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 both diagnostic and therapeutic progress in this area.

DIAGNOSIS

Sentinel Node Identification in Colon Cancer

Covarelli et al. from the University of Perugia (Italy) reported in the March issue of the *American Surgeon* (2007;73:222–226) on a study designed to assess the prognostic value of sentinel node identification by radioguided surgery in colon cancer. The study included 20 patients with colon tumors who received intraoperative, peritumoral injections of blue dye and ^{99m}Tc-labeled colloidal particles. Sentinel nodes were identified using a handheld gamma probe and labeled. After lymphadenectomy, the probe was used to confirm radioactivity in the excised tissues and to check for remaining radioactivity in the surgical field. The gamma probe technique successfully identified sentinel nodes in 19 (95%) of the patients (25 nodes total, 1 in each of 13 patients and 2 in each of 6 patients). The dye identified sentinel nodes in 14 patients but overestimated the number of nodes in a few. The authors concluded that sentinel node identification in colon cancers "is a safe, fast, and easy procedure for ultrastaging the nodal basin" and that the technique has "a relatively flat learning curve and could become standard care for identifying the presence of nodal micrometastases at a low cost, thereby also making it affordable at small health centers." The authors pointed out that these findings are especially significant given the current 5-year survival statistics for patients initially judged to be nodal disease–free at conventional surgery and staging.

American Surgeon

Pretreatment PET in Cervical Cancer

In an article e-published on March 15 ahead of print in the *International Journal of Gynecological Cancer*, Unger et al. from the Louisiana State University Health Sciences Center (Shreveport) reported on a retrospective study assessing the prognostic value of pretreatment ^{18}F-FDG PET imaging in women with cervical cancer. The study included the records of 56 women who underwent such imaging before the initiation of treatment. Abnormal tracer uptake was seen only in pelvic nodes in 14 (25%) women and in pelvic and paraaortic nodes in 10 (17.9%) women, with no uptake in these nodes in the remaining 32 (57.1%) women. The presence of positive pelvic and/or paraaortic nodes was a significant predictor of poor 20-month disease-free survival. The authors concluded that a "pretreatment FDG PET scan revealing abnormal FDG uptake consistent with nodal disease is a robust predictor of disease recurrence and may alter the therapeutic management of some patients." This finding is particularly relevant given the current risks associated with routine cervical cancer staging, which suffers from inaccuracies in the detection of nodal disease.

International Journal of Gynecological Cancer

PET/CT Advantages in Lung Cancer Staging

De Wever et al. from the University Hospitals Gasthuisberg (Leuven, Belgium) reported on March 1 ahead of print in the *European Respiratory Journal* on a study designed to determine the incremental value of PET/CT over CT or PET alone in the detection of unexpected extrapulmonary lesions in patients being staged for malignant pulmonary lesions. The retrospective study included the records of 217 patients with pathology-proven lung tumors who underwent PET/CT. CT, PET, and PET/CT images were evaluated separately for the presence of extrapulmonary lesions, with final diagnoses from medical records serving as the gold standard. PET/CT was found to detect extrapulmonary lesions and identify malignant lesions significantly better than PET or CT alone. PET/CT was found to have sensitivity, specificity, positive and negative predictive values, and accuracy of 100%, 81%, 71%, 100%, and 87%, respectively, for the detection of all extrapulmonary lesions and corresponding respective results of 92%, 98%, 89%, 98%, and 97% for the detection of malignant extrapulmonary lesions. The authors concluded that the ability of PET/CT to identify and accurately characterize more unexpected extrapulmonary lesions than either CT or PET alone makes this approach significantly more beneficial than current conventional staging work-ups.

European Respiratory Journal

PET/CT in Cancer of the Nasopharynx

In an article e-published on February 24 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics,* Gordin et al. from Rambam Health Care (Haifa, Israel) reported on a study comparing the effect of ^{18}F-FDG PET/CT

with that of standalone PET and conventional imaging alone on management and clinical course in patients with nasopharyngeal carcinoma. The retrospective study included 33 patients with the disease who underwent a combined total of 45 PET/CT studies. The authors found that PET/CT results had sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92%, 90%, 90%, 90%, and 91%, respectively, whereas the corresponding respective results for PET alone were 92%, 65%, 76%, 86%, and 80% and for conventional imaging alone were 92%, 15%, 60%, 60%, and 60%. PET/CT affected treatment and management plans in 19 (57%) patients by eliminating the need for previously planned diagnostic procedures (11 patients), changing the therapeutic strategy (5 patients), and guiding biopsies directly to specific areas of metabolic activity (3 patients).

