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

Imaging Stem Cells in Fracture Healing

In the *Journal of Orthopaedic Research* (2009;27:295–302), Lee et al. from Stanford University School of Medicine (CA) reported on the use of in vivo molecular and small animal imaging technologies in monitoring stem cell–mediated accelerated bone healing in a mouse model of skeletal injury. Bioluminescence imaging, ^{18}F-9-fluorohydroxymethylbutylguanine micro-PET, ^{18}F-fluoride ion micro-PET, and micro-CT were used to image the life cycle of adipose-derived multipotent stem cells in mice with bone injuries or sham operations, and results were compared with bioluminescence microscopy and immunohistochemistry. Molecular and small animal imaging indicated that the systemically administered stem cells traveled to the site of skeletal injury and facilitated bone healing. The authors concluded that "molecular imaging technologies can validate the usage of adult adipose tissue–derived multipotent cells to promote fracture healing" and that these techniques can be developed so that imaging can play a significant role in establishing therapeutic strategies in this setting.

Journal of Orthopaedic Research

Clinical Assessment of Breast Cancer in Chemotherapy

Prati et al. from the University of California, Los Angeles, reported in the March 15 issue of *Cancer* (2009;115:1194–1202) on the accuracy of several imaging modalities and clinical assessments in tumor and lymph node evaluation in patients receiving neoadjuvant chemotherapy for breast cancer. The study included 45 women with T3/T4 tumors. Each patient underwent physical examination, mammography, breast MR imaging, and PET imaging before and after chemotherapy, and the results were compared with tumor and lymph node staging at pathology. MR imaging was found to be more accurate than mammography at assessing tumor size at baseline, and physical examination correlated better with pathology than either MR imaging or mammography after chemotherapy. Both PET and physical examination correctly predicted positive axillary nodes after therapy but had low sensitivity. The summary finding that MR imaging was a more accurate imaging study at baseline for T3/T4 tumor and PET and physical examination correlated best with pathology suggested potential changes to standard clinical assessment in this patient group.

Cancer

HRT and Coronary Microcirculation

In an article e-published on February 26 ahead of print in the *European Heart Journal*, Schindler et al. from the University of California, Los Angeles, reported on the results of research evaluating the long-term effect of hormone replacement therapy (HRT) on coronary vasomotor function in postmenopausal women with cardiovascular risk factors. The study included 48 postmenopausal women with medically treated cardiovascular risk factors (30 on HRT, 18 without HRT) and 12 healthy premenopausal women as controls. Participants underwent ^{13}N PET imaging at baseline to quantify myocardial blood flow at rest, after cold pressor test stimulation, and during pharmacologically induced hyperemia. Studies were repeated in the postmenopausal women after a mean follow-up of 24 ± 14 mo. Several women discontinued HRT during the follow-up period. Endothelium-related change in myocardial blood flow as assessed at cold pressor test was found to decline more in postmenopausal women with HRT then without HRT over the course of the study. For those postmenopausal women who had not received HRT and those who discontinued its use during the study, endothelium-related change in myocardial blood flow at cold pressor test was significantly less at follow-up than at baseline. The authors concluded that long-term administration of estrogen may contribute to "maintain endothelium-dependent coronary function in postmenopausal women with medically treated cardiovascular risk factors."

European Heart Journal

PET and Stem Cell Therapy in Parkinson's Disease

Muramatsu et al. from the Jichi Medical University (Tochigi, Japan) reported in the February issue of *Synapse* (2009;63:541–548) on multitracer PET assessment of dopamine function after transplantation of embryonic stem cell–derived neural stem cells in a pri-

