



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. 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

rhTSH-Aided Radioiodine Ablation and Treatment

Luster et al. from the University of Wurzburg (Germany) in the March issue of *Endocrine-Related Cancer* (2005;12:49–64) presented a comprehensive international review of reports on the administration of recombinant human thyroid-stimulating hormone (rhTSH) before radioiodine ablation of thyroid remnants or as treatment of local tumors from metastatic disease in patients with differentiated thyroid cancer. The data on different administration times and doses, as well as responses, were analyzed. The authors found that when ablation was preceded by the most common regimen, 2 consecutive daily injections of 0.9 mg rhTSH, success rates were better than 84% in 90 patients administered radioiodine activities >4,000 MBq. When only 1,110 MBq were administered after the same 2-day regimen, success rates were 81.2% in a group of 16 patients and 54% in another

study of 70 patients. rhTSH before treatment of persistent and/or recurrent local or metastatic cancer, with 1–6 courses of radioiodine (1,000–1,955 MBq), achieved 2% complete remission, 36% partial response, and 27% disease stabilization rates, in 115 elderly, late-stage patients. The authors noted that although rhTSH treatment was generally well tolerated, some patients experienced adverse effects related to peritumoral edema and swelling, in some cases compressing key anatomic structures and resulting in neurologic, respiratory, or other complications. They also noted that whole-body and whole-blood radioiodine clearance may be faster in euthyroid patients after administration of rhTSH, which might have an effect on hospital stays and decreased exposure. They suggested that “rhTSH-aided treatment may be preferred in patients who are at greater risk of hypothyroid complications from withdrawal of thyroid hormone or are unable to produce sufficient endogenous TSH, and warrants additional investigation in younger patients at earlier stages of thyroid cancer.”

Endocrine-Related Cancer

Improved Pretargeting in NHL

In a study e-published ahead of print on April 7 in the journal *Leukemia*, Sharkey et al. from the Garden State Cancer Center (Belleville, NJ) reported on a comparison of the therapeutic efficacy of a new bispecific anti-CD20 monoclonal antibody (bsmAb)-pretargeting system and that of conventional direct targeting in a murine model of non-Hodgkin's lymphoma. The novel bsmAb was made by coupling the Fab' of a humanized anti-CD20 antibody to the Fab' of a murine antibody directed against histamine-

succinyl-glycine (HSG) peptide, which in this study was conjugated with ¹¹¹In or ⁹⁰Y. Nude mice bearing s.c. Ramos human B-cell lymphomas were injected with the bsmAb and, 48 hours later, with ¹¹¹In- or ⁹⁰Y-HSG. A second group of mice received the radiolabeled peptides without the pretargeting. Tumors progressed rapidly in animals given 800 μCi of ⁹⁰Y-HSG peptide alone, whereas 5 of 10 animals in the group pretargeted by the anti-CD20 bsmAb were tumor free 18 weeks later. The authors concluded that this bsmAb pretargeting procedure “significantly improves the therapeutic response of targeted radionuclides in non-Hodgkin's lymphoma, warranting further development of this method of radioimmunotherapy.”

Leukemia

European Workshop Report on ⁹⁰Y-Ibritumomab Tiuxetan

Hagenbeek and Lewington from the University Medical Center Utrecht (The Netherlands) reported in the May issue of the *Annals of Oncology* (2005;16:786–792) on the results of a multidisciplinary consensus workshop of European clinicians who had participated in clinical trials of ⁹⁰Y-ibritumomab tiuxetan (Zevalin) in the treatment of non-Hodgkin's lymphoma (NHL). The workshop was convened to develop recommendations for the clinical preparation and administration of this radioimmunotherapeutic agent in anticipation of European Medicines Agency approval for adult patients with rituximab-relapsed or -refractory CD20+ follicular B-cell NHL. The article contains a complete summary of recommended procedures and uses.

