Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role.

Therapy

^{111}In-Labeled Carbon Nanotubes in Drug Delivery

Researchers from England and France reported on February 21 ahead of print in the *Proceedings of the National Academy of Sciences USA* on the pharmocokinetics and apparent safety of intravenously administered radiolabeled carbon nanotubes, a step that brings this innovative drug and therapeutic gene delivery approach closer to clinical application. Singh and colleagues from the University of London (UK), and the Centre National de la Recherche Scientifique, Immunologie, et Chimie Therapeutiques (Strasbourg, France) functionalized water-soluble, single-walled carbon nanotubes with the chelating molecule diethylenetriaminepentaacetic (DTPA) labeled with ^{111}In. The nanotubes were administered intravenously in a mouse model, and subsequent gamma scintigraphy indicated that the tubes were not retained in the liver or spleen and were cleared rapidly from the blood through renal excretion. In addition, studies using both single-walled and multiwalled nanotubes indicated that both types of tubes were excreted intact. The authors concluded that the rapid blood clearance of the nanotubes and short half-life (3 hours) of the tracer "have major implications for all potential clinical uses." "This certainly removes the shroud that has made many people nervous about using nanotubes, especially for medical applications," Pulickel M. Ajayan, a Rensselaer Polytechnic Institute (Troy, NY) nanotube researcher told *Chemical and Engineering News*, one of many scientific media sources to cover the article. "This is the first time carbon nanotubes have been administered intravenously and fundamental pharmacokinetic parameters have been obtained," said senior study author Kostas Kostarelos. "It is also the first report showing blood clearance and urine excretion of the nanotubes."

Proceedings of the National Academy of Sciences USA

Chemical and Engineering News

Embryonic Stem Cell Therapy Visualization

In the February 21 issue of *Circulation* (2006;113:1005–114), a team of researchers from the Stanford University School of Medicine (CA) reported on work with embryonic stem cells that stably express fluorescence, bioluminescence, and PET reporter genes with a resulting imaging platform that can monitor the kinetics of stem cell survival, proliferation, and migration. Cao et al. noted that monitoring of stem cell therapy in vivo is currently limited by the use of conventional histologic tests and imaging modalities. Murine embryonic stem cells were stably transduced with a lentiviral vector carrying a novel triple-fusion reporter gene. Embryonic stems cells carrying the reporter gene were injected into the myocardium of adult nude rats, and control animals received nontransduced embryonic stem cells. Bioluminescence and PET imaging were conducted first on day 4 and at regular intervals therafter. Signals increased progressively from the first through the fourth week, indicating stem cell survival and prolifieration. Histologic analyses showed the formation of intracardiac and extracardiac teratomas; animals treated with intraperitoneal injections of ganciclovir did not develop teratomas. The authors concluded that this "versatile imaging platform should have broad applications for basic research and clinical studies on stem cell therapy."

Circulation

HAMA Titers and Survival in RIT

Azinovic et al. from the Hospital San Jaime (Torrevieja, Spain) and the University of California, Davis (Sacramento), reported on February 22 ahead of print in *Cancer Immunology, Immunotherapy* on the relationship between human antimouse antibody (HAMA) and survival in patients with B-cell malignancies administered a mouse antilymphoma monoclonal antibody (mAb), Lym-1, directed against a unique epitope of HLA-DR antigen that is upregulated on malignant B-cells. The study included 51 patients with B-cell malignancies who had been treated with ^{131}I-Lym-1 radioimmunotherapy (RIT) and who were followed both before and after therapy until HAMA negative. In addition to determining the relationship of HAMA to survival, the researchers also assessed the relationships of HAMA to prior chemotherapies and absolute lymphocyte counts before initiation of RIT. Eighteen patients (35%) developed HAMA after RIT, and maximum HAMA titers were found to be significantly associated with survival. Among 39 patients who survived at least 16 weeks, median survival of those with HAMA <5 μg/mL was 61 weeks, compared

with 103 weeks for patients with HAMA > 5 μg/mL. For the 5 patients with the highest maximum HAMA, median survival was 244 weeks. An inverse relationship was noted between maximum HAMA titer at 16 weeks and number of previous chemotherapies. The authors concluded that the longer survival of patients with B-cell malignancies who developed high HAMA titers "was not explained by risk factors or histologic grade, suggesting the importance of the immune system."