International Journal of Radiation Oncology, Biology, Physics

PET, CT, and Ultrasound in Esophageal Cancer Staging

Pfau et al. from the University of Wisconsin Medical School (Madison) reported in the March issue of *Gastrointestinal Endoscopy* (2007;65:377–384) on a study designed to determine the value and role of endoscopic ultrasound (EUS) when used with CT or PET in staging cancers of the esophagus and gastroesophageal junction. The retrospective study included the records of 56 patients who underwent staging with all 3 modalities. The results were analyzed for the ability of each modality to identify primary tumor, local tumor stage, locoregional adenopathy, and distant metastases and for effects on clinical management. Alone among the modalities, EUS identified all primary tumors and was significantly better at identifying patients with locoregional adenopathy. CT and PET identified 14.3% and 26.8%, respectively, of patients with distant metastases (information not offered by EUS). Management was affected in different ways by each modality: PET alone prevented surgery for metastatic disease in 28.3% of patients; this figure was 15.2% with CT alone; and EUS changed management by guiding the need for neoadjuvant therapy in 34.8% of patients. The authors concluded that such guidance was the "primary strength of EUS in a multimodality staging strategy." They added that "EUS is not suited to determine resectability of esophageal cancer alone and thus is most effective when used in conjunction with other imaging tests such as CT and PET."

Gastrointestinal Endoscopy

ACoSOG Report on PET in Esophageal Cancer

Participants in the American College of Surgeons Oncology Group trial Z0060, a prospective multiinstitutional trial evaluating the ability of ^{18}F-FDG PET imaging to detect evidence of metastastic disease and thereby affect management in patients with esophageal cancer, reported on the trial's latest results in the March issue of the *Journal of Thoracic and Cardiovascular Surgery* (2007;133:738–745). The results included data from 189 evaluable and eligible patients with resectable, biopsy-proven esophageal carcinoma whose chest and abdomen CT studies indicated no evidence of metastasis. Each patient underwent ^{18}F-FDG PET imaging. Positive results were verified with additional confirmation, and patients with negative results proceeded to surgery. A total of 145 (78%) patients went on to surgery, and 42 (22%) did not (in 2 patients the surgical status could not be determined). Among the patients who did not proceed to resection, the following reasons were listed: stage M1 disease identified by PET and confirmed (n = 9); M1 disease found by PET and not confirmed (n = 2); M1 disease at exploration not found by PET (n = 7); decline or death before surgery (n = 10); refusal of surgery (n = 7); unresectable local tumor at exploration (n = 5); and extensive N1 disease precluding surgery (n = 2).The authors noted that although 22% of eligible patients did not undergo esophagectomy, PET after standard clinical staging for esophageal carcinoma identified confirmed M1 disease in at least 4.8% of patients before resection and that "unconfirmed PET evidence of M1 disease and regional adenopathy (N1 disease) led to definitive nonsurgical or induction therapy in additional patients."

Journal of Thoracic and Cardiovascular Surgery

SPECT αvβ3 Imaging in Breast Cancer

Liu et al. from a consortium of researchers from Purdue University (West Lafayette, IN), Stanford University (CA), and Peking University (Beijing, China) reported in the March 21 issue of *Bioconjugate Chemistry* (2007;18:438–446) on initial studies of the potential for a novel ^{125}I-labeled RGD peptide for SPECT imaging of integrin αvβ3-positive breast cancer cells. The study was conducted in mice bearing MDA-MB-435 breast cancer xenografts. Resulting data on the compound ^{99m}Tc-HYNIC-tetramer tricine trisodium triphenylphosphine-3,3′,3′-trisulfonate indicated high integrin αvβ3 specificity, high tumor uptake, long tumor retention, metabolic stability, rapid blood clearance, and excretion mainly through the renal route. SPECT images accompanying the article showed significant radiotracer localization in tumor with good contrast as early as 1 hour after injection. The authors concluded that the high tumor uptake and fast renal excretion make this imaging compound a promising radiotracer for SPECT imaging of αvβ3-positive tumors.

