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. Many of these briefs, from across the spectrum of clinical and research efforts, illustrate the ways in which diagnosis and therapy are now combined in single or complementary approaches. 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

PET-Guided, Focal Dose Escalation IMRT

Madani et al. from Ghent University Hospital (Belgium) reported in the May issue of the *International Journal of Radiation Oncology, Biology, Physics* (2007;68:162–135) on a study using PET-guided dose estimation in intensity-modulated radiotherapy (IMRT) in head and neck cancer. The study included 41 patients with head and neck cancer who were enrolled in a phase I clinical trial designed to escalate dose to only the ^{18}F-FDG PET–delineated subvolume of gross tumor volumes. Each patient underwent PET imaging in the treatment position, followed by IMRT with an upfront simultaneously integrated boost. The study design included assessment of 2 dose levels: 25 Gy (23 patients) and 30 Gy (18 patients), delivered in 10 fractions. All patients then underwent standard IMRT for the remaining 22 fractions at 2.16 Gy. Thirty-nine patients completed the therapy, with a 14-month median follow-up for surviving patients. One treatment-related death resulted at the higher dose level. Two cases of dose-limiting toxicity were noted at the lower dosage. Complete responses were noted in 18 (86%) patients who could be evaluated after the study at the lower dosage and 13 patients (81%) at the higher dosage, with 1-year overall survival at 82% and 54% in the respective groups. In 4 of 9 patients who experienced relapse, the site was in the ^{18}F-FDG PET–delineated boost area. The authors concluded that "for head and neck cancer, PET-guided dose escalation appears to be well-tolerated," noting that the maximum tolerated dose was not reached or identified at the dose levels used in this study.

International Journal of Radiation Oncology, Biology, Physics

PET/CT Supplements FIGO Staging in Cervical Cancer

In an article e-published on May 4 ahead of print in *Gynecologic Oncology*, Loft et al. from the Copenhagen University Hospital (Denmark) reported on a study investigating the clinical value of PET/CT as a supplement to staging in patients with cervical cancer already evaluated at International Federation of Gynecology and Obstetrics (FIGO) stages of 1B or higher. The study included 120 such women, each of whom underwent whole-body PET/CT. On the basis of information from both FIGO and PET/CT staging, patients were divided into 2 groups: (1) those suitable for radical hysterectomy including lymph node dissection; and (2) those referred to combined chemo/radiation therapy. Of the 27 patients who underwent radical surgery, 4 had PET/CT studies showing foci of uptake in the pelvis. Of these, 3 studies were true-positive and 1 was false-positive. PET/CT was true-negative for pelvic lymph nodes in 22 surgical patients and false-negative in only 1 patient. For all surgical patients, then, the positive and negative predictive values, sensitivity, and specificity of PET/CT were 75%, 96%, 75%, and 96%, respectively. In the total population, PET/CT was true-negative for paraaortal nodal disease in 103 patients and true-positive in 15, with positive and negative predictive values, sensitivity, and specificity of 94%, 100%, 100%, and 99%, respectively. PET/CT was true-positive for distant metastases in 10 patients, false-positive in 9 patients, and true-negative in 100 patients, for positive and negative predictive values, sensitivity, and specificity of 63%, 100%, 100%, and 94%, respectively. The authors concluded that "whole-body FDG PET/CT scanning for newly diagnosed cervical cancer FIGO stage $\geq$1B has a high sensitivity and specificity and can be a valuable supplement to the FIGO staging procedure."

Gynecologic Oncology

Prognostic Pretransplant Imaging in Hodgkin's Lymphoma

Jabbour et al. from the University of Texas M.D. Anderson Cancer Center (Houston) reported on May 11 ahead of print in *Cancer* on a retrospective study designed to assess the prognostic value of PET and gallium scanning in predicting outcomes for patients with recurrent/refractory Hodgkin's lymphoma scheduled for high-dose chemotherapy with autologous stem cell transplantation (ASCT). The study included the records of 211 patients treated with ASCT over a decade at the authors' institution. Results of functional imaging with PET (68 patients) and gallium scanning (144 patients) were correlated with progression-free and overall survival statistics. A

total of 199 patients were followed for a mean of 3 years, with a complete or unconfirmed complete response to treatment in 51%, a partial response in 41%, and stable or progressive disease in 7%. Functional imaging was positive in only 6 (5%) of 110 patients with complete or unconfirmed complete responses, in 48 (56%) of 86 patients with partial responses, and in all 3 patients with progressive disease. For these complete response/unconfirmed complete response patients with negative functional imaging, the 3-year progression-free survival rate was 69%. This figure was 23% for those with positive functional imaging. The corresponding 3-year overall survival rates were 87% and 58%, respectively. The authors concluded that pretransplant functional imaging status not only predicts outcomes in patients with recurrent/refractory Hodgkin's lymphoma, but "positive functional imaging confers a poor prognosis, independent of other traditional presalvage prognostic factors."

