Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. 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

Histopathology of PET-Positive ^{131}I-Refractory Thyroid Cancers

In an article e-published on May 16 ahead of print in *Cancer*, Rivera et al. from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported on the histopathologic characterization of radioiodine-refractory ^{18}F-FDG PET–positive thyroid carcinomas. The study looked at the records and tissue specimens of 70 patients in whom the biopsied metastatic site corresponded to a PET-positive lesion sampled within 2 y of the PET scan. The researchers performed detailed microscopic and histologic examinations of metastatic specimens from all patients and available primary tumors from 43 patients. Histologic characterization of the metastasis/recurrence showed that 33 patients (47.1%) had poorly differentiated thyroid carcinoma (defined on the basis of mitosis and necrosis, as previously reported by these researchers in *Cancer*. 2006;106:1286–1295), 14 (20%) had the tall cell variant of papillary thyroid carcinoma, 16 (22.9%) had well-differentiated papillary thyroid carcinoma, 6 (8.6%) had Hurthle cell carcinoma, and 1 (1.4%) had anaplastic carcinoma. The histopathologic distribution of the tumor in the primaries was 51% in poorly differentiated thyroid carcinoma, 19% in the tall cell variant of papillary thyroid carcinoma, 23% in well-differentiated papillary thyroid carcinoma, and 7% in widely invasive Hurthle cell carcinoma. In 16 patients (37%) histology differed between the primary tumor and metastasis, and in the majority of these patients (10 patients, 63%), the metastases had transformed to a higher grade. Tumor necrosis and extensive extrathyroid extension in the primary tumor were identified as independent predictors of poorer disease-specific survival. In addition, 68% of the poorly differentiated thyroid carcinoma primary tumors were initially classified as better-differentiated tumors on the basis of the presence of papillary and/or follicular architecture or the presence of typical nuclear features, a classification corrected on histopathologic analysis. The authors concluded that poorly differentiated disease in ^{131}I-refractory PET-positive thyroid cancers may be underrecognized if defined by architectural and nuclear features alone. The presence of tumor necrosis was identified as a strong predictor of poor disease-specific survival, even within this group of clinically aggressive tumors. In addition, the authors noted that the significant amount of histologic differences between primary tumors and metastases may reflect the genetic instability of these tumors.

Cancer

PET in Postoperative Thyroid Cancer

Al-Zahrani et al. from the King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) reported in the May issue of the *European Journal of Endocrinology* (2008;158:683–689) on a study comparing the utilities of ^{18}F-FDG PET with diagnostic and postablation ^{131}I planar whole-body diagnostic scanning in predicting outcomes in patients with newly diagnosed differentiated thyroid cancer. The study included 26 such patients who underwent thyroidectomy and posttreatment whole-body scanning. Twenty-four patients underwent radioactive iodine ablation. PET imaging results were correlated with disease stage and long-term outcomes. Eighteen (69.2%) of the PET scans were positive for a total of 40 foci. The corresponding 26 diagnostic whole-body scans were all positive, indicating a total of 47 foci. Both diagnostic and therapeutic whole-body scanning showed similar foci in the 24 patients who underwent therapy. PET indicated tracer uptake in 26 foci (65%) outside the thyroid bed, and diagnostic whole-body imaging indicated 45 foci (95.7%) in the thyroid bed, 2 (4.3%) in the cervical lymph nodes, and no foci outside the neck area. Clear correlations were found between PET results, stage of disease (7 of 8 negative PET scans were stage 1, all patients with disease stages >1 had positive PET scans), and long-term outcome. Over a follow-up period of 10–48 mo, 7 of 8 patients (87.5%) with negative PET scans were in remission, and only 8 (44.4%) with positive PET scans were in remission. The authors concluded that in postoperative evalution of differentiated thyroid cancer, ^{18}F-FDG PET is more likely than diagnostic and postablative ^{131}I planar whole-body scanning "to reveal uptake outside the thyroid bed and to correlate with the stage of the disease and long-term outcome."

