

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. We have recently added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. 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.

DIAGNOSIS

¹²³I-MIBG Scintigraphy in Neuroblastoma

In an article e-published on January 30 ahead of print in *Pediatric Blood and Cancer*, Vik et al. from the Indiana University School of Medicine (Indianapolis) reported on the results of a prospective multicenter trial designed to assess the diagnostic performance of ¹²³I-MIBG scintigraphy in patients with known or suspected neuroblastoma. The study included 100 patients (86 children with previously diagnosed neuroblastoma, 13 children with suspected disease, and 1 adult with an abdominal tumor believed to be of neuroendocrine origin). All patients underwent whole-body ¹²³I-MIBG planar imaging, and 51 patients also underwent SPECT imaging of the thorax/abdomen/pelvis. Histopathology, additional imaging results, and laboratory results contributed to final diagnoses of

active disease in 64 patients. Thirty were found to be without disease, and 6 were categorized as indeterminate. When the imaging findings with the 2 procedures were compared with these results, ¹²³I-MIBG scintigraphy had a sensitivity of 88% and specificity of 83%. Sensitivity was 91% among the subset of subjects who had both planar and SPECT imaging. The authors noted that most false-negative findings were in patients with minimal residual disease, whereas false-positive findings usually involved atypical adrenal or other physiologic uptake. They concluded that these results documented “high sensitivity and specificity of this imaging technique in patients with both newly diagnosed and previously treated neuroblastoma.”

Pediatric Blood and Cancer

¹²³I-MIBG Imaging Predicts Sudden Cardiac Death

Tamaki et al. from the Osaka General Medical Center (Japan) reported in the February 3 issue of the *Journal of the American College of Cardiology* (2009;53:426–435) on a prospective study comparing the predictive value of cardiac ¹²³I-MIBG imaging for sudden cardiac death with those of signal-averaged electrocardiography, heart rate variability, and QT dispersion in patients with chronic heart failure. The study included 106 stable patients with congestive heart failure who underwent cardiac ¹²³I-MIBG imaging, electrocardiography, and 24-h Holter monitoring and whose radionuclide left ventricular ejection fraction (LVEF) was <40%. Over a 65-mo (± 31 mo) period, 18 patients died suddenly. Statistical analyses showed that ¹²³I-MIBG washout rate and LVEF were the only factors significantly associated with sudden cardiac death. Patients with an abnormal washout rate (>27%) had a significantly higher risk of sudden cardiac death. Even when the analysis was performed only on pa-

tients with LVEF >35%, sudden cardiac death was significantly more common in those with abnormal washout rates. The authors concluded that cardiac ¹²³I-MIBG washout rate—not electrocardiography, heart rate variability, or QT dispersion—“is a powerful predictor of sudden cardiac death in patients with mild-to-moderate congestive heart failure, independently of LVEF.”

Journal of the American College of Cardiology

CT and SPECT MPI in Suspected CAD

In the February 17 issue of the *Journal of the American College of Cardiology* (2009;53:623–632), van Werkhoven et al. from the Leiden University Medical Center (The Netherlands) reported on a study comparing the prognostic values of multislice CT coronary angiography and SPECT myocardial perfusion imaging (MPI) in patients with suspected coronary artery disease (CAD). The study included 541 patients (59% men, 41% women) who were referred for cardiac evaluation and who underwent both CT and SPECT MPI. Imaging results were compared with follow-up data, including all-cause death, nonfatal infarction, and unstable angina requiring revascularization. Of the 541 patients imaged, 517 (96%) had an interpretable CT, and these patients formed the core of analyses. Significant CAD ($\geq 50\%$ stenosis) was detected by CT in 158 (31%) patients, and abnormal perfusion (summed stress score [SSS] ≥ 4) was derived by MPI in 168 (33%) patients. During a median follow-up of almost 2 y, 23 patients (5.2%) experienced cardiac events. After analysis, multislice CT was found to be an independent predictor of these events with a somewhat better prognostic ability than MPI. The annualized hard event rate in patients with no or mild CAD (<50% stenosis on CT) was 1.8%, a figure that rose to

4.8% in patients with significant CAD ($\geq 50\%$ stenosis). Normal (SSS < 4) and abnormal (SSS ≥ 4) MPIs were associated with annualized hard event rates of 1.1% and 3.8%, respectively. The combined use of the 2 imaging techniques, however, significantly improved the predictive abilities of either alone. The authors concluded that multislice CT is “an independent predictor of events and provides incremental prognostic value to MPI” and that “combined anatomical and functional assessment may allow improved risk stratification.”

