Each month the editor of Newsline selects articles on therapeutic, diagnostic, research, and practice issues from a range of international publications. Although we have divided these into sections on diagnosis and on therapy and adjunct imaging, the increasing molecular focus of functional imaging continues to blur such traditional distinctions in the field. 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.

Therapy and Adjunct Imaging

Tolerance of Therapy After ^{131}I-Tositumomab RIT

In an article e-published on December 16 ahead of print in *Cancer*, Dosik et al. from the Weill Medical College of Cornell University and New York Presbyterian Hospital (New York, NY) reported on a study designed to determine whether patients with progressive disease after radioimmunotherapy (RIT) could tolerate subsequent therapy regimens. The study included 68 patients with non-Hodgkin's lymphoma who had progressive disease after ^{131}I-tositumomab RIT. These patients had received a median of 2 treatment regimens before RIT (66%, anthracyclines; 19%, platinum; 50% fludarabine). At the time of recurrent disease (median, 168 days after RIT), hematologic values were assessed. At that time no significant differences were found between pre-RIT and time-of-recurrence values, except for platelet counts, which were lower at progression (median, 130K cells/μL). All patients had white blood cell counts >1.0K cells/μL. Forty-four patients (65%) went on to receive additional chemotherapy regimens (median, 2 regimens; 43%, anthracyclines; 39%, platinum; 23%, fludarabine; 30%, stem cell transplantation). The remaining 24 patients received no additional chemotherapy. Most of the subsequently treated patients experienced disease improvement, although 18 (40%) died as a result of refractory disease after additional chemotherapy. The authors concluded that most patients with progressive disease after ^{131}I-tositumomab therapy were able to receive and benefit from subsequent therapy.

Cancer

^{90}Y Microsphere Treatment Response Measured by PET and CT

Lewandowski et al. from Northwestern Memorial Hospital (Chicago, IL), DataMedix Corp. (Newtown Square, PA), and the Johns Hopkins Hospital (Baltimore, MD) reported in the December issue of the *Journal of Vascular and Interventional Radiology* (2005;16:1641–1651) on a phase II study to determine the safety and efficacy of ^{90}Y microsphere treatment in patients with liver-dominant colorectal metastases in whom standard therapies had failed or were inappropriate. The study included 27 patients with unresectable hepatic colorectal metastases who were treated with the microspheres at a targeted absorbed dose of 135–150 Gy. Safety and toxicity were assessed using National Cancer Institute criteria, and response was assessed by the results of CT and ^{18}F-FDG PET imaging. PET indicators of tumor response consistently exceeded those measured by CT for both the first (88% and 35%, respectively) and second (73% and 36%, respectively) treated lobes. The authors reviewed side effects, treatment-related toxicities, and other sequelae and concluded that the microsphere administration provides "stabilization of liver disease with minimal toxicity in patients in whom standard systemic chemotherapy regimens have failed." They also noted the utility of PET in assessing disease progression and effectiveness of treatment.

Journal of Vascular and Interventional Radiology

^{131}I Therapy and Juvenile Differentiated Thyroid Carcinoma

In an article published in the December issue of *Endocrine-Related Cancer* (2005;12:773–803), Jarzab et al. from the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology (Glidice, Poland) reviewed the current status and management of juvenile differentiated thyroid carcinoma (DTC), with special attention to the role of ^{131}I therapy in children. In addition to characterizing juvenile DTC and noting clinical differences with adult DTC, the authors detailed the most common therapeutic approaches. These usually include a combination of surgery, ^{131}I ablation, and thyroid hormone therapy. Most current therapeutic designs rely on adult data and on treatment strategies based on adult outcomes, but the authors recommended distinct treatment strategies for children. An intensive approach, consisting of total thyroidectomy and central lymphadenectomy in all cases, completed by modified lateral lymphadenectomy when necessary and followed by ^{131}I administration, was preferred by the authors. They noted that many institutions choose more conservative approaches, but that most European centers employ radioiodine ablation as an essential element in

juvenile DTC treatment. The effectiveness, side effects, risks, and precautions for such therapy were reviewed. The authors concluded their comprehensive review by noting that "different therapeutic combinations should be prospectively compared using recurrence-free survival as the primary endpoint" and that "efforts also should be made to identify molecular signatures predicting recurrence, metastasis, and mortality."

