



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. Although the boundaries of “molecular imaging” remain to be clearly defined, this area of crucial importance to bench-to-bedside efforts in our field is now prominent across the spectrum of scientific publications. Beginning with this issue of *Newsline*, we will be adding highlighted articles on molecular imaging to our monthly selection of briefs. All of the 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.

Molecular Imaging

Differentiating MCI from Alzheimer's

Small et al. from the David Geffen School of Medicine at the University of California, Los Angeles, reported in the December 21 issue of the *New England Journal of Medicine* (2006;355:2652–2663) on a study investigating the utility of FDNNP PET imaging of amyloid senile plaques and tau neurofibrillary tangles in the brains of individuals with mild cognitive impairment (MCI) and Alzheimer's disease (AD). The results of the study were reported in news media around the world, with interest focusing on the ability to provide useful diagnostic information in individuals at risk of developing AD. The study included 83 volunteers with self-reported memory problems who underwent neurologic studies, psychiatric evaluation, and both FDNNP PET and ^{18}F -FDG imaging. Seventy-two individuals also underwent MR imaging. Cognitive testing divided the study group into

25 individuals with AD, 28 with MCI, and 30 with no cognitive impairment. The authors found that global values for FDDNP binding on PET were lower in the control group than in the group with MCI, and lower in the MCI group than in the AD group. FDDNP PET binding values were more successful in differentiating among the diagnostic groups than was metabolism as demonstrated on ^{18}F -FDG PET or volume on MR imaging. They concluded that “FDDNP PET scanning can differentiate persons with MCI from those with AD and those with no cognitive impairment.” In addition, they noted that the technique is potentially useful as a noninvasive method for determining regional cerebral patterns of amyloid plaques and tau neurofibrillary tangles and shows promise in the development of surrogate markers for drug discovery and diagnostics.

New England Journal of Medicine

Multiple Cardiovascular Event Biomarkers Explored

In the same issue of the *New England Journal of Medicine* (2006;355:2631–2639), researchers from the Framingham Heart Study reported on the utility of assessments of 10 biomarkers from distinct biologic pathways in predicting first major cardiovascular events and death. Wang et al. studied levels of these biomarkers during routine screening in 3,209 participants in the Framingham study. Over a median follow-up period of 7 years, 207 participants died and 169 experienced a first major cardiovascular event. Adjusting for conventional risk factors, the authors found that B-type natriuretic peptide level, C-reactive protein level, urinary albumin-to-creatinine ratio, homocysteine level, and renin level most strongly predicted cardiovascular events. However, when combined as “multimarker” scores,

these biomarkers contributed only moderately to standard risk factor assessments in these individuals. Invited commentary in the same issue of the journal (2006;355:2615–2617) emphasized the limitations of conventional risk factors in predicting cardiovascular events and the need to continue exploration of valid biomarkers and combinations of markers in cardiovascular disease.

New England Journal of Medicine

PET and Pancreatic Islet Graft Survival

Kim et al. from the University of British Columbia (Vancouver) and other institutions reported in the December issue of *Nature Medicine* (2006;12:1423–1428) on quantitative microPET imaging for in vivo determination of pancreatic islet graft survival. The study was designed as a step in identifying a sensitive and effective method for monitoring loss of transplanted islets, an essential element in the introduction of routine clinical use of islet transplantation in treating type-1 diabetes. The study used ^{18}F -FHBG PET to assess islet graft survival for 1 month after transplantation in nonobese diabetic mice, with the strength of the PET signal reflecting the insulin secretory capacity of the transplanted islets. Expression of the gene-encoding viral interleukin-10 was measurable in real time with PET, and the authors succeeded in visualizing transplanted islets in the liver (the preferred site for clinical transplantation). They concluded that “quantitative in vivo PET imaging is a valid method for facilitating the development of protocols for prolonging islet survival, with the potential for tracking human transplants.”

Nature Medicine

PET as Early Predictor of Chemotherapy Response

In a study published in the December 1 issue of *Cancer* (2006;107:

2678–2687), Kostakoglu et al. from the Mount Sinai School of Medicine (New York, NY) reported on a study to determine the predictive value of ^{18}F -FDG PET after a single cycle of chemotherapy as an early response indicator for progression-free survival in diffuse large cell lymphoma (DLCL) and classic Hodgkin's disease (HD). The study included 47 patients who underwent PET imaging after 1 cycle and after completion of chemotherapy. Patients were followed up for a median of 21 months. The authors found that all patients whose PET results were negative after a single chemotherapy cycle experienced sustained complete remission at a median follow-up of 28 months. Of the 16 patients with positive results after 1 chemotherapy cycle, 14 had refractory or relapsed disease with a median progression-free survival of 5.5 months. They concluded that these results indicated that ^{18}F -FDG PET after 1 cycle of chemotherapy provides significant information and "can be a valid alternative for posttreatment evaluation of DLCL and HD and may offer the potential for change in treatment paradigms."