Journal of the American College of Cardiology

PET and Effects of B Vitamin Therapy

Potter et al. from the University of Western Australia (Perth) reported in the February 6 issue of *Cerebrovascular Diseases* (2009;27:259–265) on a randomized, double-blind, placebo-controlled study of the use of ^{18}F -FDG PET to assess whether long-term homocysteine-lowering treatment alters arterial wall inflammation in patients with a history of ischemic stroke. The study included 30 stroke patients who were randomly assigned to B vitamin therapy or placebo for a mean treatment period of 4.0 ± 0.7 y. Data gathered at baseline and at the follow-up mark included total plasma homocysteine concentrations, carotid intima medial thickness, and flow-mediated dilation of the brachial artery. All patients underwent ^{18}F -FDG PET imaging, with standardized uptake values (SUVs) measured at 6 sites in the carotid, femoral, and aortic arteries. Areas of locally increased uptake in the arterial wall were also identified. The results indicated that long-term B vitamin treatment significantly reduced total plasma homocysteine concentrations compared with the placebo. The vitamin treatment, however, did not affect the mean arterial SUV or the number of arterial wall “hot spots,” nor were significant correlations found between mean SUVs and carotid intima medial thickness or flow-mediated dilation of

the brachial artery. The authors concluded that “these results suggest that a long-term homocysteine concentration reduction with B vitamins does not affect arterial wall inflammation assessed by ^{18}F -FDG PET.”

Cerebrovascular Diseases

^{123}I -MIBG Scintigraphy in Diabetes Cardiac Risk

In the February issue of *Metabolism* (2009;58:167–173), Anan et al. from the Oita Red Cross Hospital (Japan) reported on a study designed to determine whether elevated hepatocyte growth factor (HGF) levels are associated with insulin resistance and cardiovascular autonomic dysfunction in patients with type 2 diabetes mellitus who are not receiving insulin treatment. The study included 21 such patients with high HGF levels and 25 individuals with type 2 diabetes mellitus and normal HGF levels. All participants underwent ^{123}I -MIBG scintigraphy as well as assessment of baroreflex sensitivity, heart rate variability, and plasma norepinephrine concentrations. The researchers found that early and delayed myocardial tracer uptake values were lower and the percentage of tracer washout rate was higher in the high HGF group than in the normal HGF group. Fasting plasma insulin concentrations and homeostasis model assessment index values were also higher in the high HGF group. Additional statistical analyses indicated that the level of HGF was independently predicted by homeostasis model assessment index values and by ^{123}I -MIBG myocardial uptake at the delayed phase. The authors concluded that these results “demonstrate that high levels of HGF are associated with depressed cardiovascular autonomic function and insulin resistance in patients with type 2 diabetes mellitus.”

Metabolism

P-gp and MRP1 Expression in Parathyroid Tumors

Jorna et al. from the University Medical Center Groningen (The Netherlands) reported on February 20 ahead

of print in *Experimental and Clinical Endocrinology and Diabetes* on a study of P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1) in parathyroid tumors and their respective relations to histology, parathyroid weight, and $^{99\text{m}}\text{Tc}$ -sestamibi imaging results. The study included 33 patients with primary or secondary hyperparathyroidism. Dual-phase $^{99\text{m}}\text{Tc}$ -sestamibi scintigraphy and SPECT results were compared with surgical findings, and other data included radioactivity and weight of resected parathyroid tumors, decay-corrected intraoperative radioactivity measurements, and routine immunohistochemistry with monoclonal antibodies to P-gp and MRP1. Results showed positive P-gp and MRP1 staining in 97% and 43% of glands, respectively. P-gp staining was positive in 91% (21/23) of adenomas and in 100% (36/36) of hyperplastic glands. MRP1 staining was positive in 22% (5/23) of adenomas and 61% (22/36) of hyperplastic glands. Neither P-gp nor MRP1 expression correlated with preoperative $^{99\text{m}}\text{Tc}$ -sestamibi imaging or intraoperative radioactivity. Parathyroid weight, however, was associated with preoperative imaging results and tracer uptake measured during surgery. The authors concluded that “P-gp and MRP1 expression did not correlate with $^{99\text{m}}\text{Tc}$ -MIBI uptake in parathyroid tumors” and that “parathyroid weight remains the major known factor influencing $^{99\text{m}}\text{Tc}$ -MIBI uptake.”