Cancer

PET in Metastases from Cervical Cancer

In an article e-published ahead of print on May 1 in *Gynecologic Oncology,* Husain et al. from Stanford University School of Medicine (CA) and Memorial Sloan–Kettering Cancer Center (New York, NY) reported on a study of the utility of ^{18}F-FDG PET in identifying sites of metastatic disease before pelvic exenteration or radical resection in patients with recurrent cervical or vaginal cancers. The study included 20 patients under evaluation for surgical resection who underwent PET imaging and CT and/or MR scans. Scanning results were compared with surgical outcomes and pathologic confirmation of sites suggestive of tumor recurrence. All patients had undergone previous pelvic radiation therapy and 5 had also received chemotherapy. CT and/or MR imaging identified 3 patients with possible metastatic disease, in the iliac nodes (n = 2) and lungs (n = 1). Surgical and pathologic results indicated metastatic disease only in the lungs of the 1 patient. PET scans identified possible metastatic disease in 9 patients, in pelvic nodes (n = 4), paraaortic nodes (n = 2), axillary node (n = 1), bowel wall (n = 1), and lungs (n = 1). Surgical and pathologic results confirmed metastases in 5 patients, in the iliac nodes (n = 2), paraaortic nodes (n = 1), bowel wall (n =1), and lungs (n = 1). PET was found to have a sensitivity of 100% and a specificity of 73% in detecting sites of extrapelvic metastases and "may be the most accurate test to determine eligibility for pelvic exenteration."

Gynecologic Oncology

Choi Criteria vs. RECIST in GIST

In an article in the May issue of the *Journal of Clinical Oncology* (2007;25:1760–1764), Benjamin et al. from the University of Texas M.D. Anderson Cancer Center (Houston) expanded on their previous work comparing the relative sensitivities of the Response Evaluation Criteria in Solid Tumors (RECIST) and the Choi criteria in evaluating imatinib-treated patients with gastrointestinal stromal tumors (GISTs). The Choi criteria, which define a treatment response as a 10% decrease in tumor size or a 15% decrease in tumor density on contrast-enhanced CT, have been shown in previous small studies to more accurately predict survival than RECIST. In this study, 58 patients with imatinib-treated GISTs were evaluated by either RECIST or Choi criteria. The authors found that patients who met the Choi response criteria at 2 months had significantly longer times to progression than those who did not, whereas RECIST metrics at 2 months did not have this correlation. Disease-specific survival was also significantly correlated with Choi criteria response but not with RECIST. The authors concluded that "Choi response criteria are reproducible, more sensitive, and more precise than RECIST in assessing the response of GISTs to imatinib mesylate" and correlate significantly with time to response and disease-specific survival. They added (lyrically) that "We should desist using RECIST, at least in GIST" and added that "response by Choi criteria should be incorporated routinely into future studies of GIST."

In a separate article in the same journal (2007;25:1753–1759), Choi and the group from M.D. Anderson provided additional, PET-based evidence of the sensitivity and precision of the proposed CT criteria in comparison with RECIST. Their study correlated CT and PET findings in patients after imatinib treatment for GISTs, with a goal of developing and validating reliable, quantitative, CT response criteria. The study included 40 patients with metastatic GISTs treated with imatinib (for a total of 172 lesions selected by RECIST). All patients underwent pretreatment PET and CT and were reimaged at 2-month follow-up. PET response was used to compare the efficacy of the Choi and RECIST approaches. Mean baseline tumor size and density on CT were 5.3 cm and 72.8 Hounsfield units, respectively, and mean baseline maximum standard uptake value on PET was 5.8. PET imaging indicated that treatment response was good in 33 patients. A decrease in tumor size of >10% or a decrease in tumor density of >15% on CT (the Choi criteria) had a sensitivity of 97% and a specificity of 100% in identifying PET responders; these figures were 52% and 100%, respectively, for RECIST. Those patients who were good responders on CT at 2 months had significantly longer times to disease progression than those who did not respond. The authors concluded that "small changes in tumor size or density on CT are sensitive and specific methods of assessing the response of GISTs" and called for additional prospective studies to confirm the routine use of these criteria.