Bioconjugate Chemistry

PET and Adrenal Masses

Han et al. from Yonsei University (Seoul, Korea) reported on March 1 ahead of print in the *International Journal of Clinical Practice* on a study assessing the incremental value of ^{18}F-FDG PET in characterizing adrenal masses originally identified on CT.

The study included 105 patients with adrenal masses on CT. Each patient also underwent ^{18}F-FDG PET imaging. Positive uptake was seen in 67 sites (54 metastasic lesions, 6 primary adrenal cancers, and 7 benign tumors). The positive and negative predictive values of PET in this setting were each 90%. Positive uptake on PET was seen in all adrenocortical carcinomas, 2 of 3 pheochromocytomas, 3 of 5 neuroblastomas, and 2 of 4 cases of primary aldosteronism. The authors concluded that in patients with adrenal masses with a high probability of malignancy, PET can be used to differentiate malignant from benign adrenal lesions. They cautioned that inconsistent patterns of ^{18}F-FDG uptake in endocrine tumors could confound the modality's utility as a first-line diagnostic tool. Instead, the results suggested that PET "can offer supporting data to localize and characterize adrenal tumors."

International Journal of Clinical Practice

THERAPY

Venous Thyroglobulin Gradients in DTC

Kebebew and Reiff from the University of California, San Francisco, reported in the March issue of *Cancer* (2007;109:1078–1081) on a study suggesting that patients with differentiated thyroid cancer (DTC) have a venous gradient in thyroglobulin protein levels. The study included 15 patients who underwent thyroidectomy and/or lymph node dissection for primary (n = 10 patients) or recurrent or persistent DTC (n = 5 patients). After venipuncture, thyroglobulin protein levels were assessed by chemiluminescence assay. The authors found that the average internal jugular-to-antecubital vein thyroglobulin protein ratio was 3.4 to 1.0. This ratio was significantly higher in patients with recurrent or persistent DTC than in those with primary tumors. Results from 4 patients with positive antithyroglobulin antibodies still showed significant thyroglobulin gradients. The authors concluded that these findings suggest "that venous sampling for thyroglobulin may be used to localize DTC in some patients who have high or increasing serum thyroglobulin levels but negative radioiodine scans or imaging studies."

Cancer

Hyperthyroidism and Mortality After ^{131}I Treatment

In an article e-published on March 20 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Metso et al. from the University of Tampere (Finland) and the STUK–Radiation and Nuclear Safety Authority (Helsinki, Finland) reported on a study investigating increased mortality associated with radioiodine treatment for hyperthyroidism. The population-based, cohort study compared the health records of 2,793 patients who received ^{131}I treatment for hyperthyroidism with an equal number of age- and sex-matched reference individuals. Over a median follow-up of 9 years, mortality statistics from all causes in the patient and reference populations were 453 and 406, respectively, per 10,000 person-years. This significant difference was accounted for by cerebrovascular diseases and cancer. Increased mortality among patients was also associated with age >60 years at treatment, higher ^{131}I doses, and nodular thyroid disease. Previous treatment with partial thyroidectomy was associated with a decrease in mortality rates among patients, whereas antithyroid medication was not associated with a change in mortality. These and other results led the authors to conclude that "hyperthyroidism per se probably accounts for the increased cerebrovascular mortality after radioiodine treatment." They noted that the increased cerebrovascular and cancer mortality among these patients emphasizes the need for effective treatment of hyperthyroidism despite the risk of hypothyroidism and the importance of life-long follow-up and screening for cerebrovascular risk factors and malignant disease.

