Each month the editor of Newsline selects articles on therapeutic, diagnostic, research, and practice issues from a range of international publications. Most 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 applications 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.

Diagnosis

SLN Technique in Neck Oral Cancer

In an article e-published ahead of print on September 9 in *Head and Neck*, Terada et al. from the Aichi Cancer Center Hospital (Japan) reported on the results of a 2-part study, including a feasibility assessment and clinical evaluation of sentinel lymph node (SLN) localization and biopsy in patients with clinically negative neck oral cancer. The feasibility study included 15 individuals with previously untreated stage N0 oral cancer. Each underwent ^{99m}Tc-phytate lymphoscintigraphy, and metastases to SLNs and other nodes were compared on pathology. In this part of the study, 5 SLNs in 5 patients were positive, and two-thirds of all SLNs identified were micrometastases. SLNs with the highest to the third highest radioactivity most accurately reflected the patients' neck status. In the clinical application group, which included 12 patients, fusion SPECT/CT images were acquired, and the comparative effectiveness of multislice frozen section analysis and imprint cytology was assessed in the intraoperative diagnosis of SLN biopsies. Again, intraoperative diagnosis of the 3 most radioactive SLNs correctly predicted neck status in 10 patients. As a result of these diagnoses, 3 patients underwent modified radical neck dissection, whereas neck dissections were spared in patients with no evidence of such metastases. However, the intraoperative results were false-negative in 1 case, and another case was equivocal on intraoperative analysis. Multislice frozen section analysis was found to be superior to imprint cytology in its sensitivity, specificity, and overall accuracy. The authors noted that this technique is promising in patients with clinically negative oral cancer and that "intraoperative SLN biopsy based on fusion images of SPECT and CT proved to be an easy, accurate, and reliable method."

Head and Neck

Pediatric Serum TSH Levels After rhTSH Injection in Thyroid Cancer

In an article e-published ahead of print on September 20 in the *Journal of Clinical Endocrinology and Metabolism*, Iorcansky et al. from the Hospital de Pediatria (Buenos Aires, Argentina) and the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on a study designed to determine whether the usual adult recombinant human thyroid-stimulating hormone (rhTSH) dosing regimen as preparation for whole-body radioactive iodine scanning would result in excessive elevations of serum TSH when administered in a study population of children and teenagers with thyroid cancer. The retrospective review identified 53 children and teenagers with thyroid cancer who underwent whole-body radioactive iodine scanning (34 after thyroid hormone withdrawal, and 19 after rhTSH administration) at the authors' 2 institutions. The authors examined serum TSH changes after rhTSH administration and/or hypothyroid withdrawal, and peak TSH levels were correlated with age, weight, and body surface area. Results indicated that mean serum TSH levels at the time of radioactive iodine administration were similar in patients undergoing hypothyroid preparation and in those prepared with rhTSH. Serial metrics after rhTSH injections showed a mean serum TSH of 268 ± 76 mU/L at 6 h and 130 ± 58 mU/L at 24 h after the initial injection, and 361 ± 78 mU/L at 6 h and 134 ± 44 mU/L at 24 h after the second injection. The authors concluded that mean TSH levels achieved in children after rhTSH injections are similar to values reported in adults despite differences in clinical characteristics between children and adults. They added that, "these data suggest that dose adjustments are not generally required in children and teenagers undergoing rhTSH stimulation for radioactive iodine scanning or serum-stimulated thyroglobulin determinations."

