

ces and Radiological Health. "It is the agency's goal to help stimulate early collaborations between drug and device makers so they can develop the best medical products for treating patients." In a press release, the FDA identified HER2 protein overexpression tests prior to trastuzumab therapy as an example of companion diagnostics.

Although one purpose of the draft guidance is to clarify the FDA definition of a companion diagnostic, it was not immediately clear whether imaging, such as targeted PET studies performed to predict the success of specific chemo- or radioimmunotherapeutic regimens, is included under the definition. The wording of the

guidance does not specifically exclude imaging from this definition, and many imaging studies preceding therapeutic regimens would seem to conform to the definition.

The guidance highlights the FDA intention to conduct simultaneous reviews of a drug or biologic therapy and its corresponding diagnostic and identifies instances in which the FDA may approve a targeted medicine in the absence of a cleared or approved companion diagnostic. In cases where the therapy is intended to treat a serious or life-threatening disease or condition for which there is no available or satisfactory treatment and when the potential benefits outweigh

the risks of not having a cleared or approved companion diagnostic, the therapy could be approved first and the companion diagnostic may be approved or cleared later through the appropriate device submission process. The FDA recommends early engagement with manufacturers so that the agency's expectations can be included in development plans.

The FDA is seeking public input on the draft guidance until mid-September. For more information, see www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm262292.htm.

U.S. Food and Drug Administration

FROM THE LITERATURE

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 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. We have also added a small section on noteworthy reviews of the literature.

DIAGNOSIS

Female-Specific Angina Patterns

In an article e-published on July 8 ahead of print in the *Journal of Women's*

Health, Mieres et al. from North Shore University Hospital (Manhasset, NY) reported on a study resulting from data gathered for the What is the Optimal Method for Ischemia Evaluation in Women? Trial. The authors assessed the frequency of chest pain by measures of ischemia in women with suspected myocardial ischemia who participated in a clinical trial of exercise testing with electrocardiography (ECG) or myocardial perfusion SPECT (MPS). The study included 824 women (average age, 63 y) from 43 centers seen for evaluation of chest pain or anginal equivalent symptoms. Women were assigned randomly to either ECG or ^{99m}Tc-tetrofosmin SPECT. Each participant was also assessed with the Women's Ischemia Syndrome Evaluation, the Seattle Angina Questionnaire for chest pain, and the Duke Activity Status Index instruments. Almost half of participants were found to have family histories of premature coronary disease, hypertension, and/or hyperlipidemia. Sixty percent of participants reported at least 1–3 instances of chest pain symptoms each week. Although women reported minimal physical limitations, they also reported greater frequency of stable chest pain symptoms than did men. Women with

more frequent daily episodes of chest pain were more likely to have lower Duke Treadmill Scores, significant ST segment depression, and abnormal MPS. The authors concluded that "Women reporting frequent angina were more likely to exhibit ischemia, and this may characterize a female-specific typical angina pattern."

Journal of Women's Health

SPECT in End-Stage Renal Disease

Coffey et al. from the Royal Preston Hospital (UK) reported in the July issue of *Hemodialysis International* (2011;15:320–325) on a study assessing cardiac output, cardiac index, and left ventricular ejection fraction (LVEF) metrics in end-stage renal disease (ESRD) using gated SPECT. The study included 32 patients (18 with arteriovenous fistulae or grafts) referred for SPECT/CT cardiac assessment before renal transplant. Results in these patients were compared with those from 2 control groups: 42 normal-weight and 46 obese individuals. All participants (except for 4 renal patients who underwent pharmacologic challenge) underwent gated MIBI SPECT after exercise. Cardiac output was calculated as stroke vol-

ume \times resting heart rate, and cardiac index was calculated. The groups of renal patients had a mean coronary index of 2.6 L/min/m² compared with 2.2 and 2.3 L/min/m² for the normal-weight and obese participants, respectively. The renal patients had an average cardiac output of 4.9 L/min, as did the obese group; this number was 4.3 L/min for the normal-weight group. LVEF did not differ significantly among the groups, and cardiac output and indices did not differ significantly in those with and without arteriovenous fistulae/grafts. The authors concluded although SPECT/CT detects increased cardiac output and cardiac indices in patients with ESRD, this appears to be independent of the presence of arteriovenous fistulae or grafts, so that other factors (such as anemia and hyperparathyroidism) may contribute to the high-output cardiac function. They added that because LVEF is not increased in these patients, increased heart rate may also contribute to elevated cardiac output.