mate model of Parkinson's disease. The stem cells were unilaterally implanted in the putamen in 2 cynomolgus monkeys after neurotoxin administration to create models of chronic Parkinson's disease. Twelve weeks after cell engraftment, animals were imaged with 3 PET tracers: β-^{11}C-L-3,4-dihydroxyphenylalanine (L-β-^{11}C-DOPA), ^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl)tropane (^{11}C-β-CFT), and ^{11}C-raclopride as precursor, transporter, and receptor ligands, respectively. Uptake of L-β-^{11}C-DOPA and ^{11}C-β-CFT was found to be significantly higher in grafted putamen than in the untreated side. In 1 monkey, a methamphetamine challenge resulted in reduced ^{11}C-raclopride binding in the transplanted putamen, indicating the release of dopamine. The authors concluded that these results suggest that transplanted neural stem cells can restore dopamine function in the putamen of a primate model of Parkinson's disease and that "PET with multitracers is useful for functional studies in developing cell-based therapies against Parkinson's disease."

Synapse

Brain Tissue Characteristics After Head Injury

In an article e-published on March 18 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism*, Coles et al. from the University of Cambridge/Addenbrooke's Hospital (Cambridge, UK) reported on characteristics of lesion and nonlesion tissue soon after head injury. The study included 14 patients who underwent PET imaging within 72 h of severe head injury and MR imaging at 3–18 mo after injury. MR imaging was used to define lesion and structurally normal regions, and the earlier PET-derived metabolic characteristics in these regions were compared with normal physiology in healthy volunteers. Cerebral blood flow, oxygen utilization, and oxygen extraction fraction were lower in lesions than in nonlesion tissue (including that in controls). Regions of interest in control subjects had similar and consistent relative results in cerebral blood flow, cerebral blood volume, and oxygen utilization, whereas relationships within both lesion and nonlesion regions of interest in injured patients were abnormal. These and other results led the authors to a cautionary conclusion: "Although irreversibly damaged tissue is characterized by marked derangements in physiology, a more detailed analysis shows acute changes in physiology and physiologic relationships within regions of the brain that appear structurally normal at follow-up." They added that these pathophysiologic derangements could result in selective neuronal loss and affect functional outcomes.

Journal of Cerebral Blood Flow and Metabolism

PET-Guided Resection of High-Grade Gliomas

Pirotte et al. from the Université Libre de Bruxelles (Belgium) reported in the March issue of *Neurosurgery* (2009;64:471–481) on patient outcomes after the use of PET imaging to guide volumetric resection of supratentorial high-grade gliomas. The study included 66 patients (35 with anaplastic gliomas [20 astrocytomas, 10 oligoastrocytomas, 5 oligodendrogliomas] and 31 with glioblastomas) who underwent ^{18}F-FDG (n = 23) or ^{11}C-methionine (n = 43) PET and MR imaging to plan for surgery. Tracer uptake was used to define a PET contour on the MR scan to yield a final target volume. MR and PET imaging were repeated soon after surgery to assess tumor resection and to provide predictive information about outcomes. The authors found that in all patients, PET provided useful information in addition to that provided by MR in defining accurate target contours for surgery. After surgery, 46 patients had no residual PET tracer uptake and 23 had no residual MR contrast enhancement. Resection with no immediate PET tracer uptake was associated with a significantly longer survival in both anaplastic gliomas and glioblastoma multiforme. Absence of MR contrast enhancement was not correlated with significantly better survival. The authors concluded that complete resection of areas highlighted by PET tracer uptake in presurgical planning increases the effectiveness of resection and prolongs survival in patients with high-grade gliomas.

Neurosurgery

PET and Osteoblastic Bone Flare in NSCLC

In an article published in the March issue of the *Journal of Thoracic Oncology* (2009;4:429–431), Krupitskaya et al. from Stanford University (CA) reported on the phenomenon of osteoblastic bone flare on ^{18}F-FDG PET in patients receiving bevacizumab in addition to standard chemotherapy for non–small cell lung cancer (NSCLC). Although bone flare, or asynchronous increases in activity in metastatic bone lesions despite evidence of response or stability in other lesions, has been noted in other disease entities, this is not common in patients being treated for NSCLC. The authors described 4 NSCLC patients whose interim PET/CT scans included osteoblastic flares that proved to be misleading. All 4 patients were being treated with bevacizumab in addition to standard chemotherapy. The flares seemed to indicate isolated worsening of skeletal metastases despite apparent response or stable disease elsewhere. Follow-up scans indicated that this was merely a flare response. The authors concluded that awareness of this phenomenon is important for physicians treating NSCLC patients, particularly with bevacizumab.

