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. This month the literature offered an unusually large number of articles on sentinel lymph node investigations, evidence of the growing importance of this approach. A selection of these articles is highlighted here. 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 both diagnostic and therapeutic progress in this area.

DIAGNOSIS

SLN Detection in Early Gastric Cancer

In an article e-published on July 12 ahead of print in *Clinical Gastroenterology and Hepatology*, Morita et al. from the National Defense Medical College (Saitama, Japan) reported on an investigation of sentinel lymph node (SLN) techniques in identifying micrometastases in patients with early gastric cancer. The study included 53 patients scheduled to undergo gastrectomy for T1 or T2 N0 gastric cancer. SLN navigation surgery was performed with radiolabeled tin colloid and/or indocyanine green, followed by modified D1 lymphadenectomies and histologic analysis. The sensitivity, false-negative rate, and accuracy of SLN using this technique were 82%, 18%, and 96%, respectively, at the occult metastasis level. The authors found, however, that the accuracy of the technique was boosted to 100% when the concept of the SLN station was added. In addition, this indicated that the size of sentinel node metastasis was a predictive factor for metastasis beyond the sentinel node.

Clinical Gastroenterology and Hepatology

Review of SLN Techniques

van de Lande et al. from the Vrije Universiteit Medical Center (The Netherlands) reported on July 11 ahead of print in *Gynecologic Oncology* on a study designed to review and compare the diagnostic utility of blue dye, ^{99m}Tc-colloid, and a combination of these techniques in sentinel node (SN) detection for assessing nodal status in early-stage cervical carcinoma. The retrospective literature review included 23 articles that met inclusion criteria on populations, methodology, and data collection. These articles reflected findings on a total of 842 patients. The authors reviewed and independently pooled statistics on detection rates and diagnostic sensitivity of the SN techniques used. Studies using the combined technique showed a pooled sensitivity of 92%. These figures were 92% with the ^{99m}Tc-colloid alone and 81% with blue dye alone. The SN detection rate was 97% for the combined technique but only 88% for ^{99m}Tc-colloid alone and 84% for blue dye alone. The authors concluded that this review of the literature suggests that "the combination of ^{99m}Tc and blue dye for SN biopsy in patients with early-stage cervical cancer is a reliable method to detect lymph node metastases."

Gynecologic Oncology

SLN and Laparoscopic Surgery in Locally Advanced Cervical Cancer

In an article e-published ahead of print on July 3 in the *Annals of Surgical Oncology*, Lavoué et al. from the Université Pierre et Marie Curie (Paris, France) reported on a study of the value of the sentinel lymph node (SLN) procedure followed by pelvic and paraaortic lymphadenectomy to determine lymph node status in women with locally advanced cervical cancer. The study included a total of 21 women with locally advanced cervical cancer who underwent evaluation by both a laparoscopic SLN procedure and pelvic and paraaortic lymphadenectomy, followed by concurrent chemoradiotherapy. Preoperative lymphoscintigraphy identified sentinel nodes (SNs) in 10 (47.6%) of the women, and lymphadenectomy identified SNs in 14 (64%) women. Histologic analysis indicated that 13 of the 21 women (62%) had lymph node metastases. The total number of recovered pelvic non-SNs was 262, and 10 nodes in 8 women were positive. The total number of paraaortic non-SNs was 255, with 2 positive nodes in 2 women. The authors concluded that "this study shows the poor correlation between preoperative lymphoscintigraphy and surgical SN mapping in women with locally advanced cervical cancer" and noted the high proportion of women who had sentinel node metastases, "underlining the importance of multiple sectioning and immunohistochemical staining of SNs."