Cancer Immunology, Immunotherapy

^{131}I-Metuximab in Hepatocellular Carcinoma

In a study e-published on March 20 ahead of print in *Cancer Biology and Therapy*, Zhang et al. from the Fourth Military Medical University (Xi'an, China) reported on research on the biodistribution, localization, and imaging characteristics of ^{131}I-labeled metuximab radioimmunotherapy (RIT) in patients with hepatocellular carcinoma. The study included 24 patients with hepatocellular carcinoma who were divided into 3 groups to receive 18.5, 27.75, and 37 MBq/kg body weight of ^{131}I-metuximab. ^{99m}Tc-sodium phytate SPECT imaging was performed 2 days before and 7 days after RIT. The percentage of injected dose and time-dependent ^{131}I tumor-to-nontumor (T/NT) ratios were calculated at 12, 48, 96, and 192 hours after injection. Positive post-RIT imaging results in 24 patients indicated that the RIT agent accumulated more in tumor. Biodistribution studies indicated that the optimal imaging time for the highest T/NT ratio in liver was at 192 hours. The authors concluded that ^{131}I-labeled metuximab could deliver "relatively selective radiation" to tumor tissues and may have potential efficacy in treating hepatocellular carcinoma.

Cancer Biology and Therapy

Diagnosis

^{18}F-Labeled Insulin for PET

Guenther et al. from McMaster University (Hamilton, ON) and Hamilton Health Sciences (ON) reported in the February 23 issue of the *Journal of Medical Chemistry* (2006;49:1466–1474) on a novel method for the preparation of ^{18}F-labeled insulin for use as a PET tracer and outlined the results of initial in vitro evaluation. The preparation of the tracer was described in detail, as well as verification studies. An insulin receptor phosphorylation assay using cells overexpressing recombinant human insulin receptors showed no statistical difference in the extent of autophosphorylation stimulated by the ^{18}F-labeled insulin and by human insulin, nor were uptake differences noted in 3T3-L1 mouse adipocytes treated with the labeled insulin and human insulin. The authors concluded that "results support the use of the ^{18}F-insulin analogue as a PET tracer for imaging the distribution of insulin in vivo."

Journal of Medical Chemistry

^{18}F-FLT and ^{18}F-FDG PET in Thoracic Tumors

In a study published in the February issue of *Chest* (2006;129:393–401), Yap et al. from the University of California at Los Angeles School of Medicine compared the use of ^{18}F-FDG and ^{18}F-FLT in PET tumor staging and other characteristics in individuals with solitary pulmonary nodules (11 patients) and with non–small cell lung cancer (NSCLC; 11 patients). PET imaging with each of the tracers was performed in each patient, and uptake was assessed by standardized uptake values (SUVs). Histologic evaluation after biopsy or surgery (99 samples in total) served as the gold standard and included assessment of tumor proliferation. One-third (33.3%) of these samples were positive for tumor tissue (22 pulmonary, 9 lymph node, and 2 extrapulmonary). ^{18}F-FDG PET was false-positive in 3 and false-negative in 2 pulmonary lesions, whereas ^{18}F-FLT PET was false-positive in 1 and false-negative in 6 pulmonary lesions. ^{18}F-FDG uptake in lesions subsequently identified as positive was significantly higher than that of ^{18}F-FLT. These results led the authors to conclude that, compared with ^{18}F-FDG PET, "detection of primary and metastatic NSCLC by ^{18}F-FLT PET is limited by the relatively low ^{18}F-FLT uptake of the tumor tissue." However, a significant correlation was observed between ^{18}F-FLT uptake of pulmonary lesions and histologic assessment of tumor proliferation, an association not noted with ^{18}F-FDG. The authors added that "the correlation between ^{18}F-FLT uptake and cellular proliferation suggests that future studies should evaluate the use of ^{18}F-FLT PET for monitoring treatment with cytostatic anticancer drugs."

Chest

^{18}F-FDG PET in RT Planning

Dietl et al. from the University of Regensburg (Germany) reported on February 21 ahead of print in *Auris, Nasus, Larynx* on the results of a prospective clinical analysis of the diagnostic and therapeutic effect of ^{18}F-FDG PET on planning radiotherapy in patients with advanced head and neck cancer (stages III/IV). The study included 49 patients who were imaged with PET before radiotherapy to exclude systemic disease, synchronous second tumors, and unknown primary tumors. PET findings were compared with data from conventional imaging and clinical follow-up. In 21 patients (42.8%), PET provided new diagnostic information with therapeutic implications. Therapeutic management was changed in 14 patients, and minor modifications in portal design were made for 6 patients. PET supported a curative strategy in 9 patients and a palliative approach in 11 patients. The authors concluded that ^{18}F-FDG PET is a "useful and important diagnostic tool mainly for exclusion of systemic disease in advanced head and neck cancer."