Journal of Thoracic Oncology

Image-Guided RT in Rectal Cancer

Roels et al. from the Leuven Cancer Institute (Belgium) reported on March 14 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics* on an investigation of the feasibility of integrating MR and PET/CT into image-guided radiotherapy in patients with resectable rectal cancer. The study included 15 such patients who underwent MR and ^{18}F-FDG PET/CT

imaging before, during, and after preoperative chemoradiotherapy (CRT). The authors described the process by which tumor volumes were determined with each modality and the steps taken in registration of these data. They found that, in general, regardless of the timing, MR indicated larger tumor volumes than PET, with an ~50% mismatch in PET and MR tumor volumes before and during CRT. After CRT, MR imaging indicated residual tumor in all 6 patients with pathologic complete responses, whereas PET indicated a metabolic complete response in 3 of these patients. PET tumor volumes derived with a gradient-based method correlated more closely than MR tumor volumes with pathologic findings. The authors concluded that although integration of MR and PET imaging into radiotherapy seems feasible, spatial variance between MR imaging and PET tumor volumes should be taken into account for target definition.

International Journal of Radiation Oncology, Biology, Physics

Predictive PET/CT in Head and Neck Cancer

In an article e-published ahead of print in the March 14 issue of the *International Journal of Radiation Oncology, Biology, Physics*, La et al. from Stanford University (CA) reported on a study evaluating the prognostic value of metabolic tumor volume as assessed by ^{18}F-FDG PET and other clinical factors in patients treated for locally advanced head and neck cancer. The study included 85 such patients who underwent PET/CT-guided chemotherapy. PET maximum standardized uptake values (SUVs) and metabolic tumor volume as assessed by PET were compared with disease-free and overall survival rates over a mean follow-up of 20.4 mo for surviving patients. Estimated 2-y locoregional control, disease-free survival, and overall survival were 88.0%, 69.5%, and 78.4%, respectively. Among the 16 patients who experienced relapse, the median time to failure was 9.8 mo. In these patients specific increases in metabolic tumor volumes were significantly associated with an increased hazard of recurrence or death. No significant relationship was found between maximum SUV, stage, or other clinical factors and disease-free or overall survival rates. The authors concluded that metabolic tumor volume is a "direct measure of tumor burden and is a potentially valuable tool for risk stratification and guiding treatment in future studies."

International Journal of Radiation Oncology, Biology, Physics

THERAPY

RIT of Experimental Human Metastatic Melanoma

In an article e-published on March 17 ahead of print in *Clinical Cancer Research*, Revskava et al. from the Albert Einstein College of Medicine (Bronx, New York) and the Long Island Jewish Medical Center (New Hyde Park, NY) reported on radioimmunotherapy (RIT) of experimental human metastatic melanoma with melanin-binding monoclonal antibodies (mAbs) alone and in combination with dacarbazine, a chemotherapeutic agent. The authors evaluated the therapeutic efficacy of 2 melanin-binding IgM mAbs (6D2 and 11B11) labeled with ^{188}Re in human metastatic melanoma–bearing mice. The efficacy of RIT with the mAbs was compared with chemotherapy with dacarbazine and with combined chemotherapy and mAb RIT. The authors found that the therapeutic efficacies of ^{188}Re-labeled 6D2 and 11B11 were comparable. RIT was more effective than dacarbazine in slowing tumor growth in mice, and administration of dacarbazine followed by RIT was more effective than either modality alone. They concluded that these results provide "encouragement for the development of RIT for melanoma with melanin-binding mAbs and suggest that combining chemotherapy and RIT may be a promising approach for the treatment of metastatic melanoma."