European Journal of Endocrinology

Canadian Pediatric Thyroid Study

Seventeen collaborators from multiple sites participating in the Canadian

Pediatric Thyroid Nodule Study reported in the May issue of the *Journal of Pediatric Surgery* (2008;43:826–830) on initial findings on current management practices. The study included records of 141 patients (>70% female) with 117 palpable masses who underwent surgery for thyroid nodules over a 6-y period at 9 pediatric tertiary care hospitals. The researchers gathered information on demographics, diagnostics, operative results, and complications. Ultrasound and/or thyroid scintigraphy were the most often used preoperative imaging studies. The overall rate of malignancy was 43%, with half being papillary carcinoma. Fine-needle aspiration cytology correlated with final pathology in 49% of cases. In their conclusions, the authors highlighted a number of important issues in the management of children with thyroid nodules, including the high risk of malignancy in these pediatric lesions, wide variations in preoperative investigations and imaging protocols, inconsistency of risk factors predicting the presence of malignant lesions, and underuse of fine-needle aspiration cytology as a potentially effective tool to guide surgical treatment. To improve outcome and decrease morbidity, a staged approach may also be beneficial. The authors called for a consolidated approach and practice guidelines for perioperative management of thyroid lesions in children and proposed an algorithm for the management of pediatric thyroid nodules.

Journal of Pediatric Surgery

PET and Colorectal Liver Mets

Tan and colleagues from Washington University (St. Louis, MO) and Vanderbilt University (Nashville, TN) reported in the May issue of the *Journal of the American College of Surgeons* (2008;206:857–868) on the development of a prognostic system applicable to patients with hepatic metastases from colorectal cancer in whom extrahepatic disease was excluded by preoperative ^{18}F-FDG PET. The retrospective study included data from 285 consecutive patients undergoing liver resection for colorectal metastases who had also undergone preoperative PET imaging. The researchers at the 2 institutions extracted 15 clinicopathologic variables to identify factors predictive of outcomes. Only 16% of patients had poorly differentiated tumors, and patients with well-differentiated or moderately differentiated tumors were analyzed as an independent subgroup. In this subgroup, positive lymph node status in the primary colorectal tumor resection specimen was the sole characteristic that predicted survival. Additional analysis was performed after dividing patients into 3 prognostic categories: poor tumor differentiation, well-differentiated or moderately differentiated tumors that were node positive, and well-differentiated or moderately differentiated tumors that were node negative. The results led the authors to conclude that in patients with colorectal liver metastases staged with PET, "overall survival can be predicted directly from data in the pathology report of the colorectal primary tumor." They pointed to the need for new prognostic molecular tumor markers to complement clinicopathologic markers as essential in developing accurate and individualized predictors of outcomes and, thereby, more personalized management and treatment.

Journal of the American College of Surgeons

New PSMA Imaging Probe

In the May 15 issue of *Clinical Cancer Research* (2008;14:3036–3043), Mease and colleagues from the Johns Hopkins Medical Institutions (Baltimore, MD) and the University of Illinois at Chicago reported on ^{18}F labeling of and preliminary PET imaging with a novel prostate-specific membrane antigen (PSMA) inhibitor. The group previously reported on successful use of the compound in PET imaging of xenografts that express PSMA (*Clin Cancer Res.* 2005;11:4022–4028). In the current article, they describe the preparation of *N*-[*N*-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[^{18}F]fluorobenzyl-L-cysteine (^{18}F-DCFBC). Biodistribution and imaging studies were performed in mice engrafted with both PIP and FLU tumors. High tracer uptake was seen in the PIP tumors, and little or no uptake was seen in the FLU tumors. Mouse biodistribution results indicated the kidneys as the dose-limiting organ. The authors concluded that ^{18}F-DCFBC localizes to PSMA-expressing tumors in mice, permitting imaging by small-animal PET, and that this radiopharmaceutical is "an attractive candidate for further studies of PET imaging of prostate cancer."

Clinical Cancer Research

^{18}F-FLT PET in Bone and Soft Tissue Tumors

Also in the May 15 issue of *Clinical Cancer Research* (2008;14:2970–2997), Buck et al. from the Technische Universitat Munchen (Germany) reported on the ability of ^{18}F-fluorothymidine (^{18}F-FLT) PET to detect sites of bone and soft tissue tumors, assess tumor grading, and differentiate malignant from benign tumors. The study included 22 patients with established or suspected soft or bone tissue lesions who underwent incisional biopsy, MR imaging, contrast-enhanced CT, and ^{18}F-FLT PET imaging. Fifteen patients also underwent ^{18}F-FDG PET imaging. ^{18}F-FLT PET results were compared with histopathology, tumor grading, and corresponding results from ^{18}F-FDG PET. ^{18}F-FLT PET detected all 17 malignant bone or soft tissue tumors, with escalating uptake correlated to grades of tumor. ^{18}F-FDG uptake did not correlate significantly with tumor grading. These results suggested that ^{18}F-FLT is "a superior PET tracer for noninvasive grading of sarcomas."