Hemodialysis International

Imaging Activated Macrophages in OA

In the July issue of *Arthritis and Rheumatism* (2011;63:1898–1907), Piscaer et al. from Erasmus University Medical Center (Rotterdam, The Netherlands) reported on a study to investigate whether macrophage activation can be monitored in small animal models of osteoarthritis using a folate radiotracer and whether such imaging provides incremental information on different types of arthritis progression. The researchers used 2 rat models of osteoarthritis: the monoiodoacetate (MIA) model, a fast-progressing biochemically induced model; and the anterior cruciate ligament transection (ACLT) model, with slower disease progression. Serial images were obtained with high-resolution small animal SPECT/CT, with findings compared for specificity against elimination of macrophages with clodronate-bearing liposomes and blockade of folate receptor β in activated macrophages with cold folic acid. Macro-

phage activation differed in the 2 models and was correlated with disease progression, and SPECT/CT allowed differential monitoring. The MIA model had high initial activation, peaked after 2 wk, and disappeared after 8 wk. The ACLT model had less activation but remained active after 12 wk. The authors concluded that these findings “indicate that macrophage activation in experimental osteoarthritis can clearly be demonstrated and monitored by the folate radiotracer” and that the “high resolution, high sensitivity, and high specificity of the technique allow clear localization of macrophage activity in a disease model that is not known for abundant macrophage involvement.”

Arthritis and Rheumatism

Dual-Isotope PET

Andreyev and Celler from the University of British Columbia (Vancouver, Canada) reported on July 21 in *Physics in Medicine and Biology* (2011;56:4539–4556) on a novel approach for dual-isotope PET using positron- γ emitters and described its performance using GATE simulations. GATE is an advanced open source software developed by the international OpenGATE collaboration. The proposed method requires that 1 isotope must be a pure positron emitter and that the second must produce an additional high-energy γ emission in a simultaneous cascade with the positron emission. Two simulation studies were conducted with partially overlapping ¹⁸F/²²Na- and ¹⁸F/⁶⁰Cu-radiolabeled tracers. In both cases, the proposed approach allowed for separation of the 2 activity distributions and recovered total activities with relative errors of \sim 5%. The authors described the process in detail by which a primary dataset contained all detected keV photon pairs from both isotopes and a second smaller database contained only those events for which a coincident prompt γ emission was detected. Images reconstructed from a resulting tagged dataset showed the distribution of the positron- γ tracer

and served as a prior for reconstruction of the primary dataset.

Physics in Medicine and Biology

Spinal Cord Stimulation and Brain Tumors

In an article e-published on July 12 ahead of print in the *Journal of Neurooncology*, Clavo et al. from Negrin University Hospital (Las Palmas, Spain) reported on modification of locoregional microenvironment in brain tumors by spinal cord stimulation and on SPECT and PET monitoring of such modifications. The study included 26 patients with high-grade gliomas who were evaluated before and after spinal cord stimulation with: Doppler imaging of middle cerebral and common carotid arteries, SPECT imaging for tumor blood flow, polarographic probes (8 tumors in 5 patients) for tumor oxygenation (pO₂), and ¹⁸F-FDG PET for tumor glucose metabolism. Before spinal cord stimulation, blood flow was lower in tumors than in peritumoral areas and healthy contralateral tissue, tumor pO₂ was lower than in healthy tissue, and glucose metabolism was higher in tumors than in peritumoral and healthy contralateral areas. After spinal cord stimulation, increases were seen in arterial blood flow, tumor blood flow, tumor glucose metabolism, and tumor pO₂. The authors concluded that spinal cord stimulation can modify brain tumor microenvironments and noted that the “potential usefulness of spinal cord stimulation in improving the effectiveness of radiochemotherapy in high-grade gliomas” should be evaluated.

Journal of Neurooncology

PET and Cannabinoid Receptors

Hirvonen et al. from the National Institute of Mental Health (Bethesda, MD) reported on July 12 ahead of print in *Molecular Psychiatry* on PET studies in humans of the effects of chronic daily cannabis smoking on brain cannabinoid type-1 (CB₁) receptors. Previous animal studies have shown that chronic cannabis (marijuana, hashish) exposure results in

reversible downregulation of CB₁ receptors. The authors used PET studies in human subjects who were chronic cannabis users to demonstrate reversible and regionally selective downregulation of these receptors. Downregulation was directly correlated with years of cannabis smoking and was selective to cortical brain regions. As in animals, this downregulation was reversible: after 4 wk of monitored abstinence from cannabis in a secure research facility, CB₁ receptor density in the participants returned to normal levels. The authors called this “the first direct demonstration of cortical cannabinoid CB₁ receptor downregulation as a neuroadaptation that may promote cannabis dependence in human brain.”

