Each month the editor of Newsline selects articles on therapeutic, diagnostic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. Note that although we have divided the articles into therapeutic and diagnostic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with, therapies. 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.

Therapy

IMRT PET/CT Protocol to Boost Therapy

Researchers from the David Geffen School of Medicine at the University of California (Los Angeles, CA) reported in the November issue of the *Journal of Neurosurgery* (2004;101[suppl 3]:381–389) on a study designed to assess the feasibility of ^{18}F-FDG PET/CT targeting for a simultaneous boost for intensity modulated radiotherapy (IMRT) and radiosurgery. In a small group of patients with brain tumors, Solberg et al. selectively increased the radiation dose to tumor subregions shown by PET to be biologically active, while at the same time maintaining the overall clinically established target dose. PET/CT scans were first acquired so that tumor volume and objects at risk could be outlined, as well as PET-positive tumor subregions. In subsequent IMRT, standard doses were delivered to tumor volume and margins, with additional 10%–20% doses delivered to PET-positive subregions. Simultaneous integrated boost radiation was successfully delivered using this protocol, with excellent dose conformality in tumor volume, a documented increase in dose to PET-positive tumor subregions, and minimized doses to objects at risk. The study assessed the protocol only, and outcomes were not reported. The authors concluded that "when coupled with IMRT, PET/CT scanning allows dose escalation to biologically active subregions within the tumor volume." They added that "in extracranial sites, PET scanning should only be performed with a dedicated PET/CT device, because present image fusion technologies are inadequate for accurately registering deformable objects."

Journal of Neurosurgery

^{18}F-FMISO PET and Hypoxia in Tumors

Dubois et al. from the University Hospital Gasthuisberg (Leuven, Belgium) reported in the November 29 issue of the *British Journal of Cancer* (2004;91:1947–1954) on a study comparing ^{18}F-fluoromisonidazole (^{18}F-FMISO) uptake on PET with results of standard immunohistochemical (IHC) staining techniques in the evaluation of tumor hypoxia in a rat rhabdomyosarcoma model. Syngeneic rhabdomyosarcoma tumor pieces were transplanted subcutaneously in the flanks of WAG/Rij rats and at specific growth levels were imaged with ^{18}F-FMISO PET. Exogenous and endogenous markers of hypoxia (monoclonal antibodies to pimonidazole [PIMO] and carbonic anhydrase IX [CA IX], respectively) were used for IHC staining. The results indicated a statistically significant correlation between hypoxic volumes defined with PET and the volumes derived from both of the staining techniques. The authors concluded that "the relationship found between ^{18}F-FMISO PET and PIMO- and additionally CA IX-derived hypoxic volumes in rat rhabdomyosarcomas indicates the value of the noninvasive imaging method to measure hypoxia in whole tumors."

British Journal of Cancer

PET to Define RT Targets

In the November 15 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2004; 60:1272–1282), Black et al. from 21st Century Oncology, Inc. (Asheville, NC) reported on a series of phantom studies to determine an accurate and uniformly applicable method for using ^{18}F-FDG PET to define gross tumor volume (GTV) for radiotherapy (RT). The authors constructed a 9.0-L cylindrical tank with suspended glass spheres of varying diameters to simulate tumor volumes observed in patients with non–small cell lung cancer (NSCLC). Over several experimental set-ups, the spheres were filled with a variety of known concentrations of ^{18}F-FDG. The authors established a threshold, or unique cutoff of standardized uptake value (SUV) based on body weight for ^{18}F-FDG PET-based GTV definition and conducted a series of experiments to determine the degree to which variations in mean target SUVs, background ^{18}F-FDG concentrations, and target volumes influenced that GTV definition. Sphere images in each experiment were autocontoured (simulating a GTV) using the threshold SUV that yielded a volume matching that of the known sphere volume. In addition, a regressive function derived from the phantom results was constructed to represent the relationship between the threshold SUV and the mean target SUV, and this function was then

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applied to define the GTV in 15 patients with NSCLC. A strong linear relationship was identified between the threshold SUV and the mean target SUV. Background concentrations and target volumes were found to indirectly affect the threshold SUV because of their influence on the mean target SUV. Results of both the phantom experiments and applications in patients indicated that a much smaller deviation occurred when the threshold SUV regressive function was utilized to estimate the phantom volume than when the fixed image intensity threshold was used. This deviation was pronounced when applied to true patient GTV volumes, with a mean difference between the 2 methods of 67%. The authors concluded that "FDG PET-based GTV can be systematically defined using a threshold SUV according to the regressive function described" and that this "threshold SUV for defining the target is strongly dependent on the mean target SUV of the target and can be uniquely determined through the proposed iteration process."