Experimental and Clinical Endocrinology and Diabetes

^{18}F -FDG PET and Adrenocortical Tumors

In an article e-published on February 3 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Groussin and colleagues from a network of 7 university hospitals in Paris (France) reported on a prospective study evaluating the utility of ^{18}F -FDG PET in predicting malignancy in patients with diagnosed or suspected adrenocortical lesions and without previous histories of cancer. The study

included 77 patients: 18 who underwent surgery for hypersecretory and/or growing benign lesions, 21 for already-diagnosed adrenocortical carcinomas, and 38 for lesions that were indeterminate on CT. All patients underwent ^{18}F -FDG PET before surgery, and results were compared with those from pathology and preoperative CT. Pathology showed 43 adrenocortical adenomas, 22 adrenocortical carcinomas, and 12 nonadrenocortical lesions. The authors found that using a cut-off value of <1.45 for the adrenal-to-liver maximum standardized uptake value (maxSUV) ratio, the sensitivity and specificity of PET for differentiating adenomas from carcinomas were 100% and 88%, respectively. Among the 38 lesions that were indeterminate on CT, the authors analyzed a subgroup of 16 adrenocortical tumors with high unenhanced density and an abnormal washout. Of these, PET correctly diagnosed 13 of 15 adrenocortical adenomas as benign. They concluded that “In a multidisciplinary team approach, ^{18}F -FDG PET helps to manage suspicious CT scan lesions” and that “an adrenal-to-liver maxSUV ratio under 1.45 is highly predictive of a benign lesion.”

Journal of Clinical Endocrinology and Metabolism

Midtreatment ^{18}F -FMISO PET in Head and Neck Cancer

Lee et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) reported on February 7 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics* on a prospective study of midtreatment assessment with ^{18}F -misonidazole (^{18}F -FMISO) in a series of patients with locoregionally advanced head-and-neck cancer treated with platinum-based chemotherapy and intensity-modulated radiotherapy. The study included 20 patients (90% with an oropharyngeal primary cancer), who underwent 4 PET scans: 1 pretreatment ^{18}F -FDG PET/CT, 2 pretreatment ^{18}F -FMISO PET/CT scans, and 1 ^{18}F -FMISO PET scan performed 4 wk after initiation of chemo-

therapy. Patients received 2–3 cycles of platinum-based chemotherapy concurrent with definitive intensity-modulated radiotherapy. Detectable hypoxia was seen on the pretreatment ^{18}F -FDG PET/CT scans of 18, with heterogeneous distribution of tracer noted in the primary and/or nodal disease. Only 2 patients had persistent detectable hypoxia on the midtreatment scan. One patient experienced regional/distant failure with no detectable residual hypoxia on the midtreatment scan. The authors found that the chemotherapy/radiotherapy regimen resulted in excellent locoregional control, despite pretreatment PET evidence of hypoxia in most of the patients. They concluded that “In this prospective study, neither the presence nor the absence of hypoxia, as defined by positive ^{18}F -FMISO findings on the midtreatment PET scan, correlated with patient outcome.”

International Journal of Radiation Oncology, Biology, Physics

Prognostic Power of Preoperative PET in Liver Transplantation

In an article e-published on February 3 ahead of print in the *American Journal of Transplantation*, Kornberg et al. from the Friedrich-Schiller University (Jena, Germany) reported on the ability of preoperative ^{18}F -FDG PET to predict microvascular tumor invasion and posttransplant tumor recurrence in candidates for liver transplantation. The study included 42 patients with hepatocellular carcinoma who underwent PET imaging before liver transplantation. PET imaging was negative in 26 candidates and positive in 16. Those whose preoperative PET results were negative had a significantly better 3-y recurrence-free survival rate (93%) than those whose PET results were positive (35%). The hepatocellular carcinoma recurrence rate was 50% in the group that was PET positive and only 3.8% in the PET-negative group. Having preoperative PET-positive results was found to be an independent predictor of postsurgical microvascular tumor invasion. The authors concluded

that “Increased ^{18}F -FDG uptake on PET is predictive for microvascular tumor invasion and tumor recurrence after liver transplant for hepatocellular carcinoma” and that “its application may identify eligible liver transplant candidates with tumors beyond the Milan criteria.”