Molecular Psychiatry

Weight Loss and Cardiac Improvement

In an article e-published on July 7 ahead of print in *Obesity (Silver Spring)*, Lin et al. from the Washington University School of Medicine (St. Louis, MO) reported on a study designed to determine whether weight loss can improve obesity-related myocardial metabolism and efficiency abnormalities and whether these changes affect diastolic function. The study included 30 obese (body mass index [BMI] > 30 kg/m²) participants who underwent PET and echocardiography before and after significant weight loss from gastric bypass surgery (10 participants) or moderate weight loss from dieting (20 participants). Before weight loss, baseline BMI, insulin resistance, hemodynamics, left ventricular mass, systolic function, myocardial oxygen consumption, and fatty acid metabolism were similar in the 2 groups. After surgery or diet, total myocardial oxygen consumption decreased in both groups in direct relation to decreased BMI. Total myocardial fatty acid utilization and oxidation were also decreased after both surgery- and diet-induced weight loss. Left ventricular efficiency was unchanged, but left ventricular mass decreased by 23%

after surgical weight loss, and relaxation improved by 28%. Decreased total myocardial oxygen consumption predicted left ventricular relaxation improvement independently of BMI change. The authors concluded that not only can weight loss “ameliorate the obesity-related derangements in myocardial metabolism and left ventricular structure and diastolic function” but “decreased total myocardial oxygen consumption independently predicted improved left ventricular relaxation, suggesting that myocardial oxygen metabolism may be mechanistically important in determining cardiac relaxation.”

Obesity (Silver Spring)

“Neoadjuvant” PET/CT in Esophageal Cancer

Blom et al. from Atrium Medical Center (Heerlen, The Netherlands) reported on July 2 ahead of print in the *European Journal of Surgical Oncology* on a study assessing the value of PET/CT in the detection of interval metastases after completion of neoadjuvant therapy and before surgery in esophageal carcinoma. The study included 40 patients (41 with adenocarcinoma, 9 with squamous cell carcinoma) who underwent PET/CT before and after neoadjuvant therapy but before surgery. Therapy was a regimen of chemo- and radiotherapy, and the interval between the 2 PET/CTs was ~6 wk. Four patients (8%) whose second images showed metastatic disease confirmed by biopsy did not proceed to surgery. The authors concluded that this result suggests “an additional value of a second PET/CT in order to prevent unnecessary surgical resections.”

European Journal of Surgical Oncology

THERAPY

¹⁷⁷Lu-Nimotuzumab for RIT

In an article in the June issue of *Cancer Biotherapy & Radiopharmaceuticals* (2011;26:287–297), Vera

et al. from the Nuclear Physics Institute of the Academy of Sciences (Husinec-Rez, Czech Republic) reported on preclinical assessments of ¹⁷⁷Lu-nimotuzumab and its potential for radioimmunotherapy of epidermal growth factor receptor (EGFR)-expressing tumors. The authors described preparation and radiolabeling optimization of the radiolabeled human monoclonal antibody as well as in vitro studies in tumor model cell lines, where the radioimmunoconjugate showed specific EGFR receptor binding. Studies in xenografted mice showed uptake in both EGFR-expressing tumors and reticuloendothelial organs. The authors concluded that their success in obtaining high purity and specific activities without significant loss in immunoreactivity and with successful imaging efforts in small animals indicated that ¹⁷⁷Lu-nimotuzumab “might be a potential radioimmunoconjugate for radioimmunotherapy of tumors with EGFR overexpression.”

Cancer Biotherapy & Radiopharmaceuticals

MOLECULAR IMAGING

In Vivo Trafficking of Micellar Nanoparticles

Patil et al. from Johns Hopkins University (Baltimore, MD) reported on July 12 ahead of print in *Molecular Therapy* on a study using SPECT/CT to assess the pharmacokinetic and biodistribution profiles of polyethylene glycol-b-polyphosphoramidate (PEG-b-PPA)/DNA micellar nanoparticles when administered through intravenous infusion, intrabiliary infusion, or hydrodynamic injection. The authors described nanoparticle labeling with ¹¹¹In and quantitative analysis of SPECT/CT that showed different in vivo trafficking kinetics for different administration routes. Intrabiliary infusion resulted in higher liver uptake of micelles than did other routes. Micelles were efficiently retained in the liver, with minimal leakage from the liver to the blood stream. The authors concluded that this work

“demonstrates the utility of SPECT/CT as an effective noninvasive imaging modality for the characterization of nanoparticle trafficking in vivo and confirms that intrabiliary infusion is an effective route for liver-targeted delivery of DNA-containing nanoparticles.”