Clinical Cancer Research

PET/CT IMRT in Cervical Carcinoma

In an article e-published ahead of print on May 7 in the *International Journal of Radiation Oncology, Biology, Physics*, Esthappan et al. from

the Washington University School of Medicine (St. Louis, MO) described the use of PET/CT-guided intensity-modulated radiation therapy (IMRT) in a more aggressive treatment technique facilitating dose escalation to positive paraaortic lymph nodes (PALNs) in patients with cervical cancer. The study reported on the results of treatment plans for 10 patients generated by PET/CT to deliver 60.0 Gy to PET-positive PALNs and 50.0 Gy to the PALNs and pelvic lymph node beds. Treatment plans were optimized with the intent of delivering ≥95% of the prescribed doses to ≥95% of each target volume. Analysis of results indicated that target coverage goals were satisfied in each of the 10 plans and that treatment plans involved irradiation of approximately 50% of the bowel volume to at least 25.0 Gy, with <10% receiving at least 50.0 Gy and <1% receiving at least 60.0 Gy. Approximately 50% of the kidney volume received at least 16.0 Gy, <5% received at least 50.0 Gy, and <1% received at least 60.0 Gy. The authors presented treatment simulation and planning methods as well as guidelines for the evaluation of target coverage and normal tissue sparing using these PET/CT-guided techniques.

International Journal of Radiation Oncology, Biology, Physics

PET/CT in Choroidal Melanoma

Faia et al. from the Mayo Clinic (Rochester, MN) reported in the May issue of *Retina* (2008;28:763–769) on a study designed to correlate PET/CT findings with clinical and light microscopic features in choroidal melanoma. The study included 14 patients with choroidal melanoma who underwent preoperative PET/CT and enucleation. Standard uptake values (SUVs) were correlated with clinical and light microscopic findings. Uptake was seen in all 14 eyes, and histopathology identified choroidal melanoma in all, with 6 mixed cell, 7 spindle cell, and 1 epithelioid cell type. Individual SUV means correlated directly with lesion thickness. Those melanomas with focal necrosis and those of the mixed-cell type had higher mean SUVs, although the majority of the lesions had low-to-medium mean SUVs. Lesion size accounted for a significant proportion of the variation.

Retina

PET/CT in Primary Rectal Cancer

In an article e-published on May 7 ahead of print in *Diseases of the Colon and Rectum*, Davey et al. from the Peter MacCallum Centre (Melbourne, Australia) reported on the effect of ^{18}F-FDG PET/CT on the staging and management of primary rectal cancer. The study included 83 patients with rectal cancer who underwent PET/CT imaging after their referring physicians had assigned management plans based on conventional imaging. Using PET/CT for staging resulted in a change in stage in 26 patients (31%). Of these, 12 (14%) were upstaged and 14 (17%) were downstaged. The use of PET/CT significantly changed management plans in 7 patients (8%). Of these, 6 patients were reassigned from curative treatment to palliative care, and 1 patient was reassigned from palliative care to curative treatment. Management was altered in 10 additional patients (12%). The authors concluded that PET/CT "impacts the management of patients with primary rectal cancer and influences staging/therapy in a third of patients and should be a component of rectal cancer workup."