Annals of Oncology
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¹³¹I-Labeled mAb with Longer Retention Time

Stein et al. from the Garden State Cancer Center (Belleville, NJ) reported in the April 1 issue of *Annals of Oncology* (2005;11:2727–2734) on a novel radioiodinated monoclonal antibody (mAb) for cancer therapy designed to prolong the retention time of the radionuclide within target cells. The team developed an adduct designated as IMP-R4, which causes radioiodine to become trapped in lysosomes after antibody catabolism. In this study, they compared the properties of ¹³¹I-IMP-R4-labeled anticarcinoma embryonic antigen (CEA) humanized mAb hMN-14 with those of directly radioiodinated hMN-14 (¹³¹I-hMN-14) in CEA-expressing human colon cancer cell lines and in nude mice bearing established tumor xenografts. They found that retention of the novel radioiodinated mAb was significantly increased compared with that of the directly labeled complex. In the rat model, the novel complex showed significant improvement in therapeutic efficacy, with mean tumor volumes at 8 weeks of 0.16 ± 0.19 cm, compared with 1.99 ± 1.35 cm for the directly labeled method. Complete remissions were observed in 27% of the animals treated with the novel method, whereas no remissions were observed in the conventional group. The authors concluded that “the ability of this labeling method to lend itself to clinical-scale labeling, the broad applicability of a humanized anti-CEA mAb for CEA-expressing cancers, and the clinical benefits of radioimmunotherapy with anti-CEA mAb shown recently for small-volume and minimal residual disease combine to make ¹³¹I-IMP-R4-hMN-14 a promising new agent for radioimmunotherapy.”

Annals of Oncology

Avidin Chase Effects in Colon Cancer RIT

In the last decade, a number of researchers have investigated the

infusion of avidin as a “chase” to improve biodistribution after the injection of radiolabeled monoclonal antibodies for immunoscintigraphy or radioimmunotherapy (RIT). In the April 7 issue of the *World Journal of Gastroenterology* (2005;11:1917–1921), Li et al. from the Shanghai Institute of Applied Physics (China) reported on a study to evaluate the effects of avidin chase on RIT side effects in a mouse model of human colon carcinoma. Three groups of nude mice were grafted with human colon carcinoma. All were treated at 7 days after grafting. Mice in 1 group received injections of ¹⁸⁸Re-labeled biotinylated anti-CEA McAb (¹⁸⁸Re-CEA McAb-Bt), followed 24 hours later by injection of avidin. A second group of mice received only the ¹⁸⁸Re-CEA McAb-Bt, with no avidin. Mice in the third group received only injections of normal saline solution. All groups underwent SPECT imaging and biodistribution studies beginning 24–48 hours after treatment. Histologic analyses of tumors were also performed. They found that avidin chase significantly accelerated the clearance of the radiolabeled complex from the blood and normal tissues. Tumor uptakes of ¹⁸⁸Re-CEA McAb-Bt at 28 hours were 5.90 and 6.42% ID/g in the chase and non-chase groups, respectively, and corresponding tumor-to-background ratios were 3.19 and 0.56, respectively. White blood cell counts recovered sooner in the group with than in the group without avidin chase. The authors concluded that “avidin chase can effectively reduce the side effects of RIT, and improve therapeutic efficacy.”

World Journal of Gastroenterology

Tomoregulin as an RIT Target in Prostate Cancer

Zhao et al. from Berlex Biosciences reported in the April issue of *Cancer Research* (2005;65:2846–2853) on a prostate-expressed molecule, tomoregulin, as a target for radioimmunotherapy in prostate cancer. The authors reviewed the char-

acteristics of tomoregulin and strong indicators of its potential in this application, particularly as a target in the treatment of metastatic disease. Tomoregulin is a transmembrane protein selectively expressed in the brain, prostate, and prostate cancer but not in other normal tissues. Tomoregulin protein is expressed in primary prostate tumors and in their lymph node and bone metastases. They reported on biodistribution studies using a prostate tumor xenograft model demonstrating that ¹¹¹In-labeled anti-tomoregulin antibody 2H8 specifically recognizes tomoregulin protein in vivo, leading to a strong tumor-specific accumulation of the antibody. Efficacy studies have also shown that a single dose of ⁹⁰Y-labeled 2H8 substantially inhibits the growth rate of established LNCaP human prostate tumor xenografts in nude mice, with no overt toxicity. The authors concluded that these data “clearly validate tomoregulin as a target for radioimmunotherapy of prostate cancer.”