Journal of Clinical Oncology

Thyroid Uptake in Head and Neck Cancers

In a study e-published ahead of print on April 27 in *Clinical Endocrinology (Oxford)*, Nam et al. from the University of Ulsan College of Medicine (Seoul,

Republic of Korea) reported on the prevalence and significance of focal thyroid lesions identified by ^{18}F-FDG PET in patients with nonthyroidal head and neck cancers. The retrospective study included 689 patients with histologically identified head and neck cancer who underwent PET and CT studies. Out of this large patient group, only 19 (2.8%) patients had focal thyroid ^{18}F-FDG uptake. Of the 12 patients who proceeded to surgery or needle biopsy, histolologic results found that 5 (41.7%) had carcinomas (4 papillary and 1 follicular) and 7 had benign thyroid lesions. Although the maximum standardized uptake value on PET was not sufficient to discriminate between malignant and benign thyroid lesions, the identification of incidental thyroid diseases was useful in patient management decisions. The authors concluded that "focal thyroid lesions incidentally found on ^{18}F-FDG PET in patents with nonthyroidal head and neck cancer have a high probability of malignancy." They added that these lesions merit additional diagnostic examination before treatment to ensure adequate therapy.

Clinical Endocrinology (Oxford)

Pediatric Thyroid Cancer in Malaysia

In a supplement to the May issue of *ANZ Surgery* (2007;77[suppl 1]: A24) Harjit and Hisham from the Putrajaya Hospital (Malaysia) reviewed the incidence and pattern of childhood thyroid cancers seen at their institution over a 4-year period. The study included a total of 20 patients (16 girls, 4 boys; mean age, 16.1 years, range 6–21 years). These 20 patients represented 58.8% of the total number of pediatric goiters seen at the hospital over the study period. All patients were euthyroid at diagnosis, with differentiated thyroid cancer (18 papillary thyroid cancer and 2 follicular cancers). Twelve patients underwent total thyroidectomy, with partial surgery in 8 patients. Nine patients required additional modified radical neck dissection. All patients underwent postoperative radioiodine ablation. Although 2 patients developed nodal recurrence, all 20 patients were still alive at a mean follow-up of 22 months. The authors concluded that these results indicated that for their patient population, the "incidence of malignancy in childhood goiters is significantly high" and that the optimal approach to treatment is total thyroidectomy with or without neck dissection and followed by radioiodine ablation.

ANZ Surgery

Hepatitis C Complications Assessed in Veterans

Giordano et al. from the Baylor College of Medicine and the Michael E. DeBakey Veterans Affairs (VA) Medical Center (Houston, TX) reported in the May 9 issue of the *Journal of the American Medical Association* (2007;297:2010–2017) on a large-scale study of the risk of hematopoietic malignancies, related lymphoproliferative disorders, and thyroid cancer associated with hepatitis C virus (HCV) in a population consisting mainly of U.S. veterans. The study included 718,687 patients seen at VA facilities from 1997 to 2004, including 146,394 HCV-infected patients with at least 2 visits with a diagnostic code for HCV infection and 572,293 age- and sex-matched non-HCV-infected patients. Ninety-seven percent of participants were men. Individuals with human immunodeficiency virus were excluded from the 2 study groups. Study results indicted that risks for non-Hodgkin's lymphoma, Waldenstrom macroglobulinemia, and cryoglobulinemia were increased with HCV infection, with no significantly increased risk for other hematologic malignancies. Thyroiditis risk was slightly increased with HCV infection, but risk for thyroid cancer was not increased. The results led the authors to conclude that "hepatitis C virus infection confers a 20%–30% increased risk of non-Hodgkin's lymphoma overall and a 3-fold higher risk of Waldenstrom macroglobulinemia." These and somewhat lower increased risks for cryoglobulinemia suggested an "etiological role for HCV in causing lymphoproliferation and causing non-Hodgkin's lymphoma."

Journal of the American Medical Association

THERAPY

Antiangiogenic Antibody in Colorectal Tumors

In an article e-published on May 22 ahead of print in the *British Journal of Cancer*, El-Emir et al. from the Royal Free and University College Medical School (London, UK) reported on characterization of and experimental radiotherapy with human monoclonal antibody L19-SIP, an antiangiogenic antibody against the extra domain B of fibronectin in colorectal tumor models. The L19-SIP antibody targets the extra domain B of fibronectin, a marker of angiogenesis expressed in colorectal tumors. The authors reported on localization and retention of the antibody in 2 different types of xenografts. The antibody was labeled with ^{125}I to assess whole-body distribution in both tumor models. Based on positive results in localization, retention, and confirmation of extra domain B expression in tumor vasculature, the authors performed an in vivo radioimmunotherapy study with the ^{131}I-labeled antibody in a mouse xenograft model. Selective tumor uptake, tumor growth inhibition, and improved survival were demonstrated. The authors concluded that "^{131}I-L19-SIP shows potential as a novel treatment of colorectal tumors and provides the foundation to investigate combined therapies in the same tumor models."