Annals of Surgical Oncology

SLN in Vulvar Cancer

Hauspy et al. from the University of Toronto (Canada) reported on July 11 ahead of print in *Cancer* on a study designed to assess the feasibility, efficacy, and accuracy of the sentinel lymph node (SLN) technique in vulvar cancer. The study included 41 patients with stage I or II vulvar cancer, each of whom underwent SLN detection followed by complete inguinofemoral lymphadenectomy. The SLN technique detected at least 1 SLN in 95% of patients. Sixteen of 41 patients (39%)

and 18 of 68 groins (26%) were found on histology to have metastatic disease in the lymph nodes, and all were correctly identified by the SLN procedure, with no false-negative results. The authors documented a relationship between improved detection of bilateral SLNs and proximity of the cancer to the midline. No contralateral SLNs were identified in patients with vulvar lesions >1 cm from the midline. When lesions were ≤1 cm from the midline, SLNs were detected in 93% of ipsilateral groins, and bilateral SLNs were found in 46% of patients. When lesions directly abutted the midline, unilateral and bilateral SLN detection rates were 100% and 93%, respectively. The authors concluded that "SLN dissection is feasible and safe to perform in vulvar cancer" but that the ability to identify bilateral sentinel inguinal lymph nodes "appears to be related to the proximity of the cancer to the midline."

Cancer

SLN in Colon Cancer

In an article e-published on July 12 ahead of print in the *International Journal of Colorectal Disease*, Kelder et al. from the Martini Hospital (Groningen, The Netherlands) reported on a multicenter study of the sentinel lymph node (SLN) procedure in colon cancer. The 6-hospital study included 69 patients scheduled for localized colon cancer surgery in whom the blue dye SLN biopsy technique was used. No SLNs were found in 43 patients, with 3 cases of false-negative findings, yielding a negative predictive value of 93% and an accuracy of 96%. The SLN was positive in 24 of 27 (sensitivity, 89%) patients with lymph node metastases. The SLN was the only positive node in 15 patients (21%). Only micrometastases or isolated tumor cells were found in 9 patients, resulting in 18% upstaging. The authors concluded that the SLN procedure in localized colon carcinoma is reliable and "helpful to identify patients who would be classified as stage II with conventional staging and who might benefit from adjuvant treatment."

International Journal of Colorectal Disease

Predictive Value of Negative SLN

Soran et al. from the University of Pittsburgh Medical Center (PA) reported in the July issue of the *Journal of the American College of Surgery* (2007;205:66–71) on a study designed to determine whether nonvisualization of SLNs on lymphoscintigraphy can identify a subset of breast cancer patients at greater risk of having a substantial burden of axillary tumor. The retrospective study included the records of 1,500 women who underwent dual-tracer SLN mapping for breast cancer. Lymphoscintigraphy identified axillary SLNS in 1,366 (91%) women. Of the 134 patients with negative lymphoscintigraphy, the SLN was identified intraoperatively by either blue dye or gamma detection in 133 (99.3%). SLN was positive in 28.4% and 29.1% of lymphoscintigraphy nonvisualized and visualized groups, respectively. Despite these similarities, the authors noted that a significantly higher percentage of women >50 years of age were in the nonvisualized group and that body mass index was >30 in 42.5% of the nonvisualized group but only 26.3% in the visualized group. Thus, they concluded that "failure to demonstrate axillary uptake by lymphoscintigraphy appears to be related to technical factors and patient-related factors, such as body mass index and older age, but does not adversely affect SLN identification."

Journal of the American College of Surgery

DCIS and Positive Sentinel Nodes

In an article e-published on June 28 ahead of print in the *Annals of Surgical Oncology*, Moore et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on a study investigating the clinical relevance of positive sentinel lymph nodes (SLNs) in patients with ductal carcinoma in situ (DCIS). The 3-institution study included SLN biopsy results on 470 high-risk patients diagnosed with DCIS. In this group, 43 (9%) patients were found to have SLN metastases, and pathology and follow-up data were collected on these patients and on patients whose SLN biopsies were negative. As expected, extensive disease leading to mastectomy and/or the presence of necrosis were associated with an increased risk of nodal positivity. Of the 43 SLN-positive patients, 3 (7%) were found to have macrometastases, 4 (9%) had micrometastases, and 36 (84%) had single tumor cells or small clusters. Twenty-five of these women proceeded to completion axillary dissection, where 1 was found to have a macrometastasis. Primary lesion pathology found 2 (5%) of the 43 SLN-positive patients with a microinvasion and 2 (5%) with lymphovascular invasion. The procedure changed management in 9 (21%) of the 43 high-risk DCIS patients with positive SLNs, who were upstaged to American Joint Committee on Cancer stage I or II. The authors concluded that "SLN biopsy for high-risk DCIS patients is a means of detecting those who may have unrecognized invasive disease and therefore are at risk for distant disease."