Cancer

PET/CT in Suspected Breast Cancer Recurrence

In the same issue of *Cancer* (2006;107:2545–2551), Radan et al. from the Rambam Health Care Campus (Haifa, Israel) reported on the role of ^{18}F -FDG PET/CT in suspected recurrence of breast cancer. The study included 46 women (ages, 32–79 years) with a history of breast cancer (1–21 years in the past) who presented with elevated serum tumor markers. All patients underwent ^{18}F -FDG PET/CT imaging, the results of which were compared with information from pathology, additional imaging, and follow-up. Tumor recurrence was determined by these aggregate methods in 30 (65%) patients, with no evidence of disease in 16 (35%) patients. PET/CT identified 31 patients with abnormal studies and 15 with normal studies (overall sensitivity, specificity, and

accuracy of 90%, 71%, and 83%, respectively). PET/CT was compared with imaging results in 37 patients who also underwent contrast-enhanced CT. PET/CT was found to have a higher sensitivity, specificity, and accuracy than CT (85% and 70%, 76% and 47%, and 81% and 59%, respectively). PET/CT had a significant effect on management in 24 (51%) patients, with chemotherapy or radiotherapy initiated in 16 patients, treatment modified in 2 patients, and 6 patients referred to biopsy and/or surgery. The authors concluded that the high performance indices of ^{18}F -FDG PET and its clear superiority to CT for diagnosis of tumor recurrence make it a promising adjunct to the management and routine clinical monitoring of women with histories of breast cancer.

Cancer

Neurohormonal Activation and LVEF in Myocardial Ischemia

Wermuth et al. from University Hospital (Basel, Switzerland) reported on December 18 ahead of print in the *International Journal of Cardiology* on a rest/exercise myocardial perfusion SPECT study on the relationship between neurohormonal activation (B-type natriuretic peptide [BNP]) and left ventricular ejection fraction (LVEF) in patients referred for suspected coronary artery disease. The study included 260 such patients referred for SPECT in whom both BNP levels and LVEF were measured. The median LVEF was found to be 57%, and the median BNP level was 53 pg/mL. Although LVEF and BNP levels showed a statistically significant but weak correlation, this correlation was higher in patients in whom myocardial scar was present. In addition, the correlation was moderate in male patients but nonexistent in women. The authors concluded that "neurohormonal and morphologic assessments provide different windows to the heart" and merit additional investigation.

International Journal of Cardiology

DNA Damage in ^{131}I Treatment

In a study published in the December issue of the *Journal of Molecular Endocrinology* (2006;37:527–532), Grzesiuk et al. from the University Medical School (Warsaw, Poland) reported on an investigation designed to evaluate DNA breaks in thyrocytes and peripheral blood lymphocytes in patients being treated for hyperthyroidism with ^{131}I . The study included a group of patients who underwent ^{131}I scintigraphy and comet assay before radioiodine treatment and at 12 and 54 days after treatment. The results showed a wide range in level of DNA damage among the patients. However, at the 54-day mark, the level of DNA damage in peripheral blood lymphocytes in all patients was similar and in some cases lower than that in controls. DNA damage in hot nodules persisted until the 54th day. The authors also noted more base damage to DNA in the lymphocytes and more single-strand breaks in the thyrocytes, which may indicate different mechanisms of DNA damage induction and/or repair.

Journal of Molecular Endocrinology

Diagnosis

Whole-Body PET/CT Colonography

In a well-publicized study appearing in the December 6 issue of the *Journal of the American Medical Association* (2006;296:2590–2600), Veit-Haibach et al. from University Hospital (Essen, Germany) reported on the staging accuracy of whole-body PET/CT colonography. The study included 47 patients with clinical findings and optical colonoscopy results that suggested primary colorectal cancer. Each patient underwent whole-body PET/CT colonography 1 day after colonoscopy, and patients were followed up for a mean of 447 days. Results of PET/CT colonography in correct classification of TNM stage were compared with results from CT + PET and CT alone. The patients were found to have a total of 50 lesions, in which TNM stage was correctly determined

for 37 with PET/CT colonography (74%), 32 with CT + PET (64%), and 26 (54%) with CT alone. PET/CT colonography was significantly more accurate in defining TNM stage than was optimized abdominal CT imaging, an advantage that derived mainly from more accurate definition of the T-stage. PET/CT colonography affected subsequent therapy decisions in 4 patients (9%) when compared with conventional staging (CT alone and colonoscopy). Based on the results of this preliminary study, which indicate that PET/CT colonography is at least equivalent to CT + PET for tumor staging in patients with colorectal cancer, the authors concluded that "PET/CT colonography in conjunction with optical colonoscopy may be a suitable concept of tumor staging for patients with colorectal cancer."

