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. Also highlighted are articles on molecular imaging that fall outside the traditional boundaries of nuclear medicine and cover advances that promise to speed basic research to clinical applications across a spectrum of medical disciplines.

THERAPY

RIT in Older Adults

In an article e-published on February 20 ahead of print in the *Journal of Clinical Oncology*, Gopal et al. from the University of Washington and the Fred Hutchinson Cancer Research Center (Seattle) and the Pacific Northwest National Laboratory (Richland, WA) reported on the results of a study of high-dose ^{131}I-tositumomab radioimmunotherapy (RIT) and autologous hematopoietic stem cell transplantation in older adults with relapsed or refractory B-cell lymphoma. The study included 24 patients with relapsed B-cell non-Hodgkin's lymphoma (NHL) and a median age of 64 years (range, 60–76 years). These patients had received a median of 4 previous chemotherapy regimens, and 13 had chemotherapy resistant disease. Each patient received initial ^{131}I-labeled tositumomab anti-CD20 antibody for dosimetry, with individualized therapeutic infusions of ^{131}I-tositumomab (12.1–42.7 GBq) 10 days later. Patients were followed for a median of 2.9 years, with estimated 3-year overall and progression-free survival rates of 59% and 51%, respectively. Only 2 patients experienced grade 4 nonhematologic toxicity. The authors concluded that "myeloablative RIT and autologous stem cell transplantation is a safe and effective therapeutic option for older adults with relapsed B-NHL," noting that this group is currently undertreated with RIT because of concerns about associated morbidity.

Journal of Clinical Oncology

PET/CT and Target Volume in Rectal Cancer

Patel et al. from the Stanford University School of Medicine (CA) reported in the February issue of *Technology in Cancer Research and Treatment* (2007;6:31–36) on a study designed to determine the effect of PET/CT on interobserver variability in target volume delineation in rectal cancer and to compare the concordance of ^{18}F-FDG and ^{18}F-fluorodeoxythymidine (^{18}F-FLT) with CT results. The study included 6 patients with locally advanced rectal cancer scheduled for a regimen of preoperative chemoradiotherapy who underwent ^{18}F-FDG and ^{18}F-FLT PET and CT studies in the treatment position. Each of 4 radiation oncologists first delineated primary and nodal gross tumor volumes for a hypothetical boost treatment based on each of the 2 types of PET studies. Contours were then defined based on CT alone with observers blinded to the PET images, and again based on combined PET/CT. When interobserver similarity indices were calculated, the authors found little difference in ^{18}F-FDG and ^{18}F-FLT but that target volumes based on combined PET/CT resulted in lower interobserver variability than CT alone, particularly for nodal disease. The authors noted additional potential advantages of a hybrid imaging approach in target volume planning for radiation therapy in patients with rectal cancer.

Technology in Cancer Research and Treatment

Antithyroid Drugs and ^{131}I Treatment

In an article e-published on February 20 ahead of print in the *British Medical Journal*, Walter et al. from the University Hospital Basel (Switzerland) provided a systematic review and meta-analysis of clinical trials studying the effects of adjunctive antithyroid drugs on radioiodine treatment, with a special focus on the risks of treatment failure, hypothyroidism, and adverse effects. For the meta-analysis, the authors identified 14 relevant randomized controlled trials with a total of 1,306 individuals enrolled. They found that adjunctive antithyroid medication was associated with an increased risk of treatment failure but a reduced risk for hypothyroidism after ^{131}I treatment. They found no significant differences among different antithyroid medications and no difference in results when these drugs were administered before or after ^{131}I treatment. The aggregate results led the authors to conclude that "antithyroid drugs potentially increase rates of failure and reduce rates of hypothyroidism if they are given in the week before or after radioiodine treatment, respectively."

British Medical Journal

Radioguided Surgery for ^{131}I-Negative Thyroid Cancer

Rubello et al. from the S. Maria della Misericordia Rovigo Hospital (Italy) reported on January 29 ahead of print in the *European Journal of Surgical Oncology* on their experience in a series of patients with differentiated thyroid cancer (DTC) who were treated by ^{99m}Tc-sestamibi radioguided surgery for ^{131}I-negative locoregional