Journal of Clinical Endocrinology and Metabolism

Removing Excess Radioimmunoconjugates

Kurkus et al. from the Lund University Hospital (Sweden) reported in the March issue of *Artificial Organs* (2007;31:208–214) on the biocompatibility of a novel avidin–agarose adsorbent for removal of redundant radiopharmaceuticals from the blood of individuals undergoing targeted, radiolabeled monoclonal antibody therapy. Effective tumor immunotherapy is currently limited by toxicity to vital organs. The authors described extracorporeal affinity adsorption treatment (ECAT) using an avidin–agarose adsorbent with high binding affinity for rituximab. The study included 7 patients with B-cell lymphoma unresponsive to conventional therapy. During the ECAT procedure, which removes excess radioimmunoconjugates not bound to tumor cells in rituximab therapy, hematologic studies and other biocompatibility data were gathered. Only slight decreases in B-hemoglobin (8.3%), B-thrombocytes (11.4%), and P-albumin (14.3%) were noted and were believed to be the result of dilution of the blood with normal saline and acid citrate dextrose. No adverse effects were noted, and no additional effects were noted on blood cells, immunologic status, or P-bradykinin levels. The authors concluded that these results are encouraging and point toward the possibility of significantly increasing radiolabeled monoclonal antibody therapy doses to tumors, with lowered risk of toxicity and adverse side effects.

Artificial Organs

Improving α-Particle RIT with a Chemotherapeutic Agent

In the March 15 issue of *Clinical Cancer Research* (2007;13:1926–1935), Milenic et al. from the National Cancer Institute (Bethesda, MD) and

the Walter Reed Army Medical Center (Washington, DC) reported on a study exploring the incremental value in combining gemcitabine chemotherapy with ^{212}Pb -trastuzumab radioimmunotherapy (RIT) for treatment of disseminated peritoneal disease. The research included a series of experiments in LS-174T xenograft–bearing mice injected first with gemcitabine at 50 mg/kg and then receiving the ^{212}Pb RIT. Multiple and differing doses of both chemotherapeutic and RIT agents were assessed, with the gemcitabine clearly conferring survival benefits when compared with results from mice that did not receive the potentiating chemotherapy. Of the various protocols evaluated, the greatest benefit (median survival = 196.5 days) was noted after 2 cycles of gemcitabine and 10 μCi ^{212}Pb-trastuzumab. The authors noted evidence suggesting that this potentiating effect might not be specific to trastuzumab and that "treatment regimens combining chemotherapeutics with high-LET targeted therapy may have tremendous potential in the management and care of cancer patients."

Clinical Cancer Research

^{90}Y-Labeled mAb Treatment in Ovarian Cancer

In an article e-published on March 12 ahead of print in the *International Journal of Cancer*, Oei et al. from Radboud University Nijmegen Medical Centre (The Netherlands) described the effect of a single administration of ^{90}Y-μHMFG, a murine monoclonal antibody, on patterns of disease recurrence in patients with epithelial ovarian cancer. The study included 447 women participating in a larger phase III trial who were in complete clinical remission with FIGO stage Ic–IV disease. Patients were divided into 2 groups after negative second-look laparoscopy: (1) standard treatment plus a single intraperitoneal injection of ^{90}Y-μHMFG (n = 224) and (2) standard treatment alone (n = 223). After a median follow-up period of 3.5 years, recurrence of disease was seen in 104 patients in the treatment group and in 98 patients in the control group. Results indicated that those in the treatment group experienced significantly fewer intraperitoneal but more extraperitoneal recurrences than those in the control group. In addition, time to intraperitoneal recurrence was significantly longer and time to extraperitoneal recurrence was significantly shorter for the treatment group. The addition of consolidation radioimmunotherapy conferred no survival benefit, except in the subgroup of patients with residual disease after primary surgery.

International Journal of Cancer

MOLECULAR IMAGING

Fluorescent Molecular Tomography in Myocardial Infarct

In an article e-published on March 22 ahead of print in *Circulation Research*, Nahrendorf et al. from the Massachusetts General Hospital (Boston) reported on multichannel fluorescent molecular tomography (FMT) for spatiotemporal resolution of phagocytic and proteolytic activities mediated by macrophages and neutrophils in murine infarcts. The promising imaging approach was used to compare inflammatory responses and tissue repair after myocardial infarction in wild-type and FXIII(–/–) mice. After coronary ligation, mice received simultaneous injections of an activatable fluorescence sensor reporting on cathepsin activity and a magnetofluorescent nanoparticle for imaging of phagocyte recruitment. On FMT the infarct signal was clearly distinguishable in the infarcted lateral wall and not the uninjured septum. Additional studies indicated monocytes/macrophages and neutrophils as the source of the fluorescent signal and determined when phagocytic proteolytic activities peaked (days 6 and 4 after infarction, respectively). The authors concluded that "FMT is a promising noninvasive molecular imaging approach to characterize infarct healing," particularly because "spectrally resolved imaging agents allow for simultaneous assessment of key processes of in vivo cellular functions."