Endocrine-Related Cancer

^{99m}Tc-Labeled mAb Detection of Ganglioside Expression in Breast Cancer

In an article e-published on December 2 ahead of print in *Breast Cancer Research and Treatment*, Oliva et al. from the National Institute of Oncology and Radiobiology (Havana, Cuba) described the use of ^{99m}Tc-labeled monoclonal antibody scintigraphy for in vivo detection of GM3(NeuGc) gangliosides in human breast tumors. Gangliosides are considered promising targets for cancer immunotherapy, and the GM3(NeuGc) ganglioside of is special interest because of previous research suggesting its low expression in normal tissues and overexpression in human breast tumor. The authors applied a radioimmunoscintigraphic technique with 3 different doses of technetium-labeled 14F7, a highly specific anti-GM3(NeuGc) monoclonal antibody, in a phase I/II clinical trial, including 14 women with stage 2 breast cancer. Imaging indicated tumor antibody accumulation in 100% of patients who received a 1-mg dose of the radioimmunoconjugate but in only 60% and 33% of those receiving 0.3- or 3-mg doses, respectively. Although it is difficult to draw conclusions from these dose results based on the small number of participants, the authors succeeded in providing evidence of in vivo immune recognition of GM3(NeuGc) in breast tumors. They concluded that these findings reinforce the value of this target for cancer immunotherapy.

Breast Cancer Research and Treatment

^{18}F-FDG PET Radioguided Surgery in Thyroid Cancer

Kraeber-Bodere et al. from the Hôtel Dieu Hospital and the René Gauducheau Cancer Center (Nantes, France) and the Claude Huriez Hospital (Lille, France) reported in the December issue of *Surgery* (2005;138: 1176–1182) on the feasibility of ^{18}F-FDG PET radioguided surgery in patients with radioiodine-negative differentiated thyroid cancer. The study included 10 patients with 1–5 foci of uptake on PET who were administered a mean activity of 265 MBq ^{18}F-FDG 30 minutes before scheduled surgery. Radioactivity uptake in tumor and normal tissues was measured before and after resection. Six patients were injected with recombinant human thyroid-stimulating hormone preoperatively. The authors found complete correlation between abnormal findings detected by preoperative PET imaging and those detected with the gamma probe. All positive tissues detected with the probe were confirmed to be differentiated thyroid cancer. The surgeon's hands were exposed to 90–270 μSv of radiation, and radiation levels to patients were minimized, with complete resection of tumor contributing significantly to lessening cumulative radiation. The authors concluded that these results "show the feasibility and benefit of ^{18}F-FDG radioguided surgery with a gamma probe in the management of differentiated thyroid cancer patients with radioiodine-negative recurrence."

Surgery

Radionuclide Therapy as Palliation

Liepe et al. from University Hospital Dresden (Radeberg, Germany) reported in the November/December issue of the *American Journal of Hospice and Palliative Care* (2005; 22:457–464) on a study investigating the efficacy and toxicity of several radiopharmaceuticals in the palliation of painful bone metastases. The study included 64 patients with breast or prostate cancer. Of these, 31 were treated with ^{188}Re-hydroxyethylidene diphosphonate (^{188}Re-HEDP), 15 with ^{186}Re-HEDP, and 18 with ^{89}Sr, and data on pain symptoms, quality of life, and bone-marrow function were recorded. Blood counts were made weekly for 6 weeks and at 12 weeks. In a questionnaire format, the majority of patients reported pain relief after radiopharmaceutical treatment (77% after ^{188}Re-HEDP, 67% after ^{186}Re-HEDP, and 72% after ^{89}Sr). A smaller percentage of patients reported that they were able to discontinue analgesics and were pain free at 12 weeks (16% after ^{188}Re-HEDP, 13% after ^{186}Re-HEDP, and 17% after ^{89}Sr). Thrombocytopenia (platelet count $<100 \times 10^3/\mu L$) was noted in 3 patients during ^{188}Re-HEDP therapy, 1 during ^{186}Re-HEDP therapy, and 3 during ^{89}Sr therapy, with nadirs of platelet and leukocyte counts observed between weeks 2 and 5 after treatment. These effects were reversible by week 12. The authors concluded that these results indicate "that all evaluated radiopharmaceuticals were effective in pain palliation without induction of severe side effects."