Clinical Cancer Research

RIT and Radiosensitizing Chemotherapy

Al-Ejeh et al. from the Hanson Institute (Adelaide, Australia) reported on February 27 in the online journal *PLoS ONE* (2009;4:e4630) on a study of the therapeutic ability of ^{90}Y-labeled monoclonal antibody (mAb) conjugates, which bind specifically to the abundant intracellular La ribonucleoprotein in dead tumor cells after DNA-damaging treatment. The authors described preparation of the radiolabeled immunoconjugates and treatment of established subcutaneous tumors (EL4 lymphoma, Lewis Lung, LNCaP prostatic carcinoma, and Panc-1 pancreatic carcinoma) in mice, using either the radioconjugates alone or after radiosensitizing chemotherapy. The EL4 lymphoma–bearing mice were cured at higher doses of radioimmunotherapy (RIT) alone or lower doses of RIT with chemotherapy. RIT after radiosensitizing chemotherapy significantly slowed tumor regrowth and prolonged survival in mice bearing LL2, LNCaP, or Panc-1 subcutaneous tumor implants. The authors concluded that these data support the efficacy of "a unique form of RIT, which delivers bystander killing to viable cancer cells after targeting the universal cancer antigen, La, created by DNA-damaging treatment in neighboring dead cancer cells." They hypothesized that the targeted radiation induces additional cycles of tumor cell death that trigger a "genotoxic chain reaction."

PLoS ONE

RIT and Colon Cancer Recurrence

In the March issue of the *British Journal of Surgery* (2009;96:314–321), de Jong et al. from Radboud University Nijmegen Medical Centre (The Netherlands) reported on a study investigating the feasibility of radioimmunotherapy (RIT) as an adjuvant treatment for preventing local recurrence after resection of colon cancer. ^{177}Lu-MG1 monoclonal antibodies were administered after resection of tumors in a rat model of colon cancer (n = 39). In 13

rats, ^{177}Lu-MG1 was administered on the day of surgery (group 1), and in another 13 it was administered at d 5 after surgery (group 2). A control group of 13 rats was administered only the carrier (group 3) after surgery. At 28 d, tumor perianastomotic tumor growth was assessed. The radiolabel was found to accumulate preferentially in perianastomotic CC531 tumors in groups 1 and 2. No adverse effects, other than transient weight loss, were noted. Eight animals in group 1 and 11 animals in group 2 showed neither macroscopic nor microscopic perianastomotic tumor growth. However, 11 of 13 rats in group 3 showed macroscopic tumor growth. The authors concluded that this study suggests that "RIT may be an effective adjuvant treatment for preventing local recurrence after resection of colonic cancer."

British Journal of Surgery

RIT with High-Dose BEAM and Autologous Transplantation

Winter et al. from Northwestern University (Chicago, IL), the Mayo Clinic (Rochester, MN), the University of Texas M.D. Anderson Cancer Center (Houston, TX), and Biogen Idec (San Diego, CA) reported in the April 1 issue of the *Journal of Clinical Oncology* (2009;27:1653–1659) on a study designed to determine the maximum tolerated radiation-absorbed dose (RAD) to critical organs delivered by ^{90}Y-ibritumomab tiuxetan in combination with high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy with autologous transplantation in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (NHL). The study included 44 patients with relapsed or refractory CD20+ NHL, 30 of whom had failed to achieve partial remission in therapy and would not usually be considered eligible for autologous transplantation. Each patient was assigned to a group of 3–6 patients in whom individualized ^{90}Y activities based on dosimetry were calculated to deliver cohort-defined RAD (1–17 Gy) to critical organs. A therapeutic dose of ^{90}Y-ibritumomab tiuxetan was followed by high-dose BEAM and autologous transplantation. Because dose-limiting toxicities occurred in 2 patients at the 17-Gy dose level, 15 Gy was established as the recommended maximum tolerated RAD. This and other data suggested the need for careful and individually tailored dosimetry above and beyond a simple weight-based strategy to avoid toxicity as well as undertreatment. Over a median follow-up of 33 mo, estimated 3-y progression-free and overall survivals were 43% and 60%, respectively. The authors concluded that "dose-escalated ^{90}Y-ibritumomab tiuxetan may be safely combined with high-dose BEAM with autologous transplantation and has the potential to be more effective than standard-dose RIT."