Cancer Research

Diagnosis

Novel Technique for Scintimammography of Small Lesions

In the May issue of the *Obstetrical and Gynecological Survey* (2005; 60:312–314), Rhodes et al. from the Mayo Clinic College of Medicine (Rochester, MN) reported on results of a new technique for ^{99m}Tc scintimammography using a prototype gamma camera system to detect small tumors of the breast. The authors call their technique “molecular breast imaging.” The apparatus includes a cadmium/zinc/telluride semiconductor detector mounted on a modified mammographic gantry, yielding a 20 × 20-cm field of view and an energy resolution of 6.5%. The initial study included 40 women with lesions <2 cm in diameter that had been identified on mammography as suggestive of malignancy. Each woman underwent scintimammography with the novel apparatus, and results were compared with findings at sur-

gery. The new technique detected 33 of a total of 36 malignant lesions (sensitivity, 92%) and 19 of the 22 malignancies that were ≤ 1 cm in diameter (sensitivity, 86%). All lesions >1 cm were detected. The new technique detected 4 additional lesions that had not been identified on the original referring mammography, 3 in the contralateral breast. The authors concluded that the technique appears safe, highly reliable, and “may prove most useful for women having dense breast tissue and those with a family history of breast cancer.”

Obstetrical and Gynecological Survey

Metaanalysis of ^{18}F -FDG PET in Breast Cancer Recurrence

Isasi et al. from the Montefiore Medical Center and Albert Einstein College of Medicine (New York, NY) reported in the March issue of *Breast Cancer Research and Treatment* (2005;90:105–112) on the results of a metaanalysis of the utility of ^{18}F -FDG PET in the evaluation of breast cancer recurrence and metastases. The study included data gathered from an extensive search of literature published between 1995 and 2004 to identify articles that included sufficient information to facilitate calculation of sensitivity and specificity. Two independent reviewers surveyed and synthesized this data, and their results were compared. The final metaanalysis pool included 16 studies with 808 individuals and patient-based data, and 8 studies with a total of 1,013 lesions and lesion-based data. In the patient-based studies, median sensitivity was 92.7% and median specificity was 81.6%. The pooled sensitivity was 90% for both types of studies, and the pooled false-positive rate was 11% after the exclusion of outliers. The maximum joint sensitivity and specificity was 88%. The authors concluded that, “these results indicate that ^{18}F -FDG PET is a valuable tool for detecting breast cancer recurrence and metastases.”

Breast Cancer Research and Treatment

PET Versus Bone Scan in Arthroplasty

In the April issue of the *Journal of Bone and Joint Surgery (British)* (2005;87:465–470), Reinartz et al. from the University Hospital Aachen (Germany) reported on a study comparing the diagnostic capabilities of triple-phase bone scanning and ^{18}F -FDG PET imaging in the identification and differentiation of complications, especially loosening and infection, after hip arthroplasty. The study included 63 patients with a total of 92 prostheses. Each patient underwent both triple-phase bone scanning and PET imaging. Findings were compared with results at surgery or on follow-up. The sensitivity, specificity, and accuracy of PET were 94%, 95%, and 95%, respectively. The corresponding results for the bone scans were 68%, 76%, and 74%. The authors noted that histologic examination at surgery indicated that increased periprosthetic uptake of ^{18}F -FDG in patients with aseptic loosening was caused by “wear-induced polyethylene particles and the subsequent growth of aggressive granulomatous tissue.”

