with careful validation, ^{18}F -FLT PET imaging can be used to monitor antiproliferative therapies in tracer-avid malignancies.”

Clinical Cancer Research

PET in DLBCL Treatment

In an article e-published on December 12 ahead of print in the *Journal of Clinical Oncology*, Safar et al. from the Centre François Baclesse (Caen, France) and the Centre Henri Becquerel (Rouen, France) reported on a retrospective investigation of the prognostic value of ^{18}F -FDG PET in patients with diffuse large B-cell lymphoma undergoing chemotherapy with rituximab. The study included 112 newly diagnosed patients who were being treated with an anthracycline-based regimen and rituximab. Each participant underwent ^{18}F -FDG PET imaging after 2 cycles of treatment. Progression-free and overall survival were the study's endpoints. Visual analysis determined that 70 patients (62.5%) had negative PET scans. Subsequent follow-up showed that 3-y progression-free and overall survival rates were 84% and 88%, respectively, in those with PET-negative results. Comparable figures were 47% and 62%, respectively, in those with PET-positive results. Data were reanalyzed using a quantitative (rather than visual) approach in 85 patients, using an interim PET and a cut-off based on $>66\%$ change in maximum standardized uptake value. Using this approach, the 3-y progression free survival was

77% for patients with PET-negative results and 37.5% for those with PET-positive results. The authors concluded that “an early PET scan after 2 cycles of treatment can effectively predict the outcome in patients with diffuse large B-cell lymphoma treated with rituximab and anthracycline-based chemotherapy by using either a visual or quantitative approach.”

Journal of Clinical Oncology

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in late November and December. In an article e-published on December 21 ahead of print in *Neurology*, Buchman and Bennett from the Rush University Medical Center (Chicago, IL) reported on “Amyloid pathology in persons with ‘normal’ cognition.” In the November 30 issue of *Cancer Imaging* (2011;11:195–201), Kaira et al. from the Shizuoka Cancer Center and the Gunma University Graduate School of Medicine (both in Japan) described “The role of ^{18}F -fluorodeoxyglucose positron emission tomography in thymic epithelial tumors.” Lee et al. from the Korea Institute of Science and Technology (Seoul, Republic of Korea) provided an overview of “Multifunctional nanoparticles for multimodal imaging and theragnosis” on December 21 ahead of print in *Chemical Society Reviews*. Rasmussen and colleagues from the University of Texas Health Science Center (Houston) reported on December 3 ahead of print in *Annals of Biomedical Engineering* on “The role of lymphatics in cancer as assessed by near-infrared fluorescence imaging.”