International Journal of Radiation Oncology, Biology, Physics

^{153}Sm-EDTMP and Bone Pain

In an article in the November issue of the *Sao Paulo Medical Journal* (2004;122:208–212), Etchebehere et al. from the Universidade Estadual de Campinas (Sao Paulo, Brazil) reported on the use of ^{153}Sm-ethylenediaminetetramethylenephosphonate (^{153}Sm-EDTMP) for the treatment of bone pain secondary to metastases refractory to clinical management. ^{153}Sm-EDTMP is a short-range, β-emitting therapeutic radiopharmaceutical with avid skeletal uptake. The study included 58 patients (34 men, 24 women) with a range of cancers (31, prostate; 20, breast; 3, lung; 1 each with lung hemangioendothelioma, parathyroid adenocarcinoma, osteosarcoma, and unknown primary tumor). All patients had multiple bone metastases and underwent treatment with ^{153}Sm-EDTMP. Response to treatment was graded as good (pain reduction of 50%–100%), intermediate (25%–49%), or poor (0%–24%). All patients showed good uptake of tracer in the bone metastases, and no myelotoxicity was reported. More than 80% of patients with prostate cancer and 85% of patients with breast cancer reported intermediate or good responses. Patients with lung cancer showed poor response to treatment, and patients with lung hemangioendothelioma and unknown primary lesion showed intermediate response. Patients with osteosarcoma and parathyroid adenocarcinoma showed good response. The authors concluded that "treatment with ^{153}Sm-EDTMP can control the pain secondary to bone metastases effectively in most patients with breast and prostate cancer without significant side effects."

Sao Paulo Medical Journal

Diagnosis and Assessment

PET vs. CT in NSCLC Response After Therapy

In the December issue of *Annals of Thoracic Surgery* (2004;78:1903–1909), Cerfolio et al. from the University of Alabama at Birmingham and the Birmingham Veterans Affairs Medical Center compared the performance of ^{18}F-FDG PET and CT as predictors of pathologic response after neoadjuvant therapy in patients with non–small cell lung cancer (NSCLC). The authors correlated changes in standardized uptake values (SUV) measured on PET with pathologic changes in primary tumor in patients with NSCLC after chemotherapy. This retrospective study included a database of 56 patients with NSCLC who had undergone ^{18}F-FDG PET and chest CT imaging both before and after neoadjuvant therapy, followed by complete resection of their cancer. Maximum SUVs and tumor sizes were measured, and the percentage of change was compared with the percentage of nonviable tumor cells. The authors found that the change in the maximum SUVs had a nearly linear relationship to the percentage of nonviable tumor cells in the resected tumors. When the maximum SUV decreased by ≥80%, PET predicted complete pathologic response with a sensitivity of 90%, specificity of 100%, and accuracy of 96%, regardless of cell type or treatment variations. The authors concluded that ^{18}F-FDG PET imaging in these patients is a more accurate predictor than change of tumor size on CT imaging and that "these findings may help guide treatment strategies."

Annals of Thoracic Surgery

PET Measures Functional Differences in Healthy AD-Linked Gene Carriers

In a story carried internationally by the media in November, researchers from Columbia University (New York, NY) reported on results of a PET study indicating that individuals who carry a genetic variant linked to a heightened risk of Alzheimer disease (AD) process specific brain functions differently than do noncarriers, even when outward signs of disease are not present. The study by Scarmeas et al. appeared in the December issue of the *American Journal of Geriatric Psychiatry* (2004;12:596–605). The authors used $H_2^{15}O$ PET to investigate apolipoprotein E (ApoE)-mediated differential brain activitation in a group of 32 healthy elderly individuals, 4 of whom were and 26 of whom were not APOE ε4 allele carriers. Participants performed a serial shape-recognition memory task under 2 conditions: simple demand, in which a single shape was presented, and titrated demand, in which study list length was adjusted so that each individual recognized words at approximately 75% accuracy. Multiple-regression analyses of results were compared with results of PET imaging. Compared with noncarriers, ε4 carriers showed significantly decreased activation differences between tests in the left superior temporal, right superior frontal, left postcentral, left precuneus, and posterior cingulate

gyrus. The authors concluded that patterns of brain activation during a nonverbal memory task differed as a function of APOE genotype and, therefore, of genetic risk for AD. They noted that differences in activation did not reflect task difficulty but indicated memory-related altered cognitive processing. "Our results indicate that elderly persons with a genetic risk for AD have alterations in brain functioning even at a point in time when behavioral, cognitive or clinical evidence of the disease is absent," Scarmeas told Reuters news service. "It could be that the changes we saw in the way these carriers process memory tasks are evidence that these are people who are destined to get the disease, but we also know that not everyone who carries this genotype develops AD. It could be that the gene simply causes the brain to function differently but not in a way that necessarily does damage. So we can't say for sure that what we are observing is early evidence of AD." Scarmeas added that PET offers the possibility of answering these questions when imaging can be paired with tests that offer some biological evidence of disease.