British Journal of Cancer

SPECT and IMRT to Reduce Toxicity

Lavrenkov et al. from the Institute of Cancer Research (Sutton, UK) reported on May 8 ahead of print in *Radiotherapy and Oncology* on the use of perfusion SPECT with intensity-modulated radiotherapy (IMRT) to reduce pulmonary toxicity by avoiding functional lung

tissue and compared this approach with 3-dimensional conformal radiotherapy (3D CRT) in non–small cell lung cancer (NSCLC). The study included the analysis of 34 radiotherapy plans in 17 patients with stages I–IIIB NSCLC considered suitable for radical radiation treatment. In 6 patients with stages I–II disease, the IMRT approach showed no improvements over 3D CRT in planning target volume receiving 90% of the dose, no reductions in functional lung volume irradiated to 20 Gy, or functional mean lung dose. In 11 patients with stages IIIA–B disease, the planning target volume was equally well covered with IMRT and 3D CRT plans, with IMRT producing better results in overall targeting and reduced functional mean lung dose. The authors concluded that "the use of IMRT compared to 3D CRT improves the avoidance of functional lung defined by perfusion SPECT scan in selected patients with locally advanced NSCLC"; moreover, "if the dose to functional lung is shown to be the primary determinant of lung toxicity, IMRT would allow for effective dose escalation by specific avoidance of functional lung."

Radiotherapy and Oncology

Long-Term NHL RIT Response

In the May issue of *Cancer* (2007; 109:1804–1810), Witzig et al. from the Mayo Clinic (Rochester, MN) reviewed data from 4 clinical trials (211 patients) of the efficacy of ^{90}Y-ibritumomab tiuxetan and identified and characterized patients with long-term responses (defined as times to progression of at least 12 months). Such long-term responses were noted in 78 (37%) of patients. The median follow-up was 53.5 months (range, 12.7–88.9months) in this group of patients, with a median duration of response of 28.1 months and median time to progression of 29.3 months. A third of these patients had been previously treated with at least 3 therapies, and 37% were not responsive to the last of these previous therapies. The estimated overall survival at 5 years was 53% for all 211 patients treated with ^{90}Y-ibritumomab tiuxetan in these clinical trials and was 81% for long-term responders. The authors concluded that "a single dose of ^{90}Y-ibritumomab tiuxetan can produce durable responses and prolonged overall survival in a substantial number of patients in whom previous therapies have failed."

Cancer

Anti-CD30 Antibody in Leukemia and Lymphoma

Zhang et al. from the National Cancer Center and Clinical Center of the National Institutes of Health (Bethesda, MD) reported in the May 15 issue of the *Proceedings of the National Academy of Sciences USA* (2007;104:8444–8448) on the therapeutic efficacy of HeFi-1, an anti-CD30 antibody, labeled with ^{211}At in a leukemia (karpas299) model and with ^{90}Y in a lymphoma (SUDHL-1) model in mice. The team also investigated a combination therapy of ^{211}At-HeFi-1 and unmodified HeFi-1 in the leukemia model. They found that treatment with unmodified HeFi-1 significantly prolonged survival of the leukemia-bearing mice over that in control groups and that treatment with ^{211}At-HeFi-1 was even more effective at prolonging survival, with the combination of the unlabeled and labeled antibody producing the best results. In the lymphoma model, survival was significantly prolonged by treatment with ^{90}Y-HeFi-1 over that in controls. The authors concluded that "radiolabeled HeFi-1 is very promising for the treatment of CD30-expressing leukemias and lymphomas, and the combination regimen of ^{211}At-HeFi-1 with unmodified HeFi-1 enhanced the therapeutic efficacy."

Proceedings of the National Academy of Sciences USA

MOLECULAR IMAGING AND THERAPY

$\alpha_v\beta_3$ Integrin–Targeted ^{111}In Nanoparticles

In the May 1 issue of the *International Journal of Cancer* (2007; 120:1951–1957), Hu et al. from the Washington University Medical School (St. Louis, MO) reported on development of and studies with $\alpha_v\beta_3$ integrin–targeted ^{111}In perfluorocarbon nanoparticles for detection of tumor angiogenesis. Studies were conducted in New Zealand white rabbits 12 days after implantation with Vx-2 tumor. Eighteen hours after treatment with the radiolabeled nanoparticles, mean tumor activity was 4-fold higher than in controls treated with nontargeted nanoparticles. Biodistribution and circulatory half-life studies indicated that "$\alpha_v\beta_3$-targeted ^{111}In nanoparticles may provide a clinically useful tool for sensitively detecting angiogenesis in nascent tumors, particularly in combination with secondary high-resolution imaging modalities, such as MRI."