American Journal of Hospice and Palliative Care

Early ^{18}F-FLT PET and Response to Breast Cancer Therapy

In an article e-published on December 14 ahead of print in the *Journal of Molecular Imaging and Biology*, Pio et al. from the David Geffen School of Medicine at the University of California Los Angeles compared the utility of ^{18}F-FDG and 3'-^{18}F-fluoro-3'-deoxythymidine (^{18}F-FLT) PET imaging in predicting the long-term effects of chemotherapy in tumor viability in breast cancer. The study included 14 patients newly diagnosed with primary or metastatic

breast cancer who were scheduled to begin a chemotherapeutic regimen. Each patient was scanned with both tracers on 2 separate days within a 1-week period before beginning treatment. These studies were repeated 2 weeks after the end of the first cycle of chemotherapy and after the final cycle or 1 year after the initial PET scan (whichever was first). The authors found that mean change in ^{18}F-FLT (but not ^{18}F-FDG) uptake in primary and metastatic tumors after the first course of chemotherapy showed a significant correlation with late (average, 5.8 months) changes in CA27.29 tumor marker levels. ^{18}F-FLT tracer uptake after a first course of chemotherapy also correlated with late changes in tumor size as assessed by CT. The authors concluded that "a 10-minute FLT PET scan acquired 2 weeks after the end of the first course of chemotherapy is useful for predicting longer term efficacy of chemotherapy regimens for women with breast cancer."

Journal of Molecular Imaging and Biology

PET Targeting of HSV Oncolytic Gene Therapy in Prostate Cancer

In an article e-published on December 16 ahead of print in the *Journal of Molecular Imaging and Biology,* Mullerad et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on a proof of concept study of the ability of ^{18}F-FDG PET to predict tumor response to oncolytic herpes simplex virus (HSV) therapy in both in vitro and in vivo prostate cancer models. The authors found that after HSV therapy, androgen increased cell kill by 74% in vitro and enhanced viral yield by 2.4-fold in an animal model. They found that this enhanced efficacy was predicted by high ^{18}F-FDG accumulation in intact animals, compared with low uptake in animals after orchiectomy. They concluded that these results provide "the mechanistic basis for selecting patients for targeted oncolytic viral therapy by means of a noninvasive molecular imaging method in the treatment of prostate cancer."

Journal of Molecular Imaging and Biology

Diagnosis

^{131}I-MIBG Imaging and Pheochromocytoma

Guller et al. from University Hospital Basel (Basel, Switzerland), Durham Veterans Affairs Medical Center and Duke University (Durham, NC), and the University of Missouri (Columbia) reported in the January issue of *Annals of Surgery* (2006;243: 102–107) on a study designed to define the most sensitive biochemical test for diagnosis of pheochromocytoma and to assess the utility of ^{131}I-labeled metaiodobenzylguanidine scintigraphy (^{131}I-MIBG) in such diagnoses. The study included 152 patients (12.5% with bilateral disease, 29.6% with malignant pheocromocytoma, and 23.0% with hereditary forms of the disease). Each patient underwent ^{131}I-MIBG scintigraphy. The authors found that the most sensitive test was total urinary normetanephrine (96.9%), with the second and third most sensitive being platelet norepinephrine (93.8%) and ^{131}I-MIBG scintigraphy (83.7%). ^{131}I-MIBG scintigraphy in combination with tests for platelet norepinephrine, plasma norepinephrine, total urine normetanephrine, and urine norepinephrine yielded sensitivities of 100%, 97.1%, 96.6%, and 95.3%, respectively. The authors concluded that although the laboratory tests of choice to establish the diagnosis of pheochromocytoma are urinary normetanephrine and platelet norepinephrine, the addition of ^{131}I-MIBG further improves sensitivity. They advocated performing a ^{131}I-MIBG scan "if the diagnosis of pheochromocytoma is clinically suspected and catecholamine measurements are within the normal range."

Annals of Surgery

SLN Biopsy and Oral Cancer Staging

In the December issue of *Laryngoscope* (2005;115:2217–2220), Rigual et al. from the Roswell Park Cancer Institute (Buffalo, NY) and St. Paul's Hospital (Vancouver, Canada) reported on a study to determine the feasibility and accuracy of sentinel lymph node (SLN) biopsy in the staging of patients with T2N0 oral carcinoma. The study included 20 patients with previously untreated N0 oral cavity squamous cell carcinoma. All patients underwent SLN biopsy after preoperative technetium sulfur colloid lymphoscintigraphy with intraoperative gamma probe guidance and peritumoral injection of 1% isosulfan blue. SLNs and non-SLNs were examined for histology after neck dissection in all patients. The authors found that SLNs were identified in all patients (100%) and accurately predicted the pathologic nodal status in 18 (90%). In 6 of these patients, tumor was found exclusively in the SLNs. Occult nodal metastases were present in 60% of patients. The authors concluded that SLN biopsy is a "technically feasible and accurate procedure for staging the neck in oral carcinoma patients." They noted that the rate of occult metastases in this study group was higher than in previously reported studies with other techniques, suggesting that multiinstitutional studies of SLN biopsy could yield important data for the management of patients with oral carcinoma.