Journal of Clinical Endocrinology and Metabolism

40-Year Analysis of Differentiated Thyroid Cancer Treatment

Brierley et al. from the Princess Margaret Hospital (Toronto, Canada) reported in the October issue of *Clinical Endocrinology* (Oxford; 2005;63: 418–427) on the results of a 40-year retrospective study of patients with differentiated thyroid cancer treated with radioactive iodine and external beam radiation. The study, which included 729 patients, was designed to assess the prognostic factors and role of the 2 types of therapy. Median follow-up of

(Continued on page 30N)

(Continued from page 28N)
patients during this period was 11.3 years, and outcomes were assessed by elapsed time to cause-specific survival (CSS) and time to local-regional relapse. Results indicated that the 10-year CSS was 87.3% and the 10-year local-regional relapse-free rate (LRFR) was 84.9% in all patients. The use of radioactive iodine resulted in a statistically significant improvement in LRFR; however, in patients defined as low-risk (stage I disease at ≤45 years), no apparent benefit was seen from radioactive iodine administration. For patients older than 60 with extrathyroid extension but no gross residual disease, adjuvant external radiation beam therapy resulted in statistically significantly higher CSS and LRFR. The authors concluded that the use of radioactive iodine was associated with improved LRFR but not in low-risk patients and that external beam radiation therapy improved LRFR and CSS in high-risk patients.

Clinical Endocrinology

Routine Radiation Exposure in Nuclear Medicine Procedures

Hacker et al. from the University of Munich (Germany) reported in the journal *Nuklearmedizin* (2005;44:119–130) on a study estimating the frequency and effective radiation dose of nuclear medicine procedures performed in different subgroups of patients in 14 hospitals and 10 private practices in Germany from 1996 to 2000. Databases from the various sites were mined to yield frequencies and effective doses per examination based on published International Commission on Radiological Protection parameters. The study database included 604,771 nuclear medicine procedures performed in 433,709 patients. The median effective dose over all types of procedures was 1.7 mSv per examination and 2.3 mSv per patient. The mean effective dose per examination—but not the number of examinations per year—increased with patients' ages. Procedures focused on the thyroid (36.7%), the skeleton (27.1%), and the cardiovascular system (11.1%), and these procedures were associated with median effective doses of 0.5 mSv, 3.4 mSv, and 7.3 mSv, respectively. The number of PET procedures over the 5-year study period increased dramatically (222.3%), with lesser but significant increases in thyroid (24.5%), skeleton (17.9%), and cardiovascular system (14.9%) examinations. A decrease was observed for brain (–39.3%), lung (–20.2%), and renal (–15.0%) scans. The authors noted that the age- and gender-specific data presented in this study provide valuable information that with further analysis should provide additional insights into the practice of diagnostic nuclear medicine.

Nuklearmedizin

PEM in the Surgical Management of Breast Cancer

Tafra et al. from Anne Arundel Health Systems (Annapolis, MD) reported in the October issue of the *American Journal of Surgery* (2005;190:628–632) on a pilot clinical trial of ^{18}F-FDG PET mammography (PEM) in the surgical management of breast cancer. The multicenter study included 44 women with newly diagnosed breast cancer who underwent scanning with a high-resolution PEM scanner and ^{18}F-FDG. Images were interpreted with no previous patient data available to the readers, and results were compared with final pathology. PEM was able to detect 39 of 44 (89%) index lesions and 4 of 5 incidental breast cancers, 3 of which had not been identified on previous imaging with other modalities. Nineteen patients progressed to breast-conserving surgery, and, among these patients, PEM correctly predicted 6 of 8 (75%) patients with positive margins and all 11 (100%) patients with negative margins. The authors concluded that, "the current PEM device shows promise in detecting breast malignancies and may assist in the planning of adequate partial mastectomy procedures to better ensure negative margins."