Auris, Nasus, Larynx

PET SUVs Predict Survival After Esophageal Surgery

In a study published in the March issue of the *Annals of Thoracic*

Surgery (2006;81:1076–1081), Rizk et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on a retrospective review of patients undergoing ^{18}F-FDG PET imaging before surgical resection for esophageal adenocarcinoma to determine whether PET results could predict overall survival independently of clinical and/or pathologic stage. The study included the records of 50 patients who underwent CT and PET imaging before surgery and most of whom also underwent endoscopic ultrasound evaluation. Surviving patients were followed for a median of 27 months, and maximum standard uptake value (SUVmax) on PET was found to correlate with survival. The 3-year survival was 57% for patients with an SUVmax $>$ 4.5 and 95% for patients with an SUVmax $\leq$ 4.5. The survival advantage of the SUVmax second group was also seen in clinically early-stage patients, as well as in patients with pathologically early-stage disease. The authors concluded that not only does ^{18}F-FDG PET predict overall survival in patients undergoing surgery for esophageal adenocarcinoma but that SUVmax "identifies patients who have a poor prognosis from a subset of patients that would otherwise be considered to have early-stage disease."

Annals of Thoracic Surgery

Fused PET, MR, and CT Volume Targeting in RT

In a study e-published ahead of print on February 17 in the *International Journal of Radiation Oncology, Biology, Physics*, Milker-Zabel et al. from the University of Heidelberg (Germany) reported on the use of ^{68}GA-DOTATOC PET as a complementary modality to CT and MR imaging for target definition in fractionated stereotactic radiotherapy in patients with intracranial meningiomas. The study included 26 such patients who underwent stereotactic CT, MR, and ^{68}GA-DOTATOC PET imaging as part of treatment planning. Planning target volume (PTV) 1 was outlined using data from CT and MR imaging and was compared with PTV 2, outlined on PET. A fused version of the 2 PTVs, PTV 3, was used for therapy. PTV 3 was found to be smaller than PTV 1 in 9 patients, the same size in 7 patients, and larger in 10 patients. PET delivered additional information about tumor extension in all patients, and the treatment volume was significantly altered by PET in 19 patients (73%). The authors noted the benefits of including DOTATOC as a tracer because of its ability to target the high expression of somatostatin receptor subtype 2 in meningiomas and concluded that ^{68}GA-DOTATOC PET improves target definition for patients undergoing radiotherapy for intracranial meningiomas.

International Journal of Radiation Oncology, Biology, Physics

PET/CT in Low Rectal Cancer

Gearhart et al. from the Johns Hopkins Medical Institution (Baltimore, MD) reported in the March issue of the *Annals of Surgical Oncology* (2006;13:397–404) on a study of the staging utility of pretreatment PET/CT in patients with low rectal cancer. The study included 37 previously untreated patients with rectal cancer who underwent transrectal ultrasonography or MR imaging, CT, and ^{18}F-FDG PET/CT. Tumor location (low, mid, or high) and carcinoembryonic antigen levels were noted. Discordant findings between spiral CT and PET/CT were resolved by histologic analysis or additional imaging follow-up. PET/CT identified discordant findings in 14 patients (38%), resulting in upstaging of 7 and downstaging of 3. Discordant PET/CT findings were significantly more common in patients with low rectal cancer than in those with mid or high rectal cancers. Discordant PET/CT findings resulted in a deviation in the proposed treatment plan in 27% of patients. The authors concluded that PET/CT "frequently yields additional staging information in patients with low rectal cancer" and that improvements in the technique will allow for more appropriate stage-specific therapy.

Annals of Surgical Oncology

Preoperative PET in High-Risk Melanoma

In an article e-published ahead of print on February 15 in the *Annals of Surgical Oncology*, Brady et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on the use of preoperative whole-body ^{18}F-FDG PET in addition to routine CT (chest, abdomen, and pelvis) in high-risk patients with melanoma. The study included 103 patients who underwent imaging before surgery, with histopathology or clinical follow-up within 4–6 months used to determine the accuracy of imaging. Preoperative imaging led to changes in management in 36 (35%) patients. This information proved accurate in 32 (89%) of these patients. PET alone was responsible for changes in management in 14 patients and in combination with CT was responsible for changes in 20 patients. The most common change was the decision to cancel surgery (19 of 36 patients in whom management changed on the basis of imaging). PET was more sensitive than CT in detecting occult disease (68% and 48%, respectively), but both modalities were highly specific (92% and 95%, respectively). The authors concluded that "PET imaging in addition to CT scanning should be strongly considered before operation in patients at high risk for occult metastatic disease."