In a second article, e-published ahead of print in the *Archives of Orthopaedic and Trauma Surgery*, the same research group reported specifically on the value of PET versus triple-phase bone scan in diagnosing loosening after hip arthroplasty. In this study, 50 patients with a total of 70 hip replacements (50 symptomatic and 20 asymptomatic for hip loosening) were imaged with ^{18}F -FDG PET and bone scans to detect and differentiate between septic and aseptic loosening. The results were compared with findings from surgery or follow-up. The sensitivity, specificity, and accuracy of ^{18}F -FDG PET were 91%, 92%, and 91%, respectively. The corresponding results for the bone scans were 78%, 70%, and 74%. The authors concluded that ^{18}F -FDG PET is a “promising, highly accurate examination method to

detect polyethylene and metal wear-induced chronic inflammation followed by periprosthetic osteolysis” and that this approach “has a significantly higher sensitivity and specificity than triple-phase bone scan for differentiating between aseptic loosening and infection.”

Journal of Bone and Joint Surgery (British)

Archives of Orthopaedic and Trauma Surgery

Exposure Rates After ^{131}I Therapy

With the recently revised risk-informed and performance-based requirements of the Nuclear Regulatory Commission (NRC) 10 CFR Part 35, a number of nuclear medicine practitioners in the United States have commented on the extent of protection needed for family members of patients after ^{131}I therapy. One set of suggested guidance was issued by the SNM and the NRC in 2004 as *Guide for Diagnostic Nuclear Medicine and Radiopharmaceutical Therapy*, authored by Jeffrey A. Siegel, PhD. The question of optimal and practical protection continues to be actively addressed around the globe. In the May issue of *Health Physics* (2005;88:486–490), Mohammadi, from Tehran University of Medical Sciences (Iran), reported sequential exposure rate measurements on 78 hyperthyroid patients (including patients on 8 different dose regimens) up to 42 days after ^{131}I therapy. Measurements were acquired each day at 1, 0.6, and 0.3 m from the patient. The author presented the results and suggested that the data from this dynamic study “may serve as a database for radiation safety-related decision making.”

Health Physics

Finger Doses for Routine $^{99\text{m}}\text{Tc}$ and ^{32}P Handling

In an article e-published ahead of print in the April 7 issue of *Radiation Protection and Dosimetry*, Saether et al. from the Norwegian Radiation Protection Authority (Østerås) reported on the results of a series of

finger dose measurements acquired from personnel performing routine x-ray guided surgery, nuclear medicine procedures, and nuclear medicine research. Their findings yielded estimates of 18.8 mSv mean annual finger dose to nuclear medicine staff exposed to ^{99m}Tc . The majority of researchers handling ^{32}P received no finger dose at all, and the highest single reading for these individuals was 1.65 mSv. The mean annual finger dose to surgeons performing x-ray guided orthopedic surgery was 13.7 mSv. Surgeons and radiologists performing x-ray guided endovascular treatment of aortic aneurysms received a mean dose of 0.35 mSv per treatment. The authors noted that all occupation groups included in the study received finger doses well below the European annual limit of 500 mSv.

Radiation Protection and Dosimetry

Marking Method for SLN Localization

Laasanen et al. from the Mikkeli Central Hospital (Finland) reported in the April 7 issue of *Physics in Medicine and Biology* (2005;50:N49–54) on a novel method and device for pen marking of active nodes during ^{99m}Tc gamma camera imaging for localization of sentinel lymph nodes (SLNs) in breast cancer. The study included 11 women imaged 3–4 hours after injection of a ^{99m}Tc -labeled nanocolloid. Two polycarbonate plates with a grid of 40×32 holes (spaced 10 mm apart) were engineered for anterior and lateral side imaging and installed on the bed of a dual-head gamma camera. Two drops of ^{99m}Tc were placed into the top corners of both the plates to trace the corresponding x and y coordinates from the acquired images and from the plates. After imaging, the x and y coordinates of the SLNs were determined from the anterior and lateral side images. The location of each SLN was then marked with an ink pen on the skin through the small holes in the plates. The surgeon reported the average distance between the marks and the true location of the SLNs to be $4.5 \pm$

6.9 mm. Subsequent measurements were made in a phantom model to compare this method with the traditional method. The accuracy of the novel method was significantly higher than that of the traditional method (2.7 ± 3.0 and 9.2 ± 3.0 mm, respectively). The authors noted that unlike the novel method, the traditional approach also did not allow marking of the weakest activity. They concluded that not only was the marking process easier to use and simple enough to be adapted to most gamma cameras, but it yielded greater accuracy and higher sensitivity than the traditional method.