Journal of the American Medical Association

Management of Incidental PET/CT Findings

Wang et al. from the Sun Yat-sen University (Guangdong, People's Republic of China) reported on November 28 ahead of print in *Cancer* on the ways in which oncologists deal with focal ^{18}F -FDG abnormalities on PET/CT reported by imaging specialists to be unrelated to the referring indication. The study included PET imaging reports from a 12-month period from 1,727 consecutive patients referred mainly for thyroid imaging. Incidental ^{18}F -FDG abnormalities were classified according to the report conclusion and compared with frequency of follow-up by oncologists and final diagnosis. Incidental ^{18}F -FDG abnormalities were reported in 199 (12%) of the patients, including 181 in whom oncologists followed up on the findings. Of 59 cases in which a second malignancy was suspected on the basis of imaging, 34 (58%) were actively investigated, with 14 confirmed, 7 unexpected metastatic sites, and 10 other active pathologies. Only 1 cancer was subsequently detected in the 25 (42%) patients not actively investigated. Of 122 sites pre-

sumed to be benign, only 10 (8%) were actively investigated. Of these, 2 were malignant. The encouraging results of the study, at least in this medical setting, were that although incidental abnormalities were common, most were benign and appropriately categorized by experienced readers, providing useful information on which most oncologists followed through with diligence and beneficial results for patients.

Cancer

$^{99\text{m}}\text{Tc}$ -HL91 SPECT in NSCLC

In a study published in the December issue of the *American Journal of Clinical Oncology* (2006;29:628–633), Li et al. from the Shandong Tumor Hospital and Institute (Jinan, China) reported on serial $^{99\text{m}}\text{Tc}$ -HL91 SPECT hypoxia imaging to predict radiotherapy response and treatment outcomes in patients with non-small cell lung cancer (NSCLC). The study included 32 patients with pathologically proven NSCLC who underwent 3-dimensional conformal radiotherapy and serial SPECT scans 1 or 2 days before initiation of radiotherapy, during radiotherapy, and after completion of radiotherapy. Tumor-to-normal tissue radioactivity ratios on images at 4 hours after injection were shown to correlate well with tumor response and patient survival. The authors concluded that $^{99\text{m}}\text{Tc}$ -HL91 SPECT imaging identified hypoxia status and changes during radiotherapy and that these results "confirmed that hypoxia imaging with HL91 SPECT before radiotherapy may predict tumor response and patient survival."

American Journal of Clinical Oncology

SPECT and IMRT Dose

McGuire et al. from Duke University (Durham, NC) reported in the December 1 issue of the *International Journal of Radiation Oncology, Biology, and Physics* (2006;66:1543–1552) on a study designed to use SPECT maps of spatial distribution of lung perfusion

to divert radiation dose away from higher-functioning lung in intensity-modulated radiotherapy (IMRT) treatment planning. The study included 5 patients for whom IMRT treatment plans were generated with and without SPECT guidance. The healthy lung was segmented into 4 regions based on SPECT intensity, with dose sequentially allowed to the target via regions of increasing SPECT intensity. This process resulted in reduction of dose to functional lung. SPECT- and non-SPECT-guided plans were compared. In all cases, the SPECT-guided plan produced a more favorable dose-fraction histogram than the non-SPECT-guided plan. The area of high-functioning lung received significantly less radiation in the SPECT-guided plan. The authors concluded that "SPECT-guided IMRT shows potential for reducing the dose delivered to highly functional lung regions" and that "this dose reduction could reduce the number of high-grade pneumonitis cases that develop after radiation treatment and improve patient quality of life."

International Journal of Radiation Oncology, Biology, and Physics

Perfusion Imaging and Early Hospital Discharge

In the December 19 edition of the *Journal of the American College of Cardiology* (2006;48:2448–2457), Mahmarian et al. from the Methodist Hospital (Houston, TX) reported on a study to determine whether gated adenosine $^{99\text{m}}\text{Tc}$ -sestamibi SPECT could accurately define risk and guide therapeutic decision making in hospital discharge of stable patients after acute myocardial infarction (MI). The authors and participants are part of the multicenter INSPIRE (Adenosine Sestamibi Post-Infarction Evaluation) trial. The study enrolled 728 clinically stable survivors of acute MI who underwent SPECT imaging within 10 days of hospital admission and at subsequent 1-year follow-up. Patients were assigned to risk groups based on adenosine-induced left ventricular

perfusion defect size, extent of ischemia, and ejection fraction. Total cardiac events/death and reinfarction were significantly associated with escalating risk groups, from low (5.4%, 1.8%, respectively), to intermediate (14%, 9.2%, respectively), to high (18.6%, 11.6%, respectively) risk. Event rates at 1 year were lowest in patients with the smallest perfusion defects but progressively increased when defect size exceeded. The perfusion results improved risk stratification significantly beyond that provided by clinical variables and ejection fraction. The low-risk INSPIRE group (including more than one-third of all enrolled patients) had shorter hospital stays and lower associated costs compared with higher-risk groups. The authors concluded that gated adenosine ^{99m}Tc -sestamibi SPECT performed early after acute MI “can accurately identify a sizeable low-risk group who have a <2% death and reinfarction rate at 1 year” and that “identifying these low-risk patients for early hospital discharge may improve utilization of health care resources at considerable cost savings.”