American Journal of Surgery

PETRRA: Evaluation of a Large-Area Prototype PET System

Divoli et al. from the Royal Marsden Hospital/Institute of Cancer Research (Sutton, UK) reported in the September 7 issue of *Physics in Medicine and Biology* (2005;50:3971–3988) on the design, characteristics, and physical evaluation of a novel PET system. The PETRRA positron camera is a large-area (600 × 400-mm sensitive area) prototype system that uses technology involving the coupling of 10-mm thick barium fluoride scintillating crystals to multiwire proportional chambers filled with a photosensitive gas. Evaluations detailed in the study indicated that the prototype has a 3D spatial resolution of approximately 7.5 mm full-width-at-half-maximum (FWHM), a timing resolution of approximately 3.5 ns (FWHM), a total coincidence count-rate performance of at least 80–90 kcps, and a randoms-corrected sensitivity of approximately 8–10 kcps kBq/mL. For an average concentration of 3 kBq/mL, an estimated 20% of the data would represent true events. The authors noted that count-rate performance is limited in the prototype by the obsolete off-camera read-out electronics and computer system, and that the sensitivity is limited by the use of thin (10-mm thick) crystals. The existing camera is also susceptible to high levels of scatter and out-of-field activity. Despite these difficulties, which are being remedied in successive versions of the prototype, the authors noted that the large axial field of view of 400 mm makes the camera "ideally suited to whole-body PET imaging." Preliminary clinical images obtained with the prototype system are also included in the article.

Physics in Medicine and Biology

PET Imaging of Microglial Activity in Parkinson's

In an article e-published on September 20 ahead of print in *Neurobiology of Disease*, Gerhard et al. from the

Imperial College (London, UK) compared the results of PET imaging with ^{18}F-dopa and with ^{11}C-R-PK11195, a novel tracer with promise in highlighting peripheral benzodiazepine sites, which are selectively expressed by activated microglia in idiopathic Parkinson's disease (PD). The study included 18 patients and 11 healthy controls who were examined clinically and who underwent PET imaging with both ^{18}F-dopa and ^{11}C-R-PK11195. The group of patients showed significantly increased mean levels of ^{11}C-R-PK11195 binding in the pons, basal ganglia, and frontal and temporal cortical regions when compared with healthy volunteers. In a follow-up study, 8 of the patients were examined over a 2-year period, during which the ^{11}C-R-PK11195 signal remained stable. Levels of microglial activation did not correlate with either clinical severity or putamen ^{18}F-dopa uptake. The authors concluded that these findings "confirm that widespread microglial activation is associated with the pathological process in PD" and that "the absence of significant longitudinal changes suggests that microglia are activated early in the disease process, and levels then remain relatively static, possibly driving the disease via cytokine release."

Neurobiology of Disease

^{11}C-Raclopride PET and Amphetamine-Induced Dopamine Release

In an article e-published on September 21 ahead of print in *Neuropsychopharmacology,* van Berckel et al. from Columbia University (New York, NY) reported on an animal study designed to assess the involvement of glutamate transmission in regulating the effect of amphetamine-induced dopamine release. The relationship is significant because of a growing body of evidence supporting the hypothesis that the disregulation of dopamine function seen in amphetamine challenge in patients with schizophrenia may be the result of a deficit or disconnect in glutamate transmission. The study included 4 baboons that were pretreated with the metabotropic glutamate receptor agonist LY354740, followed by amphetamine-induced decreases in ^{11}C-raclopride equilibrium-specific binding. Under control conditions, the amphetamine-induced reduction (without LY3554740) was 28% ± 7%. With the addition of LY354740, the reduction was significantly greater, at 35% ± 7%, a difference that went beyond a simple additive effect, because LY354740 alone did not reduce ^{11}C-raclopride equilibrium-specific binding. The authors concluded that these data document the involvement of glutamate transmission in regulating the effect of amphetamine-induced dopamine release and provide support for additional studies of this mechanism in patients with schizophrenia.