Physics in Medicine and Biology

Exercise SPECT and Risk Stratification in Elderly Patients

Valeti et al. from the Mayo Clinic (Rochester, MN) reported in the April 12 issue of *Circulation* (2005;111:1771–1776) on a study designed to evaluate the prognostic value of exercise SPECT in elderly patients. The study included 247 patients (75 years or older; 108 women, 139 men) who underwent exercise ^{201}Tl SPECT and were then followed for a median period of 6.4 years. The following SPECT variables were found to be significantly associated with cardiac death: summed stress score (SSS), summed difference score, increased lung uptake, and left ventricular enlargement. These results were compared with corresponding Duke prognostic treadmill scores, which were not significantly associated with cardiac death. The SPECT SSS accurately classified the majority of patients as low (49%) or high risk (35%); the Duke score classified the majority (68%) as at intermediate risk. Annual cardiac mortality rates for patients categorized by SPECT SSS as low risk and high risk were 0.8% and 5.8%, respectively. Cardiac survival rates according to SPECT SSS risk categories were also significantly different for women and men, and SPECT accurately predicted outcomes in both sexes. The authors concluded that, “if these results can be validated in future studies, exercise SPECT rather than standard treadmill testing may

emerge as the initial noninvasive testing strategy in elderly patients who are able to exercise.”

Circulation

^{99m}Tc -Ciprofloxacin Scintigraphy in Abdominal Infection

In the March/April issue of *Hepato-gastroenterology* (2005;52:491–495), Artiko et al. from the Institute for Nuclear Medicine (Belgrade, Serbia and Montenegro) reported on the use of ^{99m}Tc -ciprofloxacin scintigraphy in the detection and evaluation of abdominal and gastrointestinal foci of infection. The study included 21 patients with suspected infection who underwent planar liver/spleen scintigraphy after injection of ciprofloxacin chloride (3.5 mg) mixed with ^{99m}Tc (555 MBq) in 3 mL physiologic solution. Dynamic acquisition was performed during the first 60 minutes, followed by static acquisition anterior and posterior views of the abdomen and pelvis after 1 and 4 hours. Patients with negative or equivocal findings also underwent SPECT imaging. Interpretations were compared with findings from ultrasonography, CT, and MR imaging; laboratory analyses; and surgical or microbiological confirmation of infection. Results were true-positive in 11 patients, true-negative in 7, false-negative in 2, and false-positive in 1 (as a result of intestinal obstruction), yielding a sensitivity of 79%, specificity of 91%, positive predictive value of 92%, negative predictive value of 77%, and accuracy of 84%. The authors concluded from these results that “scintigraphy with radiolabeled ciprofloxacin is a useful method for detection and assessment of exact localization of abdominal and gastrointestinal infections.”

Hepato-gastroenterology

Education and Cognitive Reserve in Alzheimer’s Disease

Liao et al. from the National Yang-Ming University School of Medicine (Taipei, Taiwan) reported in the April 12 issue of *Dementia and Geriatric*

Cognitive Disorders (2005;20:8–14) on a study assessing the associations among level of education, cerebral perfusion, and cognitive test performance in individuals with Alzheimer's disease (AD). The study included 132 patients with 0–19 years of formal education who had been previously diagnosed with AD and who were exhibiting mild-to-moderate dementia. Each patient underwent ^{99m}Tc -HMPAO SPECT imaging, and cognitive performance was assessed by administration of the Mini-Mental State Examination and the Cognitive Abilities Screening Instrument. The authors found that years of formal schooling had negative associations with cerebral perfusion and positive associations with cognitive test scores. The association between lower levels of education and increased perfusion could be seen most significantly in bilateral posterior areas in mild dementia and bilateral parietotemporo-frontal areas in moderate dementia. The authors suggested that “the cognitive reserve effect starts at the low end of the education range” and that “the main effect of more education is a more facile use of alternative brain circuits instead of locally increased synaptic connections.”