recurrent disease. The study included 58 patients with recurrent papillary ($n = 41$), follicular ($n = 13$), or Hurthle cell ($n = 4$) tumors who were selected for radioguided surgery because of progressive increases in serum thyroglobulin after previous treatment follow-up, a negative high-dose ^{131}I whole-body scan, and positive preoperative ^{99m}Tc-sestamibi scintigraphy for the presence of locoregional disease. Each patient underwent ^{99m}Tc-sestamibi guided bilateral neck exploration in which a hand-held 11-mm gamma probe was used as the intraoperative detector. A total of 147 metastastic foci (4–51 mm in diameter) were removed. Of these, preoperative scintigraphy had identified 85 (58%). After surgery, 43 patients were categorized as disease free (serum thyroglobulin levels were normalized); 12 patients had microscopic disease (slightly increased serum thyroglobulin levels with no imaging evidence of metastatic disease); and 3 patients who developed lung metastases saw significant increases in serum thyroglobulin. The surgeon who performed the procedures reported the radioguided technique to be "very useful" in 14 patients in whom metastatic foci were embedded in fibrotic tissues or located behind blood vessels, "useful" in 22 patients, "moderately useful" in 17 patients, and "not useful" in only 5 patients.

European Journal of Surgical Oncology

Targeted mAbTherapy in Advanced Solid Tumors

Milowsky et al. from the Weill Medical College of Cornell University (New York, NY) reported in the February 10 issue of the *Journal of Clinical Oncology* (2007;25:540–547) on the results of a phase I trial of monoclonal antibody (mAb) J591, which targets the extracellular domain of prostate-specific membrane antigen (PSMA) in solid tumors. The study included 27 patients with advanced solid tumor malignancies previously shown to express PSMA on the neovasculature. Each received an initial infusion of ^{111}In-labeled J591 for scintigraphy and assessment of pharmacokinetics, followed 2 weeks later by treatment infusion of J591 with a reduced amount of the radiolabel for additional pharmacokinetic assessment. The protocol included 6 weekly administrations of J591, and patients with a response or stable disease were eligible for retreatment. Twenty (74%) patients were found to have 1 or more areas of known metastatic disease targeted by ^{111}In-J591, with positive imaging in patients with kidney, bladder, lung, breast, colorectal, and pancreatic cancers and melanoma. The authors concluded that "acceptable toxicity and excellent targeting of known sites of metastases were demonstrated in patients with multiple solid tumor types, highlighting a potential role for the anti-PSMA antibody J591 as a vascular-targeting agent."

Journal of Clinical Oncology

DIAGNOSIS

^{18}F-DOPA PET in Congenital Hyperinsulinism

Hardy et al. from the Children's Hospital of Philadelphia (PA) reported in the February issue of the *Journal of Pediatrics* (2007;150:140–145) on a study designed to assess the accuracy of ^{18}F-fluoro-L-dihydroxyphenylalanine (^{18}F-DOPA) PET in differentiating focal from diffuse disease and in localizing focal lesions in infants with congenital hyperinsulinism. The study included 24 infants with hyperinsulinism who were unresponsive to medical therapy. Each patient underwent ^{18}F-DOPA PET, and resulting images were coregistered with abdominal CT images. The diagnosis of focal or diffuse hyperinsulinism was correct in 23 patients (96%) and equivocal in 1. PET imaging identified focal areas of high uptake of radiopharmaceutical in 11 patients, and subsequent pathology results indicated focal adenomatosis in each of these patients, with lesion locations that matched areas of increased uptake on the scans. The authors concluded that "these results suggest that ^{18}F-DOPA PET imaging should be considered in all infants with congenital hyperinsulinism who need to have pancreatectomy."

Journal of Pediatrics

PET/CT Nodal Staging in NSCLC

Kim et al. from the Sungkyunkwan University School of Medicine (Seoul, Korea) reported on February 20 ahead of print in *Cancer* on a prospective study designed to evaluate the efficacy of ^{18}F-FDG PET/CT in mediastinal nodal staging in patients with non–small cell lung cancer (NSCLC) in a tuberculosis-endemic country. The study included 674 patients with NSCLC who underwent PET/CT imaging and subsequent surgical nodal staging (121 by mediastinoscopy only and 553 by thoracotomy). Criteria for imaging classification of nodes as malignant included greater nodal than mediastinum tracer uptake on PET (without benign calcification) and high attenuation (>70 HU) on unenhanced CT, and these results were compared with histologic assessments. In a total of 2,477 mediastinal nodal sites evaluated in this patient population, 275 (11%) sites in 180 (27%) patients were found to be malignant. The overall sensitivity, specificity, and accuracy of PET/CT for mediastinal nodal staging were 61%, 96%, and 86%, respectively. On a per-nodal station basis, these results were 46%, 98%, and 92%. The authors concluded that although PET/CT provides high specificity and reasonably high accuracy, it has relatively low sensitivity for mediastinal nodal staging of NSCLC. They added that PET/CT's "high specificity is achieved at the expense of sensitivity by interpreting calcified nodes or nodes with high attenuation at CT, even with high FDG uptake at PET, as benign in a tuberculosis-endemic region."