Journal of Clinical Oncology

MOLECULAR IMAGING

Tracking and Targeting of Cancer Stem Cells

Vlashi et al. from the University of California, Los Angeles, reported in the March 4 issue of the *Journal of the National Cancer Institute* (2009;101:350–359) on studies designed to assess the feasibility of in vivo fluorescence imaging of cancer-initiating cells by monitoring 26S proteasome activity. The authors described the development of a fluorescent fusion protein (ZsGreen) that preferentially accumulated in cells in the absence of 26S proteasome activity. Proteasome activities were assessed and monitored in vitro by quantitative reverse transcription–polymerase chain reaction, sphere formation assay, and immunohistochemical staining for known stem cell markers. In vivo fluorescence imaging tracked cancer-initiating cells after radiation in tumor-bearing mice, with specific targeting mediated by a thymidine kinase–degron fusion construct. Cancer cells with low proteasome activity were monitored in vitro and in vivo by the accumulation of the ZsGreen–degron construct. ZsGreen-positive cells were found to be more than 100-fold more tumorigenic than ZsGreen-negative cells when injected into mice, and the number of cancer-initiating cells in tumors was found to be increased at 72 h after radiation. Elimination of targeted cancer-initiating cells with a suicide gene resulted in tumor regression. The authors concluded that "reduced 26S proteasome activity is a general feature of cancer-initiating cells that can easily be exploited to identify, track, and target them in vitro and in vivo."

Journal of the National Cancer Institute

Assessing Renal Ischemia with Microbubbles

Andonian et al. from the North Shore–Long Island Jewish Health System (New Hyde Park, NY) and VisualSonics (Toronto, Canada) reported on February 26 ahead of print in the *Journal of Endourology* on an animal study using microbubbles with anti-P-selectin antibodies targeted at an established marker of inflammation and ischemic injury to quantitate microvascular reperfusion injury and regional blood flow in the kidney during ischemia–reperfusion injury. Renal ischemia was induced in the left renal artery and vein in mice, and microbubbles coated with anti-P-selectin antibodies were injected. After unclamping, micro-ultrasound imaging was used to noninvasively measure microvascular flow and quantitate targeted microbubbles bound to P-selectin. Regional blood flow was measured in the renal cortex, medulla, and corticomedullary junction. Dedicated software allowed quantitative comparison of different regions of the kidney. After 30 min of ischemia, P-selectin expression increased by 41%, 25%, and 14% in the corticomedullary junction, cortex, and medulla, respectively, compared to control animals that underwent sham procedures. P-selectin expression was highest in the corticomedullary junction area in treated animals, suggesting the highest degree of microvascular ischemic injury after reperfusion. The authors noted the novel nature of this technique for quantifying in vivo nephron and microvascular renal damage after reperfusion.