Laryngoscope

PET/CT vs CT in Adrenocortical Carcinoma

In an article e-published on December 20 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Leboulleux et al. from the Institut Gustave Roussy (Villejuif, France) reported on a study comparing PET/CT and CT in diagnosis and prognosis of adrenocortical carcinoma. The study included 28 patients with adrenocortical cancer.

Each underwent ^{18}F-FDG PET and thoraco-abdomino-pelvic CT (TAP-CT) imaging. A gold standard of progression on follow-up TAP-CT or as identified at pathology revealed a total of 269 lesions in 57 organs in 22 patients. The sensitivities for the detection of lesions and identification of metastatic organs were 90% and 93%, respectively, for PET/CT and 88% and 82%, respectively, for TAP-CT, with 12% of lesions and 18% of metastatic organs identified only with PET/CT and 10% of lesions and 7% of metastatic organs identified with TAP-CT only. Thirty-eight percent of local relapses were seen only with PET/CT. PET/CT findings modified treatment in 5 cases, 1 of which was found to have been false-positive on PET. ^{18}F-FDG uptake was a significant prognostic factor for survival. The authors concluded that ^{18}F-FDG PET/CT is "complementary to TAP-CT and of special interest in the diagnosis of local relapses."

Journal of Clinical Endocrinology and Metabolism

PET/CT and Thyroid Nodules Before Surgery

Mitchell et al. from Harvard Medical School (Boston, MA) reported in the December issue of *Surgery* (2005;138:1166–1175) on a study assessing the utility of ^{18}F-FDG PET/CT in the preoperative evaluation of thyroid nodules. The study included 31 patients with a total of 48 lesions who underwent fine-needle aspiration and ^{18}F-FDG PET/CT imaging before surgery. Pathologic results indicated that 15 of 48 lesions were malignant and 33 were benign. ^{18}F-FDG PET/CT had a 60% sensitivity (9 of 15 malignant lesions) and 91% specificity (30 of 33 benign lesions). The combined-modality PET/CT imaging had positive and negative predictive values of 75% and 83%, respectively. The authors concluded that PET/CT "provides a high negative predictive value for malignancy, making this a potentially useful tool in the evaluation of thyroid nodules with indeterminate fine-needle aspiration" and called for additional studies to determine the true accuracy of this approach.

Surgery

PET Assessment Before Radical Hysterectomy

Unger et al. from the Louisiana State University Health Sciences Center (Shreveport) reported in the November/December issue of the *International Journal of Gynecological Cancer* (2005;15:1060–1064) on a retrospective study to evaluate the ability of whole-body ^{18}F-FDG PET imaging to select appropriate candidates for radical hysterectomy and pelvic lymphadenectomy. The study included 14 women undergoing planned radical hysterectomy and pelvic lymphadenectomy with clinically localized cervical cancer and either negative or inconclusive metastatic nodal disease as assessed by PET. Pelvic lymph nodes were clearly negative on PET in 12 of the women. The remaining 2 had focal tracer uptake that was deemed suspicious although not definitive for nodal metastasis. These pelvic nodes were positive at surgery in both women, in each of whom CT had failed to detect nodal disease. Neither PET nor CT could detect parametrial disease, and each also failed to detect primary tumor in some cases. The results led the authors to conclude that ^{18}F-FDG PET findings that are clearly negative for nodal disease indicate good candidates for radical hysterectomy who are at low risk for subsequent chemoradiation.

International Journal of Gynecological Cancer

PET, CT, and Size of Lymph Nodes in NSCLC

In an article e-published on December 5 ahead of print in the *European Journal of Cardiothoracic Surgery*, de Langen et al. reported on the results of a meta-analysis of published studies on metastatic involvement for different size categories of enlarged lymph nodes in patients with non–small cell lung cancer (NSCLC). Although a number of studies have suggested that ^{18}F-FDG PET is superior to CT in staging the mediastinum in patients with the disease, other findings indicate that PET performance may vary with nodal size as seen on CT. The authors noted that the association between size and probability of malignancy should be clearly elucidated if PET is to be used to successfully predict outcomes and if both PET and CT are to be used to stratify patients for mediastinoscopy or thoracotomy. Fourteen multi-institutional analyses were included in the meta-analysis. The prevalence of metastatic involvement and related test performance of CT and ^{18}F-FDG PET in these studies were calculated for lymph nodes measuring 10–15, 16–20, and $>$20 mm. In patients with a negative PET scan and lymph nodes measuring 10–15 cm, the post-test probability of N2 disease was 5%, suggesting that these patients should be planned for thoracotomy, because the yield of mediastinoscopy would be quite low. In patients with a negative PET and lymph nodes measuring $\geq$16 mm, the post-test probability for N2 disease was 21%. The authors concluded that these patients should proceed to mediastinoscopy before possible thoracotomy to lower the numbers of unnecessary thoracotomies in this subset.