Cancer

PET in SCLC

In an article in the February issue of the *American Journal of Clinical Oncology* (2007;30:45–50), Kut et al.

from Northwestern University (Chicago, IL) reported on a prospective study designed to evaluate the role of ^{18}F-FDG PET in staging and monitoring small cell lung cancer (SCLC). The study included 21 patients with SCLC who underwent a collective total of 39 PET examinations (18 before first-line chemotherapy and 21 during or after treatment). PET imaging results were compared with those from CT scans of the chest or abdomen and from bone scans. Discordant findings were identified in only 14 of 383 comparisons. In the thorax and abdomen, PET agreed with CT scans in 92%–100% of examinations assessing potential disease sites. PET agreed with bone scans in detecting bony lesions in 27 of 32 (84%) imaging studies. In the 5 instances of discordance in bony lesion detection, PET findings were true-positive in 4 and indeterminate in 1. PET was equal in effectiveness to the sum of other staging procedures in baseline staging of disease in this patient group. The authors concluded that "PET is potentially useful for the initial staging and monitoring of patients with SCLC, and it may be superior to bone scan in detecting bone metastasis." They added, however, that the cost effectiveness of PET in SCLC remains to be determined.

American Journal of Clinical Oncology

Gated SPECT and Subendocardial Ischemia

In the February issue of *Circulation Journal* (2007;71:256–260), Kawasaki et al. reported on the results of a study designed to determine whether volumetric variables obtained by gated SPECT are useful in detecting exercise-induced subendocardial ischemia in patients with hypertrophic cardiomyopathy. The study included 26 patients with nonobstructive, mild hypertrophic cardiomyopathy (ventricular septal thickness ≤20 mm) who underwent exercise ^{99m}Tc-tetrofosmin myocardial scintigraphy. The authors found that the exercise-induced percentage change in left ventricular end-systolic volume was higher in the 9 patients with subendocardial ischemia than in the 17 without, although the percentage change in left ventricular end-diastolic volume was similar in the 2 groups. The receiver-operator characteristics curve of percentage changes in left ventricular end-systolic volume identified an optimal cutoff point of 17%, which yielded a useful and valid diagnostic value for the presence of subendocardial ischemia, with sensitivity and specificity of 82% and 89%, respectively.

Circulation Journal

Canadian Position Statement on Cardiac Imaging

In the February issue of the *Canadian Journal of Cardiology* (2007;23: 107–119), a consortium of Canadian cardiac and imaging associations summarized a joint position statement on the clinical use of advanced noninvasive cardiac imaging with PET, MR imaging, and multidetector CT angiography in the diagnosis and evaluation of ischemic heart disease. After an extensive literature review and assessment, recommendations were presented to panels of experts who compiled the final consensus statement. The recommended indications for PET included detection of coronary artery disease (CAD) with perfusion imaging and the use of ^{18}F-FDG viability assessment to determine left ventricular function recovery and/or prognosis after revascularization. In general, the authors concluded that cardiac imaging using the advanced modalities assessed in the study is useful for CAD detection, viability definition, and, in some cases, prognosis. They noted that "given the rapid evolution of technology, initial guidelines for clinical use will require regular updates" and that "evaluation of their integration in clinical practice should be ongoing" and will require a joint effort among specialties.

Canadian Journal of Cardiology

SPECT with PET in Diagnosis of Jaw Necrosis

Catalano et al. from the Federico II University (Napoli, Italy) reported on February 7 ahead of print in the *Annals of Hematology* on a study assessing the combined use of ^{99m}Tc-sestamibi SPECT and ^{18}F-FDG PET to differentiate osteonecrosis from neoplastic osteolyis of the maxillary or mandibular bone. Osteonecrosis of the jaw has received considerable attention in the last 4 years as an infrequent but severe result of long-term treatment with bisphosphonates. The study included 4 patients with multiple myeloma and jaw osteonecrosis who underwent both ^{99m}Tc-sestamibi SPECT (planar anterior and posterior whole-body and head and neck scans) and ^{18}F-FDG PET/CT imaging, as well as clinical, radiologic, and histologic evaluation. No uptake was evident on the SPECT scans, whereas focal uptake was evident in all PET/CT scans. The authors concluded that the study "suggests that the combined use of sestamibi scintigraphy and FDG-PET/CT could support the clinical diagnosis of oral osteonecrosis avoiding the risks of a surgical biopsy."