Annals of Surgical Oncology

Large-Scale Heart Failure Trial Underway

In the July issue of the *American Heart Journal* (2007;154:45–53), Bensimhon et al. from the Moses Cone Hospital (Greensboro, NC) described the nuclear medicine aspects of a substudy of the ongoing Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION), a National Institutes of Health/National Heart, Lung, and Blood Institute–funded randomized controlled trial designed to evaluate the role of exercise training in patients with heart failure resulting from left ventricular dysfunction. The 5-year, 3,000-patient HF-ACTION trial extends across 50 institutional sites in the United States and Canada and continues to enroll participants. For this substudy, a total of 300 patients assigned either to the exercise training or standard care arms of the HF-ACTION trial will undergo resting ^{99m}Tc-gated SPECT at baseline and after 12 months to compare changes in left ventricular function. These changes will be assessed along with changes in exercise

parameters, inflammatory markers, and clinical outcomes, including death, cardiovascular hospitalization, and quality of life scores. A smaller subset of these 300 patients will undergo first-pass radionuclide ventriculography to assess relationships among ventricular dyssynchrony, ejection fraction, changes in exercise parameters, and outcomes. Additional information about the HF-ACTION trial is available from local sites, listed at www.hfaction.org.

American Heart Journal

Imaging Contraction-Induced Glucose Uptake

Kalliokoski et al. from the University of Turku (Finland) reported in the July issue of *Clinical Physiology and Functional Imaging* (2007;27:239–241) on the potential for imaging glucose in human lower extremities using high-resolution ^{18}F-FDG PET (ECAT High-Resolution Research Tomograph). ^{18}F-FDG uptake was studied in a 30-year-old man during voluntary and stimulated isometric muscle contractions. In the resulting images, activated muscle or muscles were clearly delineated, as was the load-induced gain in tendon uptake. The authors noted the potential for such studies in providing important information on the in vivo mechanical function of force-transmitting tissues. They concluded that the high-resolution PET scanner "is an appropriate tool for investigating physiological processes within the human extremities, and the very high resolution yields a potential for more accurate conclusions when target tissues are limited in size."

Clinical Physiology and Functional Imaging

Ventricular Function and Brain Natriuretic Peptide

In a study e-published on July 3 ahead of print in the *European Journal of Heart Failure*, Vogelsang et al. from the Rigshospitalet (Copenhagen, Denmark) and the University of Copenhagen reported on a study designed to assess the relative contributions of the right and left ventricular functions to the increases in plasma brain natriuretic peptide (BNP) associated with heart failure. The study included 105 patients who underwent first-pass radionuclide ventriculography and multiple electrocardiograph-gated equilibrium radionuclide ventriculography to assess right and left ventricular ejection fractions (RVEF and LVEF, respectively), and LV end-diastolic volume index (LVEDVI). Immunoassay analyses were conducted to assess BNP levels. Initial results indicated that mean LVEF was 0.51, with a reduced LVEF in 36% of patients. Mean RVEF was 0.50, with a reduced RVEF in 43% of patients. Mean LVEDVI was 92 mL/m^2, with 22% above the upper normal limit, and mean BNP was 239 pg/mL. In a multivariate analysis, only RVEF and LVEF showed significant correlations with BNP levels, and these correlations were similar. The authors concluded that "BNP, which is a strong prognostic marker in heart failure, independently depends on both left and right ventricular systolic function" and noted that this finding might, in part, explain the stronger prognostic value of BNP than LVEF alone in heart failure.

European Journal of Heart Failure

PET and Cerebral Oxygen Carrier Imaging

Awasthi et al. from the University of Oklahoma Health Science Center (Oklahoma City) reported in the July issue of the *Journal of Applied Physiology* (2007;103:28–38) on PET imaging of a liposome-encapsulated hemoglobin (LEH) under development as an artificially assembled, low-toxicity, and spatially isolated oxygen carrier. They developed the delivery system in response to challenges in evaluating oxygen carriers using surrogate indicators of physiology in animal models of shock. In this study, the authors presented imaging and other findings from ^{15}O PET imaging of LEH in a rat model of 40% hypovolemic shock. PET images allowed the investigators to determine the cerebral metabolic rate of oxygen as a direct indicator of LEH oxygen-carrying capacity as well as oxygen delivery and metabolism in the rat brain. These and additional resuscitation studies led to the conclusion that ^{15}O PET "can be successfully employed to evaluate potential oxygen carriers and blood substitutes and that LEH resuscitation in hemorrhage enhances oxygen delivery to the cerebral tissue and improves oxygen metabolism in brain."