European Journal of Cardiothoracic Surgery

^{99m}Tc-Sestamibi Scans and ^{18}F-FDG PET in Multiple Myeloma

Hung et al. from the Changhua Christian Hospital (Taiwan) reported in the November/December issue of *Anticancer Research* (2005;25:4737–4741) on a comparison of ^{99m}Tc-sestamibi scans and ^{18}F-FDG PET imaging in the assessment of multiple myeloma. The study included 12 patients with multiple myeloma. Each underwent a conventional radiologic skeletal survey, ^{99m}Tc-sestamibi scan, and ^{18}F-FDG-PET imaging. The 3 approaches detected 34 lesions and

5 cases of bone marrow involvement. The skeletal X-ray survey detected 4 soft tissue lesions (21.1%), 12 skeletal lesions (80%), but no bone marrow involvement (0%). The ^{99m}Tc-sestamibi scan found 4 cases of bone marrow involvement (80%), 13 soft tissue lesions (68.4%), and 12 skeletal lesions (80%). The PET scan detected 5 cases of bone marrow involvement (100%), 17 soft tissue lesions (89.5%), and 14 skeletal lesions (93.3%). The authors concluded that although both ^{99m}Tc-sestamibi and ^{18}F-FDG PET have value in patients with multiple myeloma, PET imaging can detect more lesions than the ^{99m}Tc-sestamibi scan.

Anticancer Research

PET and Brain Ammonia in Cirrhosis

In an article e-published in the December issue of *Hepatology* (2005; 43:42–50), Keiding et al. from the Aarhus University Hospital (Denmark) reported on the methodology and implications of PET imaging of brain metabolism of ^{13}N-ammonia during acute hepatic encephalopathy (HE) in patients with cirrhosis. Previous studies have suggested that disturbances in brain ammonia metabolism are key actors in the pathogenesis of HE. The authors used ^{13}N-ammonia PET to study brain ammonia kinetics (in cerebral cortex, basal ganglia, and cerebellum) in 8 patients with cirrhosis and an acute episode of clinically overt HE, 7 patients with cirrhosis without HE, and 5 healthy volunteers. Arterial ^{13}N-ammonia, ^{13}N-urea, and ^{13}N-glutamine concentrations levels were measured in blood samples. Differences were noted in permeability/surface area product of ^{13}N-ammonia transfer across the blood–brain barrier in the 3 groups of patients. Metabolic trapping of blood ^{13}N-ammonia in the brain, however, did not correlate to specific regions or patient groups. Mean net metabolic flux of ammonia from blood into intracellular glutamine in the cortex varied significantly, at 13.4 μmol/min/L tissue in patients with cirrhosis with HE, 7.4 in patients without HE, and 2.6 in healthy controls. The authors concluded that "increased cerebral trapping of ammonia in patients with cirrhosis with acute HE was primarily attributable to increased blood ammonia and to a minor extent to changed ammonia kinetics in the brain."

Hepatology

PET and Surgical Management in Melanoma

In an article e-published on December 1 ahead of print in the *British Journal of Surgery*, Bastiaannet et al. from the University Medical Centre Groningen (The Netherlands) reported on a retrospective, multicenter study of the effect of ^{18}F-FDG PET imaging on surgical management in patients with melanoma. The study included 257 patients with melanoma, and data collection included indications for imaging, imaging findings, unexpected findings of tumors other than melanoma, and treatment plans before and after imaging. The majority of scans (71.2%) were ordered for staging to detect distant metastases in patients with stage III disease. PET imaging resulted in upstaging in 56 patients (21.8%) and in treatment changes in 44 patients (17.1%). Unexpected tumors were detected in 11 patients (4.3%). The authors concluded that ^{18}F-FDG PET is "most valuable in patients with stage III melanoma for detection of distant metastases and identification of candidates for surgery and/or systemic treatment" and cautioned that unexpected findings on PET should not be disregarded.

British Journal of Surgery