Neuropsychopharmacology

^{15}O-CO_2 PET in Bipolar Disorder

In an article e-published on September 16 ahead of print in *Biological Psychiatry*, Deckersbach et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) and the University of Kansas Medical Center (Kansas City) reported on a study in which ^{15}O-CO_2 PET was used to examine the functional neuroanatomy of episodic memory impairment in euthymic individuals with bipolar I disorder. Previous studies have suggested that individuals with bipolar disorder have cognitive impairments, particularly in verbal episodic memory, not only during mood episodes but also when they are euthymic. This study included 8 euthymic patients with bipolar I disorder and 8 control subjects matched for age, gender, education, and intelligence. Each participant underwent ^{15}O-CO_2 PET imaging while completing a verbal learning paradigm that consisted of learning several lists of words. The bipolar subjects had more difficulties learning the lists of words than the control subjects and also showed blunted regional cerebral blood flow increases in the left dorsolateral prefrontal cortex during this task. The authors concluded that these images verified the clinical observations that individuals with bipolar I disorder are impaired in learning new verbal information and provided valuable information on the relationship of these impairments to abnormalities in brain regions involved in learning and episodic memory.

Biological Psychiatry

Multimodality Image Fusion to Determine Gross Tumor Volume for RT

Grosu et al. from the Technical University of Munich (Germany) reported in the October 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2005;63: 511–519) on a study using multimodality fusion imaging techniques to develop a novel treatment strategy for recurrent high-grade gliomas using stereotactic hypofractionated reirradiation. The trial included 44 patients with recurrent high-grade gliomas (1 patient with anaplastic oligodendroglioma, 8 with anaplastic astrocytoma, 33 with glioblastoma multiforme, and 2 with gliosarcoma) after previous surgery and postoperative conventional radiotherapy with or without chemotherapy. For fractionated stereotactic radiotherapy (SFRT) treatment planning, the gross tumor volume was defined in 82% of patients by ^{11}C-methionine PET (MET-PET) or ^{123}I-alpha-methyltyrosine (IMT) SPECT fused with CT and MR imaging and in 18% of patients by CT and T1 + gadolinium-MR image fusion. All patients received SFRT (5 Gy administered in 6 days), and 29 patients also received chemotherapy with temozolomide in 1 to 2 cycles before and 4 to 5 cycles after SFRT. Patients were followed and evaluated by MR or CT every 3 months after SFRT until death. The median survival time for the study group was 8 months. Treatment planning based on PET or SPECT/CT/MR imaging was associated with improved survival over that seen with planning based on CT/MR imaging alone (9 and 5 months, respectively). Median survival times were 11 months for patients

who received SFRT based on biologic imaging and who also received temozolomide but were significantly lower (6 months) for patients treated with SFRT who did not undergo biologic imaging, did not receive temozolomide, or both. The authors noted that this is the first study of biologic imaging–optimized SFRT plus temozolomide in recurrent high-grade gliomas and pointed to the "most striking result of the trial": statistically significant longer survival time in the univariate analysis for patients reirradiated using MET-PET or IMT-SPECT/CT/MR image fusion in the treatment planning, in comparison with patients treated based on the results of MR/CT alone. They noted that the multitude of variables (both imaging and chemotherapy) in the study calls for additional research to determine whether treatment planning with SPECT/PET independently influences survival.

International Journal of Radiation Oncology, Biology, Physics

PET/CT in Conformal RT Planning

In a second study on radiation therapy planning in the October 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2005;63:340–345), Moureau-Zabotto et al. from the Tenon Hospital (Paris, France) reported on the use of ^{18}F-FDG PET and CT imaging in conformal radiotherapy (RT) planning in esophageal carcinoma. The study included 34 patients with esophageal cancer who were referred for concomitant RT and chemotherapy preparatory to radical resection. Each patient underwent CT and PET imaging for simulation treatment in the same treatment position. PET images were coregistered using 5 fiducial markers, and target delineation was initially performed on CT images, with corresponding PET data subsequently used as an overlay to define the target volume. PET identified previously undetected distant metastases in 2 patients, sparing them from conformal radiotherapy. The previously assessed gross tumor volume (GTV) was decreased by CT and PET image fusion in 12 patients (35%) and increased in 7 (21%). The GTV reduction was ≥25% in 4 patients because of a reduction in the length of the esophageal tumor. The GTV increase was ≥25% in 2 patients because of PET detection of occult mediastinal lymph node involvement in 1 and an increased length of the esophageal tumor in the other. Changes in assessed GTV with the coregistered imaging affected planning treatment volume in 18 patients. Changes in GTV and also in the isocenter of the planning treatment volume as assessed by PET in 25 patients (74%) also changed the percentage of total lung volume receiving >20 Gy, with a dose reduction in 12 patients and dose increase in 13. The authors concluded that CT and ^{18}F-FDG PET image fusion "appeared to have an impact on treatment planning and management of esophageal carcinoma."