Journal of Applied Physiology

MOLECULAR IMAGING

Tracking Transplant Cells in Spinal Cord Injury

Callera and de Melo, from the Serviço de Hematologia e Hemoterapia de São José Dos Campos (São Paulo, Brazil) reported in the June issue of *Stem Cells and Development* (2007;15:461–466) on the use of MR imaging to track the delivery of autologous bone marrow precursor cells labeled with magnetic nanoparticles into the spinal cord via lumbar puncture (LP) in patients with spinal cord injury (SCI). The study included 16 patients with chronic SCI. Ten patients received LP-route spinal cord injections of autologous labeled-CD34$^+$ cells; the remaining 6 patients received similar injections of magnetic beads without stem cells. Patients underwent MR imaging before and at 20 and 35 days after transplantation. The labeled precursor cells were visible in 5 patients at the lesion site as hypointense signals at 20 and 35 days after transplantation; no such signals were visible in the control group. The authors concluded that this visual proof that autologous bone marrow CD34$^+$ cells labeled with magnetic nanoparticles delivered into the spinal cord via LP technique migrated into injured sites in patients with chronic SCI holds great promise for future therapeutic investigations.

Stem Cells and Development

MR and Cellular Migration

In an article released in June in a special issue on "Neurotrauma: New Insights into Pathology and Treatment" in *Progress in Brain Research (*2007;

161C:367–383), Sykova and Jendelova from Charles University (Prague, Czech Republic) reported on a study of the use of cellular MR imaging in visualizing and tracking superparamagnetic iron oxide (SPIO) nanoparticle–labeled stem cells in rat models of stroke and spinal cord injury (SCI). The authors intracerebrally grafted or injected embryonic stem cells (ESCs) and bone marrow mesenchymal stem cells (MSCs) labeled with SPIO nanoparticles and human $CD34^+$ cells labeled with magnetic microbeads into rats with a cortical or spinal cord lesions. As early as the first week after transplantation, MR imaging indicated hypointensive signal from grafted MSC and ESC migration to lesions in the cortex and spinal cord, with signal persisting for more than 30 days. Moreover, in the rat model of SCI, an increase in functional recovery was noted after implantation of MSCs or a freshly prepared mononuclear fraction of bone marrow cells or after an injection of granulocyte colony stimulating factor. Additional studies indicated increased white matter volume in the center of lesions in cell-treated rats. The authors described improved cellular uptake results with a new polycation-bound SPIO and concluded that MR imaging "of grafted adult as well as ESCs labeled with iron oxide nanoparticles is a useful method for evaluating cellular migration toward a lesion site."

Progress in Brain Research

In Vivo Optical Tumor Imaging

Venisik et al. from the University of California at Los Angeles reported on June 19 ahead of print in *Molecular Imaging and Biology* on the fusion of the bioluminescent protein Gaussia luciferase to an engineered anticarcinoembryonic antigen (CEA) antibody fragment (diabody) for in vivo optical imaging. They found that a 15-amino acid *N*-terminal truncation (GLΔ15) resulted in a brighter protein. Results with the fused diabody and full-length Gaussia luciferase or the truncation showed high affinity for the antigen, emitted light, and exhibited enzymatic stability. In vivo optical imaging in tumor-bearing mice showed specific targeting of diabody–GLΔ15 to CEA-positive xenografts, with ^{124}I-diabody–GLΔ15 microPET imaging confirming specific tumor uptake. The authors concluded that "although further optimization of this fusion protein may be needed to improve in vivo performance, the diabody-GLΔ15 is a promising optical imaging probe for tumor detection in vivo."