American Journal of Geriatric Psychiatry

^{11}C-SB-13 PET in β-Amyloid Plaque Imaging

In a second report in the same issue of the *American Journal of Geriatric Psychiatry* (2004;12:584–595), Verhoeff et al. from the Baycrest Centre for Geriatric Care, the Centre for Addiction and Mental Health, and the University of Toronto (Canada) described the use of novel tracers for in vivo imaging of β-amyloid plaques in 6 healthy women and 5 women diagnosed with Alzheimer's disease (AD). Each participant underwent PET imaging with both ^{11}C-stilbene 13 (^{11}C-SB-13) and the ^{11}C benzothiazole ^{11}C-6-OH-BTA-1 (also known as ^{11}C-PIB). The authors found that the 2 tracers demonstrated similar binding properties with respect to regional distribution of retention (increased retention in the frontal and posterior temporal-inferior parietal association cortices in individuals with AD but not in healthy individuals). The authors concluded that ^{11}C-SB-13 is an effective PET tracer for fibrillar β-amyloid imaging in vivo and is similar in performance to ^{11}C-PIB. They outlined several additional avenues of research.

American Journal of Geriatric Psychiatry

^{11}C-TMSX PET and Brain Adenosine Receptors

Ishiwata et al. from the Tokyo Metropolitan Institute of Gerontology (Japan) will report in the February issue of *Synapse* (2005;55:133–136) on what they term the "first visualization of adenosine 2A receptors in the human brain" using [7-methyl-^{11}C]-E-8-3,4,5-trimethoxystyryl-1,3,7-trimethylxanthine (^{11}C-TMSX), a new PET radiologand. The authors compared ^{11}C-TMSX PET with measurement of adenosine 2A receptors and dopamine D2 receptors by [1-methyl-^{11}C]8-dicyclopropylmethyl-1-methyl-3-propylxanthine (^{11}C-MPDX) PET and ^{11}C-raclopride PET, respectively, in a healthy male volunteer. They found comparatively high baseline distribution volumes of ^{11}C-TMSX in the caudate nucleus, putamen, and thalamus and relatively low distribution volumes in the cortical regions. After infusion of theophylline, distribution volumes of ^{11}C-TMSX were slightly reduced in the caudate nucleus and putamen but not in the other regions with much lower levels of adenoside 2A receptors, demonstrating the adenoside binding power of ^{11}C-TMSX, a binding potential demonstrated by ^{11}C-raclopride only in the striatum. The authors concluded that in the absence of other appropriate radioligands, ^{11}C-TMSX is an applicable PET ligand for mapping adenosine 2A receptors in the caudate nucleus and putamen in clinical studies and "is of great interest for studying the pathophysiology of neurological and psychiatric disorders together" with the ^{11}C-raclopride PET for dopamine D2 receptor evaluation and/or the ^{11}C-MPDX PET for adenosine 1A receptors.

Synapse

PET in Drug-Induced Neurodegeneration

In a survey article published in the November issue of the *Annals of the New York Academy of Sciences* (204;1025:584–589), Weissman et al. from the Israel Institute for Biological Research (Ness Ziona) reported on the potential for PET imaging of peripheral benzodiazepine receptors as a method of monitoring drug-induced neurodegeneration. They noted that despite a wide array of methods designed to assess brain neuropathologies resulting from drugs of abuse, none have focused on assessing neuronal damage on the basis of reactive glial cells, which almost universally appear at the site of degeneration. Such cells are rich in benzodiadepine receptors compared with surrounding cells. Measurement of the binding of specific ligands to these receptors offers a unique indirect marker for reliable impairment estimation in the central nervous system and an indicator of the behavorial and cognitive deficits accompanying neuronal injury. They cited the availability of agents such as ^{11}C-PK-11195 for in vivo animal and human brain PET imaging of these receptors and noted the promise of this approach.