Annals of Surgical Oncology

PET/CT in Carcinoma of the Larynx

Gordin et al. from the Rambam Medical Center and the Carmel Medical Center (Haifa, Israel) reported in the February issue of *Laryngoscope* (2006,116:273–278) on a study designed to compare the efficacies of ^{18}F-FDG PET/CT with PET or CT alone in patients with carcinoma of the larynx. The study included 42 patients,

whose imaging results were interpreted prospectively with knowledge of clinical histories and previous imaging tests. The performances of imaging modalities were compared by study type and lesion type for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. For PET/CT, sensitivity = 92%, specificity = 96%, PPV = 96%, NPV = 92%, and accuracy = 94%. For PET alone, these respective percentages were 92%, 73%, 76%, 91%, and 82%, and for CT alone, these percentages were 88%, 8%, 48%, 40%, and 51%. PET/CT led to changes in management in 25 patients (59%; by canceling additional diagnostic procedures in 13 patients, changing planned therapy in 9 patients, and by redirecting biopsy area in 3 patients). The authors concluded that "the performance of PET/CT is better than standalone PET or CT in patients with cancer of the larynx."

Laryngoscope

PET vs Scintigraphy in Staging of Nasopharyngeal Cancer

Liu et al. from the Chang Gung Memorial Hospital (Taipei, Taiwan) reported in the February 1 issue of the *Journal of Clinical Oncology* (2006;24:599–604) on a study comparing ^{18}F-FDG PET and skeletal scintigraphy in the detection of bone metastasis in endemic nasopharyngeal carcinoma (NPC) at initial staging. The study included 212 patients with untreated NPC who underwent both PET and skeletal scintigraphy. Thirty (15%) of these patients were found to have bone metastases. PET was more sensitive than scintigraphy in both the patient-based analysis and a region-based analysis at the spine. The results also indicated that advanced stage at initial diagnosis and the coexistence of hepatic metastases were significant predictors of poor survival. The authors concluded that ^{18}F-FDG is more sensitive than skeletal scintigraphy for detecting bone metastases in NPC at initial staging and that skeletal scintigraphy should be considered "supplementary" in this setting.

Journal of Clinical Oncology

SPECT/CT and Functional Mapping of Brain Tumors

In a study published in the February issue of *Cancer Biotherapy and Radiopharmaceuticals* (2006;21:41–48), Filippi et al. from the University Tor Vergata (Rome, Italy) reported on research to assess the clinical usefulness and incremental value of fused ^{99m}Tc-tetrofosmin SPECT/CT for the functional anatomical mapping of brain tumors. The study included 30 patients, 20 of whom were imaged with both modalities in a single session before surgery and 10 of whom were imaged after surgery and before radiotherapy planning. SPECT images alone were assessed first and then reinterpreted after fusion with CT images. SPECT/CT was found to have a significant clinical effect in 13 (43.3%) patients. Of specific note was the fact that SPECT/CT accurately characterized 8 lesions near sites of physiologic uptake and localized viable tumor tissue in 5 patients imaged after surgery. The authors concluded that SPECT/CT with ^{99m}Tc-tetrofosmin using their hybrid device "represents a useful clinical tool in brain tumor imaging, both correctly categorizing focal areas near sites of physiological uptake and localizing viable tumor tissue after surgery."

Cancer Biotherapy and Radiopharmaceuticals

Hurthle Cell Thyroid Cancer Therapy

Besic et al. from the Institute of Oncology (Ljubljana, Slovenia) reported in the January issue of *Thyroid* (2006;16:67–72) on a study designed to determine the factors associated with survival in patients with Hurthle cell papillary thyroid carcinoma (HCPTC) in Slovenia, an iodine-deficient region. Out of a total of 1,552 patients with thyroid carcinoma seen at the authors' institution over an almost 30-year period, 42 patients (33 females, 9 males; age range, 10–85; tumor diameters, 1–9 cm) had histopathologically verified HCPTC. Nineteen patients were found to have extrathyroid tumor growth, 13 patients had lymph node metastases, and 2 patients had distant metastases Thirty-nine patients underwent total or near-total thyroidectomy, 2 underwent lobectomy, 37 underwent radioiodine ablation of thyroid remnant, 14 received external irradiation, and 3 underwent chemotherapy. The 5- and 10-year survivals were 94% and 87%, respectively, with respective disease-free intervals of 93% and 81%. Factors significantly correlated with survival included age, extrathyroid tumor growth, primary tumor stage, and regional and distant metastases. The authors concluded that long-term survival and locoregional control of disease are likely after radical tumor resection, radioiodine ablation of the thyroid remnant, and external irradiation.

Thyroid