International Journal of Radiation Oncology, Biology, Physics

MicroPET in Antibody-Based RT of Prostate Cancer

Parry et al. from Berlex Biosciences (Richmond, CA) reported in the September 15 issue of *Cancer Research* (2005;65:8397–8405) on the use of small animal PET to monitor the efficacy of a novel prostate tumor target for antibody-based radiotherapy of prostate cancer. Previous gene expression analysis showed that mindin/RG-1, a human mindin homologue, is expressed selectively in prostate tissues and that its expression level is elevated in some prostate tumors. A fully human antibody was generated against mindin/RG-1 protein and was shown to accumulate at high abundance in LNCaP tumor xenografts. Conjugates of this antibody were generated and radiolabeled with ^{111}In, ^{90}Y, or ^{86}Y. Of these, small animal PET with the ^{86}Y-radiolabeled conjugate showed highly specific accumulation of antibody in LNCaP tumor xenografts with clear tumor delineation at 4 hours. The therapeutic efficacy of ^{90}Y-labeled conjugate was evaluated in mice bearing LNCaP xenografts. Significant antitumor effects (at levels below toxicity) were noted with a single administration of radiolabeled antibody to animals bearing 200–400-mm^3 tumors. Tumor growth was inhibited in all treated animals over a 49-day period, and recurrence of growth after that period could be inhibited by a second administration of antibody at day 49. The authors concluded that their novel antibody conjugate "has considerable promise for therapy of metastatic prostate cancer in androgen-unresponsive patients."

Cancer Research

PET Reveals Extent of Radiation-Treatment Induced Changes

In a study published in the September issue of *Chest* (2005;128:1448–1452), Hassaballa et al. from Midwest Pulmonary Associates (Lombard, IL) described the use of PET to demonstrate radiation-induced changes to nonirradiated lungs in cancer patients treated with radiation and chemotherapy. The retrospective study included 16 patients undergoing radiation therapy for lung cancer who had undergone ^{18}F-FDG PET imaging after receiving treatment. Of these patients, 13 (81.2%) showed increased uptake in shielded nonirradiated lung in 4 distinct patterns: (1) contralateral peripheral pleural uptake (5 patients; 31.2%); (2) ipsilateral peripheral pleural uptake (5 patients; 31.2%); (3) bilateral peripheral pleural uptake (1 patient; 6.2%); and (4) bilateral diffuse background uptake (1 patient, who developed clinically evident radiation pneumonitis; 6.2%). The authors concluded that "PET scanning of lungs in irradiated patients may provide an early demonstrable barometer of pulmonary toxicity." This technique could be useful in monitoring patients receiving radiation therapy for thoracic malignancies and could also have predictive value for subsequent fibrosis. They added that "PET scanning may also be an important tool in future studies

(Continued on page 35N)

(Continued from page 32N)
to further elucidate the pathogenetic mechanism of radiation-induced lung injury."