Journal of Endourology

Recanalization of Plaques with Photothermal Microbubbles

In the March issue of *Lasers in Surgery and Medicine* (2009;41:240–247), Lukianova-Hleb et al. from the A.V. Lykov Heat and Mass Transfer Institute (Minsk, Belarus) reported on a method for disruption and recanalization of atherosclerotic plaques in coronary vessels using photothermal microbubbles generated around gold nanoparticles. For the studies, the authors used 3 in vitro models: a layer of living fibroplast, epoxy layers, and human arteries and plaques. Photothermal microbubbles were generated around 30–250-nm gold spheres within each of these models, and 10-nanosecond laser pulses were used to propel the microbubbles into the model obstructions. Complete removal of all obstructive material was seen after 1–10 single pulses, with resulting cleared areas measured at 500–1,000 times larger than the nanoparticle sizes used. Generation of the microbubbles did not increase the temperature in the model microenvironments, nor was any debris of significant size noted. The authors concluded that this method for nonthermal mechanical and localized removal of plaque tissue can provide "safe and rapid canalization of totally occluded and calcified arteries without collateral damage."

Lasers in Surgery and Medicine

Quantum Dot Imaging of Pancreatic Cancer

In an article e-published on February 25 ahead of print in *ACS Nano*, Young et al. from the State University of New York (Buffalo) and the Johns Hopkins University School of Medicine (Baltimore, MD) described the use of noncadmium-based quantum dots as efficient and nontoxic optical probes for imaging live pancreatic cancer cells. They detailed the preparation and design of these quantum dots, the surfaces of which were functionalized with mercaptosuccinic acid to make them highly dispersible in aqueous media. The resulting constructs were functionally bioconjugated with pancreatic cancer–specific monoclonal antibodies to allow in vitro targeting of pancreatic cancer cell lines. Targeted delivery of the bioconjugates was confirmed by optical imaging and additional experiments. The authors concluded that the described quantum dots have great promise as "noncadmium-based safe and efficient optical imaging nanoprobes in diagnostic imaging, particularly for early detection of cancer."

ACS Nano

Biodegradable Luminescent Silicon Nanoparticles

Park et al. from the University of California, San Diego (La Jolla) reported on February 22 ahead of print in *Nature Materials* on the development of luminescent porous silicon nanoparticles that can carry a drug payload and that can be monitored with photoluminescent imaging in vivo from accumulation through subsequent degradation. In mouse studies, the particles were found to self-destruct into renally cleared components in a short period of time and with no noted toxicities. The authors also reported on preliminary in vivo applications in tumor imaging, using dextran-coated particles. They concluded that these results "demonstrate a new type of multifunctional nanostructure with a low-toxicity degradation pathway for in vivo applications."

ACS Nano

Imaging Tissue-Specific mdr1a Gene Expression

Gu et al. from the Beckman Research Institute at City of Hope (Duarte, CA) reported on March 12 ahead of print in the *Proceedings of the National Academy of Sciences of the USA* on the creation of a unique mouse model that allows noninvasive bioimaging of mdr1 gene expression in vivo and in real time, with specific promise for elucidating the role of mdr1 expression in multidrug resistance. The authors described the creation of an mdr1a firefly luciferase gene construct (mdr1a.fLUC) that was shown to be a reliable reporter for mdr1a expression in vivo in mice. Additional studies validated xenobiotic-inducible regulation of mdr1a.fLUC expression in real time, providing a more detailed understanding of the kinetics of mdr1a gene induction. The authors concluded that this "represents a unique tool with which to study the magnitude and kinetics of mdr1a induction under a variety of physiologic, pharmacologic, genetic, and environmental conditions."

Proceedings of the National Academy of Sciences of the USA

(Continued from page 28N)

SNM and the International Partnership for Critical Markers of Disease report plans to host other collaborative symposia and forums dedicated to accelerating biomarker and radiopharmaceutical development for patient care, including the 7th annual Critical Markers of Disease Biomarkers and Surrogate Endpoints Symposium, October 19–21, in Bethesda. This symposium, with the theme "Streamlining to Promote Innovation and Efficiency," will also be held in collaboration with representatives from the FDA, NIH, Centers for Disease Control and Prevention, U.S. Agency for Healthcare Research and Quality, Canadian Institutes for Health Research, Radiological Society of North America, and other public and private research organizations. Registration for the fall symposium is available at www.cmod.org.

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