Circulation Research

Immunobubble Imaging of Human Thrombus

Alonso et al. from the University of Heidelberg (Germany) and Bracco Research (Geneva, Switzerland) reported on March 22 ahead of print in *Stroke* on a study describing the use of a novel microbubble carrier (immunobubble) for abciximab, a glycoprotein IIb/IIIa receptor inhibitor, in ultrasonographic molecular imaging of human clots. Human thrombi incubated with immunobubbles conjugated with abciximab were imaged in a rat model of carotid artery occlusion. The authors found that ultrasonic detectability of carotid thrombi was significantly higher for clots targeted with abciximab immunobubbles than those targeted with control microbubbles. Additional in vitro and in vivo studies led to the conclusion that abciximab immunobubbles improve visualization of human clots in models of acute arterial thrombotic occlusion and suggested the "feasibility of using a therapeutic agent for selective targeting in vascular imaging."

Stroke

Molecular MR Imaging of Cerebral Vein Thrombosis

Also reporting on March 22 ahead of print in *Stroke* were Stracke et al. from the University of Cologne (Germany), Aachen University (Germany), and EPIX Pharmaceuticals (Cambridge, MA), who described a study on the feasibility of a novel fibrin-targeted MR contrast agent for selective imaging of sinus venous thrombosis. Cerebral vein thrombosis is currently performed with combinations of CT, MR, MR angiography, and conventional digital subtraction angiography, each of which has distinct limitations. The researchers studied their approach in 6 swine with induced human blood thrombosis of the

superior sagittal sinus. Before and up to 2 hours after injection with the contrast agent, 3D high-resolution MR imaging was performed. After imaging, thrombi were surgically removed and assessed for gadolinium concentration. The thrombi showed enhancement immediately after injection of the contrast agent, with continuous contrast-to-noise ratio increases between thrombus and blood pool up to the 2-hour mark. The authors concluded that "the fibrin-targeted molecular MR contrast EP-2104R allows selective and high-contrast imaging of cerebral sinus vein thrombosis in an animal model."

Stroke

PET Imaging of GRPRs

Biddlecombe et al. from the Washington University School of Medicine (St. Louis, MO), Erasmus Medical College (Rotterdam, The Netherlands), and BioSynthema, Inc. (St. Louis, MO) reported on March 23 ahead of print in *Bioconjugate Chemistry* on a study evaluating the PET imaging capabilities of a radiolabeled peptide that binds to gastrin-releasing peptide receptors (GRPR). The bombesin peptide, MP2346, was radiolabeled with either ^{64}Cu or ^{86}Y, and the resulting compounds were evaluated for in vitro cellular internalization by GRPR-expressing human prostate adenocarcinoma (PC-3) cells. In vivo tissue and biodistribution studies of both compounds were conducted in mice with PC-3 tumors. Small animal PET/CT imaging was carried out in mice bearing PC-3 tumors and rats bearing AR42J tumors. Although both compounds produced significant images, ^{86}Y-MP2346 PET images were superior because of lower uptake in clearance organs and lower background activity. The authors concluded that "the ^{86}Y analogue demonstrated excellent PET image quality in models of prostate cancer for the delineation of the GRPR-rich tumors and warrants further investigation."

Bioconjugate Chemistry

(Continued from page 16N)

will provide modest growth for radiographic and fluoroscopic systems despite maturing markets. Nuclear medicine and ultrasound equipment are predicted to fare better than X-ray and fluoroscopy systems in the health care sector. New 4-dimensional imaging systems for existing markets and laptop and handheld devices for point-of-care testing will boost overall growth prospects for diagnostic ultrasound equipment.

Demand for medical imaging consumables (contrast media, supplies, radiopharmaceuticals, etc.) is projected to expand 3.6% annually to $5.3 billion in 2010. Radiopharmaceuticals will provide the best growth opportunities, based on the rising numbers of nuclear medicine and PET procedures as well as increasing professional preferences for high value–added, biotechnology-derived substances that enhance image resolution and detail.

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