Annals of the New York Academy of Sciences

Estrogen Replacement and Dopamine Transporter Availability

The benefits and recently identified negative aspects of estrogen replacement therapy (ERT) have been the focus of much public and professional attention. In the November/December issue of the *American Journal of Geriatric Psychiatry*

(2004;12:621–630), Gardiner et al. from the University of Pennsylvania School of Medicine (Philadelphia) and a consortium of pharmaceutical companies reported on a pilot study to assess the effect of ERT on brain dopamine transporter availability in healthy postmenopausal women. The study included 13 such women who were administered ERT and underwent ^{99m}Tc-TRODAT-1 SPECT neuroimaging before therapy, then after 4 weeks of 0.625 mg/day of conjugated estrogens, and finally after an additional 2 weeks of 0.625 mg/day conjugated estrogens and 10 mg/day of medroxyprogesterone acetate. Specific uptake values were calculated for the caudate and putamen. The authors found that after 4 weeks of therapy, tracer binding exhibited a small but statistically significant increase in the left anterior putamen and, after the entire 6-week course of therapy, both the left and right anterior putamen showed an increase in uptake values. The authors concluded that short-term administration of ERT in postmenopausal women is associated with a modest increase in dopamine transporter availability in the putamen and that "these findings may further the understanding of how ERT is associated with improvement in Parkinson's disease and late-onset schizophrenia."

American Journal of Geriatric Psychiatry

PET in Staging and Prognosis in Hodgkin's Disease

Although ^{18}F-FDG PET has been shown to be effective in evaluating residual masses after treatment and in early diagnosis of relapse in patients with Hodgkins' disease (HD), it is not routinely used in initial staging. In a report published in the November issue of *Annals of Oncology* (2004;15:1699–1704), Munker et al. from the Louisiana State University Health Sciences Center (Shreveport) reported on a multicenter study of the effectiveness of ^{18}F-FDG PET in staging and prognosis in patients with newly diagnosed HD. The study included 73 such patients who were staged with conventional methods and whole-body PET imaging, with a median follow-up time of 25 months (range, 1 month–5 years). The response to treatment was determined by standard clinical and diagnostic criteria. Twenty-one patients (28.8%) were assigned a higher stage by PET than by conventional methods, and 2 patients (2.7%) were assigned a lower stage by PET. Of the 12 patients designated as stage 1 by conventional methods, 7 were upstaged by PET (4 to stage 2, 1 to stage 3, and 2 to stage 4). Of 12 patients in stage 3 by conventional methods, 6 were upstaged to stage 4 by PET. Results at follow-up indicated that upstaging by PET may represent a risk factor for a more advanced stage or a biologically more aggressive tumor. The authors concluded that "patients with early-stage disease as identified by conventional methods have a significant risk of treatment failure if a more advanced stage is indicated by PET" and that, at present, "major stage changes suggested by PET imaging should be confirmed by an independent diagnostic method."

Annals of Oncology

PET/CT vs. PET and CT in Tumor Staging

Antoch et al. from the University Hospital Essen (Germany) reported in the November issue of the *Journal of Clinical Oncology* (2004;22:4357–4368) on a retrospective study designed to compare the accuracy of PET/CT, PET images alone, CT images alone, and PET and CT viewed side by side in staging solid tumors. The study included 260 patients with solid tumors and various oncologic diagnoses who had previously been staged according to the TNM standard. Histopathology and a clinical follow-up at 311 (±125) days served as standards of reference. PET/CT was found to be significantly more accurate in assessing TNM stage than CT alone, PET alone, or side-by-side PET and CT. Combined PET/CT changed the treatment plan in 16, 39, and 43 patients when compared with side-by-side PET and CT, CT alone, and PET alone, respectively. The authors concluded that "tumor staging with PET/CT is significantly more accurate than CT alone, PET alone, and side-by-side PET + CT" and that "this diagnostic advantage translates into treatment plan changes in a substantial number of patients."

Journal of Clinical Oncology

^{18}F-FDG Uptake and HK1 Expression in Primary Tumor

In an article e-published on October 27 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Hooft et al. from the VU University Medical Center (Amsterdam, The Netherlands), reported on a study comparing ^{18}F-FDG uptake in vivo in patients with suspected recurrence of differentiated thyroid cancer with biomarkers expected to be involved in the underlying biologic mechanisms. The study included 19 patients with recurrent differentiated thyroid cancer who underwent ^{18}F-FDG PET imaging before surgery. Tracer uptake was compared with histologic and immunohistochemical features in specimens of both recurrent and primary tumor. They found that in 13 of the 19 pages, recurrences were positive on PET and that ^{18}F-FDG uptake was associated with expression of hexokinase type 1 (HK1). All lesions with HK1 overexpression were positive on PET. The authors concluded that "in suspected recurrent thyroid cancer, stratification for ^{18}F-FDG PET may benefit from pretest immunohistochemical analysis of HK1 of the primary tumor, as HK1 negativity indicates a low likelihood of PET positivity."