Molecular Therapy

Molecular Optoacoustics in Arthritis

In an article e-published on July 5 ahead of print in *Nanomedicine*, Fournelle et al. from the Fraunhofer Institut für Biomedizinische Technik (St. Ingbert, Germany) reported on the synthesis of elongated gold nanorods modified with the antibodies infliximab and certolizumab for targeting tumor necrosis factor- α (TNF- α) and designed to detect inflammation in a mouse model of arthritis. The authors used a fast-scanning optoacoustic imaging platform based on a pulsed neodymium-doped yttrium aluminium garnet laser and a single focused ultrasound transducer to demonstrate differential enhancement of optoacoustic signal amplitudes after injection of antibody-modified and pegylated control particles in arthritic and healthy mice. The photoacoustic properties of the gold nanorods clearly showed overexpression of TNF- α in mice with arthritic knees. The authors concluded that because of the “the uncomplicated coupling chemistry and the scalability of ultrasound-based imaging approaches, these results potentially allow a transfer to various preclinical and clinical applications.”

Nanomedicine

SPECT/CT and Oncolytic Virus Dispersion

Penheiter et al. from the Mayo Clinic (Rochester, MN) reported on July 14 ahead of print in *Gene Therapy* on a study designed to validate the ability of pinhole micro-SPECT/CT to elucidate the intratumoral dispersion pattern and quantify the infection percentages in solid tumors of an oncolytic measles virus encoding the

human sodium iodide symporter (MV-NIS). The study was conducted in control and MV-NIS-infected BxPC-3 pancreatic tumor cells and mouse xenografts using reverse transcriptase, polymerase chain reaction, autoradiography, and ^{125}I or $^{99}\text{TcO}_4$ pinhole SPECT/CT. NIS RNA levels and dispersion patterns were assessed, and tumor dimensions and tracer localization were determined. Tumor infection percentage and radionuclide uptake were found to be significantly correlated. A detection threshold 1.5-fold above control tumor uptake (background) yielded a sensitivity of 2.7% MV-NIS-infected tumor cells, and it was possible to distinguish multiple intratumoral zones of infection from noninfected regions. The authors concluded that “pinhole micro-SPECT/CT imaging using the NIS reporter demonstrated precise localization and quantitation of oncolytic MV-NIS infection and can replace more time-consuming and expensive analyses (for example, autoradiography and immunohistochemistry) that require animal killing.”

Gene Therapy

^{125}I -Gold Nanoparticles

In an article in the July 18 issue of *Small* (2011;7:2052–2060), Kim et al. from the Seoul National University College of Medicine (South Korea) reported on tumor targeting and imaging using cyclic RGD-pegylated gold nanoparticles (AuNPs) with directly conjugated ^{125}I . The authors described the development of probes and tests confirming stability in a range of pHs and high-salt and -temperature conditions. The probes were found to selectively target and be taken up by tumor cells via integrin $\alpha_v\beta_3$ -receptor-mediated endocytosis with no cytotoxicity. In vivo small animal SPECT/CT indicated that the ^{125}I -cRGD-PEG-AuNP probes target tumor sites as early as 10 min after injection. Additional work suggested that cyclic RGD peptides are necessary for efficient and long-term in vivo monitoring, which suggests that the probes circulate

through the whole body, including renal filtration, and are excreted. The authors concluded that “these promising results show that radioactive-iodine-labeled gold nanoprobe have potential for highly specific and sensitive tumor imaging or for use as angiogenesis-targeted SPECT/CT imaging probes.”

Small

REVIEWS

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in late June and July. In an article e-published on June 29 ahead of print in *Clinical Gastroenterology and Hepatology*, Lin et al. from the University of New South Wales and the Liverpool Hospital (Australia) reviewed “Management of patients following detection of unsuspected colon lesions by PET imaging.” On June 28, ahead of print in *Medicinal Chemistry*, Velikyan from Uppsala University (Sweden) described “Positron-emitting ^{68}Ga -based imaging agents: chemistry and diversity.” Romer et al. from the Ludwig Maximilians University Munich (Germany) and ChromoTek GmbH (Planegg-Martinsreid, Germany) reported on June 25 ahead of print in *Current Opinion in Biotechnology* on “Engineering antibodies and proteins for molecular in vivo imaging.” In an article in the August issue of *Current Opinion in Neurology* (2011;24:386–393), Duyn and Koretsky from the National Institutes of Health (Bethesda, MD) reported on “Novel frontiers in ultra-structural and molecular MRI of the brain.” Boogers et al. in the July issue of *Heart Failure Reviews* (2011;16:411–423) provided an overview of “The role of nuclear imaging in the failing heart: myocardial blood flow, sympathetic innervation, and future applications.”