Chest

Sequential PET Treatment Planning in Cervical Cancer

In an article e-published on September 8 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics,* Lin et al. from the Alvin J. Siteman Cancer Center (St. Louis, MO) reported on a study evaluating the utility of sequential ^{18}F-FDG PET in brachytherapy treatment planning in patients with carcinoma of the cervix. The study included 24 patients with stages Ib ($n = 7$), IIa ($n = 1$), IIb ($n = 7$), and IIIb ($n = 9$) carcinoma of the cervix. The treatment regimen for the group included irradiation and brachytherapy, with most also receiving concurrent weekly cisplatin chemotherapy. Patients underwent diagnostic ^{18}F-FDG PET imaging before treatment, sequential PET brachytherapy imaging during treatment, and follow-up PET imaging 3 months after treatment completion. All scans included delineation of gross tumor volume, bladder, and rectum using a commercially available treatment-planning system. Actual treatment delivery was based on 2-dimensional orthogonal planning. The mean gross tumor volume and percentage covered by the target isodose surface for the initial, middle, and last brachytherapy implant were 37 cm^3, 17 cm^3, and 10 cm^3 and 68%, 76%, and 79%, respectively. The maximal bladder and rectal doses obtained from 3D dose-volume histograms were significantly higher than the International Commission on Radiation Units and Measurements-stipulated bladder and rectal points obtained by 2D treatment-planning. The authors concluded that, "sequential FDG PET brachytherapy imaging identifies the tumor response in individual patients, potentially making patient-specific brachytherapy treatment planning possible."

International Journal of Radiation Oncology, Biology, Physics

Therapy

Combined RIT and Chemotherapy of Breast Tumors

Crow et al. from the City of Hope National Medical Center (Duarte, CA) reported in the September 21 issue of *Bioconjugate Chemistry* (2005;16: 1117–1125) on an animal study to assess the potential efficacy in breast cancer treatment of combined radioimmunotherapy (RIT) and chemotherapy using ^{90}Y-labeled anti-Her2 and anti-carcinoembryonic antigen (anti-CEA) antibodies with taxol. Studies were performed on mice bearing xenografts from MCF7, a cell line with low Her2 and CEA expression, in an effort to more accurately reflect the usual clinical situation in breast cancer. Results indicated that although tumor uptake of ^{111}In-anti-CEA was lower than that for ^{111}In-anti-Her2, RIT with ^{90}Y-anti-CEA was equally as effective as that with ^{90}Y-anti-Her2. When combined separately with a split chemotherapeutic dose of taxol, both of these ^{90}Y-labeled antibodies showed enhanced antitumor effects. ^{90}Y-anti-CEA and a single dose of taxol was as effective as the split-dose regimen. When mice were initially treated with ^{90}Y-anti-Her2 and imaged 1–2 weeks later with ^{111}In-anti-CEA or ^{111}In-anti-Her2, tumor uptake was higher for anti-CEA and improved over tumor uptake with no previous RIT. The authors concluded that these studies suggest "that combined RIT and taxol therapy are suitable in breast cancers expressing either low amounts of Her2 or CEA, thus expanding the number of eligible patients for combined therapies." They noted that these results also suggest that split-dose RIT using different combinations of ^{90}Y-labeled antibodies may be effective in antitumor therapy.

Bioconjugate Chemistry

CEA RIT in Colorectal Metastases

Liersch et al. from the Medical Center of the Georg-August University (Gottingen, Germany) reported in the September 20 issue of the *Journal of Clinical Oncology* (2005; 23:6763–6770) on 5-year safety and efficacy results of a phase II trial of carcinoembryonic antigen (CEA) radioimmunotherapy (RIT) with ^{131}I-labetuzumab, a radiolabeled humanized anti-CEA monoclonal antibody, in patients after salvage resection of colorectal metastases to the liver. The study included 23 patients who had undergone surgery for liver metastases of colorectal cancer and then received a dose of 40–60 mCi/m^2 of ^{131}I-labetuzumab. Over a median follow-up period of 64 months, the median overall survival time from the first liver resection for was 68.0 months, and the median disease-free survival time was 18.0 months. The 5-year survival rate was 51.3%. The major adverse effects noted were episodes of transient myelosuppression. The authors concluded that because both median overall survival and 5-year survival rates seem to be improved with adjuvant RIT after complete liver metastases resection in colorectal cancer, "these results justify further evaluation of this modality in a multicenter, randomized trial."

Journal of Clinical Oncology