American Journal of Transplantation

PET and CT in Oropharynx Tumor Treatment Assessment

Chepeha et al. from the University of Michigan (Ann Arbor) reported on February 2 ahead of print in *Head and Neck* on the effects of ^{18}F -FDG PET and CT for estimating tumor volume reduction in patients undergoing induction chemotherapy for advanced squamous cell carcinoma of the oropharynx. Results were compared with those from conventional assessment by endoscopy with biopsy under general anesthesia. The study included 12 patients with oropharyngeal squamous cell carcinoma enlisted in a phase II induction chemoradiation and organ preservation trial. Each participant underwent assessment by PET, CT, and endoscopy with biopsy. PET, CT, and endoscopy results agreed in estimation of tumor reduction in 9 of 12 patients. Two patients had discordant results, and PET failed to adequately evaluate tumor reduction in 1 patient. Statistical comparison of PET versus endoscopy results showed substantial agreement, whereas CT versus endoscopy was rated as fair agreement. The authors concluded that PET “may be as efficacious as endoscopy with biopsy under general anesthesia for estimating tumor volume reduction with induction chemotherapy.”

Head and Neck

THERAPY

^{166}Ho -Hydroxyapatite Particles for Liver Cancer Therapy

Das et al. from the Bhabha Atomic Research Center (Mumbai, India) on February 13 ahead of print in *Cancer*

Biotherapy and Radiopharmaceuticals described the development and initial biodistribution/imaging studies of ^{188}Ho -labeled hydroxyapatite particles. The high-energy β -emission, short half-life, and potential for production with high specific activity and radionuclide purity make this a promising agent for targeted therapy in liver cancer. The authors described the production and radiolabeling of the particles, as well as initial biodistribution and imaging in a rat model. In addition to high specific activity and 100% radionuclidic purity, the particles showed in vitro stability up to 7 d. Particle contents were shown on imaging to be retained well ($\sim 89\%$ of injected activity after 2 d) in the liver without significant uptake elsewhere. They concluded that the ^{166}Ho -hydroxyapatite particles “exhibited promising features as an agent for liver cancer therapy in preliminary studies and warrants further investigation.”

Cancer Biotherapy and Radiopharmaceuticals

MOLECULAR IMAGING AND THERAPY

^{11}C -Erlotinib PET in Lung Tumors

Memon et al. from Aarhus University Hospital (Denmark) reported in the February 1 issue of *Cancer Research* (2009;69:873–878) on ^{11}C radiolabeling and preclinical assessment of erlotinib, a drug that targets epidermal growth factor receptors (EGFRs) overexpressed in many human cancers, including lung cancer. In vitro and in vivo studies, including microPET imaging in murine xenografts, showed the HCC827 lung cancer cell line to be the most sensitive to erlotinib. Dynamic microPET imaging also showed that HCC827 tumors had the highest ^{11}C -erlotinib uptake and retained the activity significantly longer than other lung cancer cell lines. Biodistribution studies confirmed the promise of ^{11}C -erlotinib imaging for identifying tumors most likely to respond to therapeutic regimens of erlotinib. The authors con-

cluded that “These results pave the road for studies examining the benefit of ^{11}C -erlotinib PET in patients with lung tumors or other tumors overexpressing EGFR.”

Cancer Research

Biodegradable Luminescent Porous Silicon Nanoparticles

In an article e-published on February 22 ahead of print in *Nature Materials*, Park et al. from the University of California, San Diego (La Jolla), reported on development of and initial studies with luminescent porous silicon nanoparticles (LPSiNPs) that can carry a drug payload and have intrinsic near-infrared photoluminescence that enables monitoring of both accumulation and degradation in vivo. The most innovative aspect of these dextran-coated particles is that, unlike most optically active nanomaterials (carbon nanotubes, gold nanoparticles, etc.), the LPSiNPs self-destruct into renally cleared components. The authors described the development of the particles, results of preliminary studies, and validation of tumor imaging in a mouse model, including particle self-destruction and elimination in a short period of time. They concluded that “these results demonstrate a new type of multifunctional nanostructure with a low-toxicity degradation pathway for in vivo applications.”