Journal of the American College of Cardiology

MDCT Angiography vs Myocardial Perfusion Imaging in CAD

Also in the December 19 issue of the *Journal of the American College of Cardiology* (2006;48:2508–2514), Schuijff et al. from the Leiden University Medical Center (The Netherlands) reported on a comparison of multislice CT angiography and myocardial perfusion imaging (MPI) in patients with an intermediate likelihood of coronary artery disease (CAD) and on a comparison of these findings with those from invasive coronary angiography. The study included 114 patients, most with intermediate likelihood of CAD, who underwent both multislice CT angiography and MPI. CT images were classified as having no CAD, nonobstructive (<50% luminal narrowing) CAD, or obstructive CAD.

MPI studies were classified as showing normal or abnormal (reversible and/or fixed defects) results. A subset of 58 patients also underwent conventional invasive coronary angiography. On the basis of the CT data, 41 patients (36%) were classified as having no CAD, and 90% of these patients had normal MPI results. CT indicated a total of 33 patients (29%) with nonobstructive CAD, missing at least 1 significant lesion ($\geq 50\%$ luminal narrowing) identified by MPI in the remaining 40 patients (35%). Only 45% of patients with an abnormal CT had abnormal MPI results, with more than 50% of patients with obstructive CAD on CT having normal MPI results. The agreement between CT and invasive angiography was high. The authors concluded that although MPI and CT provide different and complementary information on CAD (ie, detection of atherosclerosis versus detection of ischemia, respectively), that multislice CT shows exceptional promise, especially when compared with the current gold standard of invasive angiography, in evaluating patients with an intermediate likelihood of CAD.

Journal of the American College of Cardiology

Therapy

^{90}Y Microspheres in Hepatocellular Carcinoma

Kulik et al. from the Northwestern Memorial Hospital (Chicago, IL) reported in the December 1 issue of the *Journal of Surgical Oncology* on experience with ^{90}Y microsphere treatment of unresectable hepatocellular cancer (HCC) with the specific intent of downstaging to resection, radiofrequency ablation (RFA), United Network for Organ Sharing (UNOS) stage T2, or liver transplantation. The study included 150 patients with unresectable HCC, including 34 classified as UNOS stage T3 at the time of microsphere treatment. These 34 patients were followed for toxicities; alterations in model for end-stage-liver

disease (MELD) score; tumor response; downstaging to RFA, resection, or transplantation; and survival. Nineteen (56%) were successfully downstaged from T3 to T2 after treatment; 11 (32%) were downstaged to target lesions <3.0 cm; and 23 (66%) were downstaged to either T2 status, lesion <3.0 cm (RFA candidate), or resection. Seventeen (50%) had an objective tumor response by WHO criteria, with 8 patients (23%) successfully downstaged to undergo orthotopic liver transplantation after treatment. The authors concluded that “these data suggest that intra-arterial ^{90}Y microspheres can be used as a bridge to transplantation, surgical resection, or RFA.”

Journal of Surgical Oncology

Peptide Receptor Therapy in Neuroendocrine Tumors

In a study published in the December issue of *Surgery* (2006;140:968–977), Frilling et al. from University Hospital (Essen, Germany) reported on experience with ^{90}Y - and ^{177}Lu -DOTATOC therapy in the management of metastatic somatostatin receptor-expressing neuroendocrine tumors (NETs). The study included 20 patients with metastatic nonresectable NETs (15, pancreas; 2, midgut; 1, gastrinoma; 1 paraganglioma; and 1 NET of unknown origin) who had undergone ^{111}In -DTPAOC or ^{68}Ga -DOTATOC PET/CT to determine suitability for treatment. All patients received ^{90}Y -DOTATOC as an initial treatment, with additional treatments in 8 patients who showed relapse. ^{177}Lu -DOTATOC was used for some of the subsequent treatments to avoid side effects. No serious adverse events were documented, although 8 patients showed moderate toxicity after ^{90}Y treatment. After restaging, 5 patients were in partial remission, 11 had stable disease, and tumor progression was noted in 4 patients. The authors concluded that “peptide receptor-targeted radionuclide therapy is a promising, safe, and feasible approach in the palliative therapy of patients with NET.”

Surgery