Journal of Clinical Endocrinology and Metabolism

^{201}Tl and Pentavalent DMSA in Staging Cartilaginous Tumors

Choong et al. from the University of Melbourne and St. Vincent's Hospital (Melbourne, Australia) reported in the November 8 issue of *International Seminars in Surgical Oncology* (2004;1:10) on a study examining correlations between uptake of 2 radionuclides and malignancy grade in cartilaginous tumors. The study included 92 patients with cartilaginous tumors (50 benign, 42 nonmetastatic malignant) who underwent nuclear scanning first with ^{201}Tl and 48 hours later with pentavalent dimercaptosuccinic acid (DMSAV). Static and SPECT images were obtained at 30 minutes and 4 hours after injection of each tracer. Results of the scans and measurements of uptake at 4 hours were compared with histologic results. Twenty-five patients with negative DMSAV imaging had benign tumours. Fifteen of seventeen tumors positive on ^{201}Tl were malignant. Eleven of thirteen patients with both positive DMSAV and ^{201}Tl scans had intermediate- or high-grade tumors, and 4 of these developed metastases. The authors discussed the development of an algorithm for management of patients with tumors that aims to avoid overtreatment of low-grade tumors and undertreatment of high-grade tumors. They concluded that "functional nuclear scanning with ^{201}Tl and DMSAV complements other imaging modalities in the management of cartilaginous tumors."

International Seminars in Surgical Oncology

Additional Value of PET in Initial Staging of Esophageal Carcinoma

In a study e-published on November 22 ahead of print in *Cancer*, Kato et al. from the Gunma University School of Medicine (Maebashi, Japan) assessed whether ^{18}F-FDG PET provided additional information to standard diagnostic CT imaging in lymph node involvement or distant metastases in 149 patients with esophageal carcinoma. Of the patients in the study, 81 underwent radical esophagectomy without pretreatment, 17 received chemoradiotherapy and surgery, 3 underwent endoscopic mucosal resection, and the remaining 48 patients received radiotherapy and chemotherapy. All patients underwent ^{18}F-FDG PET and CT imaging at the time of diagnosis. PET visualized the primary tumor in only 80% of patients, but had 32% sensitivity, 99% specificity, and 93% accuracy for individual lymph node group evaluation and 55% sensitivity, 90% specificity, and 72% accuracy for lymph node staging evaluation. PET provided additional information on lymph node status in 14 of 98 patients who underwent surgery: 6 patients with negative CT findings were found to have lymph node metastases on the basis of positive PET findings; 6 patients with positive CT findings were deemed on the basis of negative PET findings not to have such metastases; and 2 patients were shown on PET to have cervical lymph node metastases in addition to other metastases identified on PET. Among the remaining patients, PET showed incremental value over CT with regard to distant organ metastases in 6 patients. The authors concluded that the incremental benefits of ^{18}F-FDG PET were significant and that, "at present, combined PET/CT may be the most effective method available for the preoperative staging of esophageal tumors."

Cancer

PET in Extrahepatic Metastases

Sugiyama et al. from the Hamamatsu University School of Medicine (Japan) reported in the October issue of the *Journal of Gastroenterology* (2004;39: 961–968) on a study designed to assess the effectiveness of ^{18}F-FDG PET in detecting distant metastases from hepatocellular carcinoma (HCC). The study included 19 patients with suspected extrahepatic HCC. All patients underwent conventional imaging and laboratory studies, which showed extrahepatic lesions in 14 patients (group A) and no extra- or intrahepatic lesions in the remaining 5 patients (although tumor marker levels were elevated). All patients underwent ^{18}F-FDG PET imaging, which detected 24 of 29 (83%) extrahepatic metastases larger than 1 cm and 1 of 8 (13%) smaller lesions. PET identified 2 bone metastases not indicated on previous bone scans and nodal metastasis and intestinal metastases that had been inconclusive on CT. PET findings led to resection of extrahepatic lesions in 5 patients in group A. Although PET accurately indicated that there were no extrahepatic lesions in any patient in group B, intrahepatic HCCs were detected within 4 months in 4 patients. The authors concluded that "^{18}F-FDG PET could provide additional information and contribute to the management of HCC patients suspected of having extrahepatic metastases."

Journal of Gastroenterology