Dementia and Geriatric Cognitive Disorders

Predictive Value of Primary Lesion SUV in Lung Cancer

Sachs et al. from the University of New York Stony Brook School of Medicine reported in the March issue of *Clinical Lung Cancer* (2005;6:310–313) on a study investigating whether PET standardized uptake values (SUVs) in the primary lesion, regardless of size, correlated with the presence of nodal or distant metastases at the time of initial presentation. The study included 139 patients whose CT and PET images and histologic findings were reviewed retrospectively. Only patients with primary non-small-cell lung cancer and pathologic confirmation of nodal status or conventionally

accepted non-PET proof of distant metastases were included, and this patient group represented a wide range of disease stages. The authors found a highly significant correlation between primary lesion SUV and the presence of nodal or distant metastases. They calculated a 13% increase in the likelihood of nodal or distant disease for every unit increase in SUV. They concluded that PET SUV in the primary lung cancer lesion, regardless of size, may serve as a surrogate for biologic aggression and that “elevated SUV in the primary lesion at presentation should prompt high suspicion and mandates meticulous search for nodal or distant disease.”

Clinical Lung Cancer

PET and Effects of “Ecstasy”

In an article e-published ahead of print on April 20 in the journal *Neuropsychopharmacology*, McCann et al. from the Johns Hopkins School of Medicine (Baltimore, MD) reported on the use of first- and second-generation serotonin transporter (SERT) ligands in quantitative PET studies of the effects of methylenedioxymethamphetamine (MDMA or “Ecstasy”) in humans. The study included 23 regular MDMA users who had abstained from use for a specified period and 19 non-MDMA-use control individuals who underwent quantitative ^{11}C -McN5652 and ^{11}C -3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzotrile (^{11}C -DASB) PET imaging. The ability of these respective first- and second-generation SERT ligands to detect MDMA-induced brain serotonin neurotoxicity had been previously validated in baboons. In the current study, results showed excellent correlations between the various binding parameters of ^{11}C -McN5652 and ^{11}C -DASB, both in individual brain regions and individual subjects. Both PET ligands showed global SERT reductions in MDMA users. Comparisons in 15 regions of interest demonstrated reductions in selected cortical and subcortical structures in MDMA users. The authors noted that exploratory correlational analyses

suggested that SERT measures recover with time, but that loss of SERTs is directly associated with the intensity of MDMA use. They concluded that these quantitative PET data “provide strong evidence of reduced SERT density in some recreational MDMA users.”

Neuropsychopharmacology

PET Imaging of Melanoma

McQuade et al. from the Washington University School of Medicine (St. Louis, MO) and the University of Missouri–Columbia reported in the April 21 issue of the *Journal of Medical Chemistry* (2005;48:2985–2992) on the use of ^{64}Cu - and ^{86}Y -DOTA-ReCCMSH(Arg(11)), a cyclized peptide analog of α -melanocyte-stimulating hormone (α -MSH) in PET imaging of early melanoma in a murine model. Small animal PET imaging and biodistribution studies were conducted with radiolabeled peptide analogs in mice implanted with B16/F1 murine melanoma tumors, and results were compared with similar studies using ^{18}F -FDG in the same animal. Subsets of animals were also injected with unlabeled peptide analog. Tumor concentration for both the ^{86}Y - and ^{64}Cu -labeled complexes peaked at 30 min. Nontarget organ concentration was considerably lower with the ^{86}Y than the ^{64}Cu analog, except in the kidneys, where the ^{64}Cu complex had lower accumulation at all time points. The tumors could be visualized on small animal PET images with both complexes after 30 min, with the standardized uptake value analysis following a similar trend as the biodistribution data. The authors concluded that the data obtained suggested that “DOTA-ReCCMSH (Arg(11)), when labeled with β^+ -emitting radionuclides, has the potential for early detection of malignant melanoma by exploiting the sensitivity and high resolution of PET.”

Journal of Medical Chemistry