Annals of Hematology

Scintigraphy and Scaphoid Fractures

In an article published on February 16 ahead of print in *Injury*, Beeres et al. from the Medisch Centrum Haaglanden (The Hague, The Netherlands) correlated the results of bone scintigraphy and clinical outcomes in suspected scaphoid fracture. The study included 50 patients with signs of a scaphoid fracture on physical examination but no radiographic evidence of such injury. All patients underwent follow-up assessments at fixed intervals to define clinical outcomes. Bone scintigraphy indicated 16 (32%) occult scaphoid fractures and 20 (40%) other occult fractures in the study group. Clinical outcomes indicated that bone scintigraphy was false-positive in 5 patients and false-negative in 1 scaphoid fracture. The authors concluded that "bone scintigraphy in combination with protocolized physical examination is the gold standard for patients with signs of a scaphoid fracture that

cannot be proven on scaphoid radiographs."

Injury

PET and Echinococcus Assessment

Stump et al. from the University Hospital Zurich (Switzerland) reported in the February issue of *Infection* (2007;35:11–18) on a study of the efficacy of ^{18}F-FDG PET in the diagnosis of echinococcus multilocularis liver lesions and in the evaluation of response to benzimidazole therapy. The study included 26 patients with newly diagnosed alveolar echinococcus who underwent baseline PET and CT imaging. Half of the patients underwent resection, and the other half, who were determined to have unresectable disease, received benzimidazole therapy. PET and CT scanning were repeated at 6, 12, and 24 months of therapy. An additional group of 12 patients with newly diagnosed cystic echinococcosis of the liver also underwent baseline PET imaging. Baseline PET showed multifocally increased ^{18}F-FDG uptake in hepatic lesion peripheries in 21 of 26 patients with alveolar echinococcosis, whereas PET scans were negative in 11 of 12 patients with cystic echinococcosis. The intensity of tracer uptake decreased or disappeared in 5 of the 10 nonresectable patients within the initial 6 months after initiation of benzimidazole therapy. The authors concluded that ^{18}F-FDG PET is a "sensitive and specific adjunct in the diagnosis of suspected alveolar echinococcosis and can help in differentiating alveolar echinococcosis from cystic echonicoccosis." They added that "the rapid improvement of positive PET scans with benzimidazole therapy in some patients indicates that absent FDG uptake does not necessarily reflect parasite viability."

Infection

MOLECULAR IMAGING

Quantum Dots and Neuroblastoma Cells

Choi et al. from McGill University (Montreal, Canada) reported in the February 12 issue of the *Journal of Nanobiotechnology* (2007:5:1) on a study of the mechanisms of quantum dot–induced cell death in human neuroblastoma cells. Quantum dots are semiconductor nanostructures with great appeal for biological research because, among other advantages, their surfaces can be modified for varying functions. Although their use has been suggested in the development of novel nanotherapeutics and diagnostics in oncology, questions remain about the biocompatibility of modified quantum dots. In this study, researchers showed that quantum dot surface modifications with *N*-acetylcysteine alter the dots' physical and biological properties. In in vitro studies in human neuroblastoma (SH-SY5Y) cells, these modified dots were internalized to a lesser extent and were less cytotoxic than corresponding unmodified quantum dots. The degree of cytotoxicity was correlated with Fas upregulation on the surface of treated cells as well as increased membrane lipid peroxidation, as measured by fluorescent dye tests. Additional reduction assays and confocal microscopy also identified these peroxidized lipids at the mitochondrial level. The authors concluded that quantum dot core and surface compositions, as well as dot stability, "all influence nanoparticle internalization and the consequent cytotoxicity," findings with promise for the eventual translation of quantum dots to tumor targeting in neuroblastoma treatment and monitoring of therapy.