Nature Materials

Toward Combined EGFR- and Proteasome-Targeted Therapies

Kesarwala et al. from Washington University (St. Louis, MO) reported in the February 1 issue of *Cancer Research* (2009;69:976–983) on the development of a chimeric epidermal growth factor receptor (EGFR) firefly luciferase fusion reporter to directly monitor processing of EGFR in real time and to explore the dynamics of ligand-induced EGFR processing and regulation. The authors described development and validation, including in vitro studies of bioluminescence analy-

sis, subcellular localization of an EGFR-green fluorescent protein (GFP) fusion protein, pharmacologic responses, and signaling competency. They found that in cells expressing EGFR-GFP, pretreatment with proteasome inhibitors trapped virtually all of the receptor at the cell membrane both before and after ligand-induced activation with EGF. Proteasome inhibition enhanced receptor ubiquitination in both the basal and ligand-activated states and delayed processing of ligand-activated phosphorylation of the receptor. They concluded that “these observations point to a potential mechanism for the synergistic therapeutic effects of combination EGFR- and proteasome-targeted therapies.”

Cancer Research

Gold Nanospheres in Melanoma

Lu et al. from the University of Texas M.D. Anderson Cancer Center (Houston, TX) reported in the February 1 issue of *Clinical Cancer Research* (2009;15:876–886) on targeted photothermal ablation of melanomas in a mouse model using melanocyte-stimulating hormone analog-conjugated hollow gold nanospheres. They described the development of the nanospheres, which were stabilized with a polyethylene glycol coating and attached to an α -melanocyte-stimulating hormone analog that is a potent agonist of melanocortin type-1 receptor overexpressed in melanoma. In vitro studies in murine melanoma cells assessed uptake and distribution, and the photothermal ablation effect of the nanoparticles was evaluated both in excised tissue and in vivo with ^{18}F -FDG PET. The nanoparticles were specifically taken up by melanoma cells, with intracellular action indicating the involvement of receptor-mediated endocytosis. This resulted in enhanced extravasation of the nanoparticles from tumor blood vessels and dispersion into tumor matrix. The authors confirmed successful selectively targeted photothermal ablation of B16/F10 melanomas with histology. They concluded that these

nanoparticles “have the potential to mediate targeted photothermal ablation of melanoma.”

Clinical Cancer Research

Screening Nanoparticle Delivery Systems for Cancer Photodetection

In the February issue of *Nanomedicine* (2009;4:125–143), Zeisser-Labouebe and colleagues from the University of Geneva and the University of Lausanne (Switzerland) reported on a model proposed and validated as an effective screening system to assess novel strategies for fluorescence-based imaging in cancer. They described the development of a screening model using the chorioallantoic membrane (CAM) of the developing chick embryo. The CAM model was used to investigate the vascular extravasation and tumor

targeting of hypericin encapsulated into nanoparticles for photodetection of ovarian metastases, and results were compared with those with free (non-encapsulated) drug. They concluded that “rodent and CAM models led to the same conclusion regarding the benefits of nanoencapsulation to improve selective accumulation of drug in ovarian micrometastases.” The result of wider use of such models could be not only faster assessment of nanoparticle delivery systems but a reduction in the numbers of small animal studies in drug development.

Nanomedicine

$\alpha_v\beta_3$ -Targeted Superparamagnetic Nanoparticles

Khemtong et al. from the University of Texas Southwestern Medical Center

(Dallas) reported in the February 15 issue of *Cancer Research* (2009;69:1651–1658) on a study combining the high sensitivity of superparamagnetic polymeric micelles (SPPM) and an off-resonance saturation (ORS) method to enhance the MR imaging efficacy of tumor biomarkers in vivo. In studies described in the article, SPPM nanoparticles encoded with cyclic RGDfK targeted $\alpha_v\beta_3$ -expressing microvasculature in A549 non-small cell lung tumor xenografts in mice. Tumor detection accuracy was significantly better than that with conventional T2-weighted methods because of the ability to “turn on” the contrast of SPPM. The authors concluded that “This combination of ORS imaging with a tumor vasculature-targeted, ultrasensitive SPPM design offers new opportunities in molecular imaging of cancer.”

Cancer Research