Molecular Imaging and Biology

Nanoparticles for US Tumor Imaging and Chemotherapy

In the July 18 issue of the *Journal of the National Cancer Institute* (2007;99: 1095–1106), Rapoport et al. from the University of Utah reported on a multifunctional nanoparticle technology with potential for combining ultrasound tumor imaging and targeted chemotherapy. The authors prepared and investigated the properties of mixtures of drug-loaded polymeric micelles and perfluoropentane nano/microbubbles. In vitro and in vivo studies of the effect of the nano/microbubbles on ultrasound-mediated cellular uptake of doxorubicin in MDA MB231 breast tumors were conducted in mice. Doxorubicin was found to localize in the microbubble walls formed by the block copolymer, and, after injection into mice, doxorubicin-loaded micelles and nanobubbles extravasated selectively into the tumor interstitium, where the nanobubbles coalesced and produced microbubbles with strong and durable ultrasound contrast. Doxorubicin was retained in the microbubbles but was released in response to application of therapeutic ultrasound. The authors concluded that these nanoparticles that can simultaneously function as tumor-targeted drug carriers, long-lasting ultrasound contrast agents, and enhancers of ultrasound-mediated drug delivery "deserve further exploration as cancer therapeutics."

Journal of the National Cancer Institute

Molecular Imaging of Atherosclerotic Inflammation

Kaufmann et al. from the Oregon Health and Sciences University (Portland) reported in the July 17 issue of *Circulation* (2007;116:276–284) on the use of contrast-enhanced ultrasound (CEU) for molecular imaging of vascular adhesion molecule-1 (VCAM-1) expression in vascular inflammatory response. Initial in vitro studies verified attachment of VCAM-1-targeted and control microbubbles to cultured endothelial cells, and in vivo studies in mice verified microbubble attachment to aortic plaque. The experiments were continued with intravenous injection of VCAM-1-targeted and control microbubbles in wild-type or apolipoprotein E-deficient mice on either a chow or hypercholesterolemic diet. CEU molecular imaging of the thoracic aorta was performed at 10 minutes after injection. Aortic attachment of microbubbles and CEU signal for VCAM-1-targeted microbubbles differed between treatment groups, according to extent of VCAM-1-positive plaque formation. The authors concluded that "CEU molecular imaging of VCAM-1 is capable of rapidly quantifying vascular inflammatory changes that occur in different stages of atherosclerosis" and noted the potential of this approach for early risk stratification according to inflammatory phenotype.

Circulation

Bone Marrow Cell Engraftment in Ischemic Myocardium

In a study e-published on July 12 ahead of print in *Stem Cells*, Sheikh et al. from Stanford University (CA) reported on a study of bioluminescent molecular imaging of bone marrow mononuclear cell (BMMC) homing and engraftment in ischemic myocardium. Donor BMMCs were harvested from adult male L2G85 transgenic mice expressing both firefly luciferase and enhanced green fluorescence protein reporter gene. Thirty-eight adult female recipient mice were randomized to

sham surgery or acute ischemia/reperfusion injury. Animals in the sham ($n = 16$) and ischemia/reperfusion ($n = 22$) groups were injected with 5×10^6 of the L2G85-derived BMMCs. Bioluminescence imaging was used to track cell migration and survival for 4 weeks and showed preferential BMMC homing to hearts in the ischemia/reperfusion injury group within the first week after cell injection. Ex vivo analyses later confirmed the imaging results. Functional evaluation by echocardiography indicated a trend toward improved left ventricular fractional shortening in animals receiving BMMCs. The authors concluded that "these data demonstrate that molecular imaging can be used to successfully track BMMC therapy in murine models of heart disease" and that "systemically delivered BMMCs preferentially home to and are retained by injured myocardium."

Stem Cells

(Continued from page 13N)

What can an individual physician do? First, devote a portion of your CME time to developing expertise in dealing with a radiological event. Encourage your institutional planners who deal with disaster plans to involve you in their discussions. Reach out to your first responder community and develop links with them so that you know their capabilities and they know yours. Talking and training together will improve all of your skills. Assume that for at least a while your local community will have to bear the burden of responding to an event should one occur. Our military counterparts developed their techniques during a period of relative peace; we must do the same.

Like our military colleagues, we may believe that we are developing a plan for something that will never happen. The success of military medicine today, however, is rooted in planning for possible events. We cannot risk being unprepared, because one day, quite suddenly, we could find ourselves on the front line.

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