Journal of Nanobiotechnology

Novel PET Brain Imaging Probes

In an article e-published on February 14 ahead of print in the *Journal of Medicinal Chemistry*, Chitneni et al. from Katholieke Universiteit Leuven (Belgium) reported on the synthesis and preliminary evaluation of ^{18}F- and ^{11}C-labeled bicylic nucleoside analogues (BCNAs) as potential PET reporter probes for varicella-zoster virus thymidine kinase (VZV-tk) gene expression imaging in the brain. The authors detailed promising in vitro evaluation of the 2 tracers, with ^{11}C-labeled BCNA showing a 53-fold higher uptake than control cells. Initial in vivo studies in mice indicated that the ^{11}C-labeled tracer was quite stable, but biodistribution studies showed low uptake in the brain. The authors concluded that, "these data warrant further evaluation of these tracers as noninvasive imaging agents for VZV infection and VZV-tk reporter gene expression in vivo."

Journal of Medicinal Chemistry

PET and Glycolysis in Early Huntington's Disease

Powers et al. from the Washington University School of Medicine reported on February 13 ahead of print in the *Proceedings of the National Academy of Sciences USA* on an investigation of mitochondrial oxidative metabolism in vivo in the striatum of individuals with early Huntington's disease. The study included 20 individuals with early, genetically proven Huntington's disease and 15 age-matched controls, in whom direct measurement of the molar ratio of cerebral oxygen metabolism to cerebral glucose metabolism ($CMRO_2/CMR_{glc}$) was provided by PET. The results, including an increase in the striatal $CMRO_2/CMR_{glc}$ ratio in individuals with Huntington's disease and no differences in $CMRO_2$ between controls and patients, were inconsistent with a defect in mitochondrial oxidative phosphorylation resulting from reduced activity of the mitochondrial electron transport system (ETS). This result and selective reductions in striatal CMR_{glc} indicated that reduced activity in the mitochondrial ETS is not a factor in the mechanism of neuronal death in early Huntington's disease. The authors concluded that "because glycolytic metabolism is predominantly astrocytic, the selective reduction in striatal CMR_{glc} raises the possibility that astrocyte dysfunction may be involved in the pathogenesis of Huntington's disease."

Proceedings of the National Academy of Sciences USA

Cancer-Targeted Optical Imaging and Photodynamic Therapy

In an article e-published on February 14 ahead of print in *Bioconjugate Chemistry*, Stefflova et al. from the University of Pennsylvania (Philadelphia) and the University of Toronto (Ontario) reported on the design and synthesis of a folate receptor–targeted, water-soluble, and pharmacomodulated photodynamic therapy (PDT) agent that selectively detects and destroys targeted cancer cells while sparing normal tissue. The authors reported that this action was achieved by minimizing normal organ uptake and by discriminating between tumors with different levels of folate receptor (FR) expression. This therapy approach with a "pyro-peptide folate" (PPF) consisted of 3 components: (1) pyropheophorbide as an imaging and therapeutic agent; (2) a peptide sequence as a stable linker and modulator improving delivery efficiency; and (3) folate as a homing molecule targeting FR-expressing cancer cells. In in vitro experiments, an enhanced accumulation of PPF was seen in FR-expressing cells and not in FR-negative cells, resulting in post-PDT killing of FR-expressing cells. In addition to other advantages, the authors found that incorporating a short peptide sequence significantly improved the delivery efficiency of the probe, a process they attributed to a possible peptide-based pharmacomodulation as demonstrated by a 50-fold reduction in PPF accumulation in liver and spleen when compared with the accumulation of a peptide-lacking probe. They concluded that "this approach could potentially be generalized to improve the delivery efficiency of other targeted molecular imaging and photodynamic therapy agents."

Bioconjugate Chemistry

(Continued from page 29N)

- The potential cost differential in medical isotope production in the reactors and target processing facilities if the products were derived from production systems that do not involve fuels and targets with highly enriched uranium.

To view more details about the NAS "State of the Science in Nuclear Medicine" or "Medical Isotope Production Without Highly Enriched Uranium" studies, please visit the NAS Web site at www.nasonline.org.

NRC/NARM Final Rule Delayed

The Nuclear Regulatory Commission (NRC) release of the final rule on naturally occurring and accelerator-produced radioactive material (NARM) has been delayed until this summer. The NARM final rule was originally scheduled for a February 7 release per the short timeframe mandated by Section 651(e) of the Energy Policy Act of 2005 but is still being revised by the relevant working group at NRC.

HPRA Newsletter

The SNM/ACNP Health Policy and Regulatory Affairs (HPRA) Department now provides a monthly electronic newsletter covering government relations and practice management topics and activities. We encourage any and all interested parties to sign up for the newsletter distribution list by sending your name and e-mail address to hpra@snm.org.

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