International Journal of Cancer

Current State of Imaging Protein–Protein Interactions

In a review article e-published on April 26 ahead of print in *Annual Reviews of Biomedical Engineering*, Villalobos et al. from Washington University School of Medicine (St. Louis, MO) described the current state of imaging protein–protein interactions in vivo with genetically encoded reporters. The review focused on the development and validation of bioluminescent protein fragment complementation reporters that use either Renilla luciferase or firefly luciferase in vivo. This approach provides "a platform for near real-time detection and characterization of regulated and small-molecule-induced protein–protein interactions in intact cells and living animals and enables a wide range of novel applications in drug discovery, chemical genetics, and proteomics research." The authors discussed the ways in which novel imaging tools can advance research and the promise for combining these molecularly targeted techniques with other forms of imaging in translational studies.

Annual Reviews of Biomedical Engineering

Optical Glutamate Sensor for Synaptic Transmission

Namiki et al. from the Nagoya University Graduate School of Medicine (Japan) reported in the April issue of the *European Journal of Neuroscience* (2007;25:2249–2259) on the development of a novel glutamate probe capable of producing high-resolution optical images of glutamate release. The probe, which includes a glutamate receptor (GluR2) subunit and a small-molecule fluorescent dye, was designed to report on microenvironmental protein conformational changes elicited by glutamate binding. The authors were able to demonstrate in situ spatial mapping of synaptically released glutamate after presynaptic firing and obtained images that reflect the results of even a single firing. These and additional investigations indicated that the probe can be "generally applicable to evaluation of presynaptic modulation and plasticity" and that this imaging method "is useful to address numerous fundamental issues about glutamatergic neurotransmission in the central nervous system."

European Journal of Neuroscience

Peptide-Based MR Contrast Agent in Alzheimer's Disease

In an article-published on May 15 ahead of print in the *Journal of Pharmacology and Experimental Therapeutics*, Kandimalla et al. from Florida A&M University (Tallahassee, FL) reported on the plasma and brain pharmacokinetics of a novel MR contrast agent based on a derivative of human amyloid-β peptide previously shown to cross the blood–brain barrier (BBB) and bind to amyloid plaques in mouse models of Alzheimer's disease (AD). They found rapid plasma elimination but also rapid absorption at the BBB. Additional studies indicated the preferential localization of the contrast agent on the amyloid plaques for extended periods of time, with indications of excellent signal-to-noise ratios for longer MR scanning times. These and other characteristics elicited in the study indicated that the contrast agent shows great promise in plaque targeting. The study provided valuable pharmacokinetic information that can inform dose, mode of administration, and scan times for future in vivo MR imaging of amyloid plaques in Alzheimer's disease transgenic mice.

Journal of Pharmacology and Experimental Therapeutics

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of the SNM in Washington, DC, highlighted advances in these areas and underscored the abundance of new radiopharmaceuticals for cancer imaging with PET and SPECT. Researchers are also using the unique properties of nanoparticles for designing improved cancer imaging probes. Some other examples of cancer-selective probes include the development of high-impact agents for targeting key cancer biomarkers such as $\alpha^v\beta^3$ integrin, σ2 receptors, bombesin receptors, and a host of new receptors being discovered by technologies such as in vivo phage display.

Based on these encouraging results, proponents of personalized and targeted anticancer therapy are making a strong case in favor of inclusion of molecular imaging into clinical trial design. It is also a powerful tool with which clinicians can noninvasively assess the phenotypic signature of a tumor in an individual patient.

A survey of recent research indicates that new and improved molecular imaging strategies are surfacing at a rapid rate. This is a harbinger of success for molecular imaging in the diagnosis and treatment of cancer.

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Each module is designed to allow the user to work toward meeting Part II (Lifelong Learning and Self-Assessment) of the MOC requirements, earn continuing education credits (2.5–4.0 credits per module), assess medical knowledge and patient care competencies, and enhance knowledge of clinical applications of the latest technologies. The LLSAP approach offers instant access to educational materials, with all work completed online. Users can save work in progress on each component, interrupting a session and coming back to it later. Once all questions are answered, immediate access to scoring and a detailed peer-comparison scoring report are available. Continuing education certificates can be printed and downloaded directly from the site. Once released, modules remain available for 3 years. LLSAP modules are currently available to SNM members at "4 for 3" pricing, which allows members to obtain at a discounted rate the 8 self-assessment credit hours required annually by the ABNM.

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