Diseases of the Colon and Rectum

PET in Residual Tumors in Children

André et al. from the Hôpital de La Timone (Marseille, France) reported in the May issue of the *Journal of Pediatric Hematology/Oncology* (2008; 30:343–346) on a study determining the utility and potential role of ^{18}F-FDG PET in assessing residual masses in children after treatment for solid tumors. The initial review included 238 PET scans performed in children followed up in the pediatric oncology and hematology departments, and the authors focused on the medical files of 18 children (median age, 8 y) in whom PET was performed to evaluate a residual mass. These patients had been previously treated for Hodgkin's disease (n = 5), lymphomas (n = 5), osteosarcomas (n = 3), rhabdomyosarcomas (n = 2), and other malignant disease (n = 3). Among the variables assessed were remission or persistent disease on follow-up and clinical, radiologic, and biopsy data. Posttherapy PET findings were negative in 13 cases and positive in 5. Among the children with negative findings, 1 patient relapsed during follow-up and 12 remained in remission. Among the children with positive PET findings, 4 patients relapsed. PET sensibility, specificity, and positive and negative predictive values were 0.8, 0.92, 0.8, and 0.92, respectively. The authors concluded that "PET seems to be an interesting tool to assess the nature of posttherapeutic residual masses in children, regardless of the underlying malignancy" and called for additional multicenter studies focusing on specific underlying disease.

Journal of Pediatric Hematology/Oncology

MOLECULAR IMAGING AND THERAPY

In Vivo Embryonic Stem Cell Imaging

Swijnenburg et al. from Stanford University (CA) reported ahead of print on May 20 in *Stem Cells and Development* on the use of in vivo bioluminescent imaging to noninvasively track the fate of intramuscularly transplanted murine embryonic stem cells stably transduced with a double fusion reporter gene consisting of firefly luciferase and enhanced green fluorescent protein. The cells survived and differentiated into teratomas. These results were contrasted with those when allogeneic murine embryonic stem cells transplants were infiltrated by a variety of inflammatory cells, leading to rejection within 28 d. Acceleration of rejection was observed when stem cells were allotransplanted after prior sensitization of the host. The studies also

provided evidence that murine embryonic stem cell derivatives were more rapidly rejected than undifferentiated murine embryonic stem cells. The authors concluded that these data suggest that murine embryonic stem cells "do not retain immune-privileged properties in vivo and are subject to immunological rejection as assessed by novel molecular imaging approaches."

Stem Cells and Development

Integrin-Targeting with RGD4C-TNF Fusion Protein

Wang et al. from the Stanford University School of Medicine (CA) reported in the May issue of *Molecular Cancer Therapeutics* (2008;7:1044–1053) on the use of integrin $\alpha_v\beta_3$ as a target for tumor-specific delivery of tumor necrosis factor-α (TNF). Cell reptor binding assay and microPET imaging verified that the fusion protein RGD4C-TNF bound specifically to $\alpha_v\beta_3$. ^{64}Cu-DOTA-RGD4C-TNF was found to have significantly higher activity accumulation in integrin-positive tumors than ^{64}Cu-DOTA-TNF. The authors also found that tumor accumulation of ^{64}Cu-DOTA-RGD4C-TNF was effectively blocked by c(RGDyK) peptide in $\alpha_v\beta_3$-positive tumor models, suggesting the $\alpha_v\beta_3$ specificity of RGD4C-TNF fusion protein in vivo. RGD4C-TNF was also significantly more potent than TNF in inhibiting orthotopic MDA-MB-435 tumor growth. Ex vivo tissue staining confirmed the specific cytotoxicity of RGD4C-TNF against integrin-positive tumor cells and tumor vasculature.

Molecular Cancer Therapeutics

^{11}C-Acetoacetate for PET in Breast and Prostate Tumors

In an article e-published on May 3 ahead of print in *Molecular Imaging and Biology*, Authier et al. from the Université de Sherbrooke (Canada) reported on a study evaluating the potential of ^{11}C-acetoacetate as a tracer of ketone body utilization by breast and prostate tumors and comparing the potential of this compound with that of ^{11}C-acetate as a PET tracer. Biodistribution studies were performed with both ^{11}C-labeled tracers in mice bearing breast or prostate tumors, followed by dynamic PET imaging and dosimetry calculation. ^{11}C-acetoacetate uptake was optimal between 5 and 30 min, with maximal uptake ranging from 2.19% to 2.72% injected dose/g for several types of tumor. ^{11}C-acetate uptake was optimal within 15 min, with maximal uptake ranging from 0.96% to 2.30% injected dose/g for the same types of tumors. Tumor retention of ^{11}C-acetoacetate was higher (but not significantly so). The authors found these results promising and called for additional studies "to determine if this tracer can detect slow-growing breast and prostate cancers in the clinical setting."

Molecular Imaging and Biology

Nanocarriers in PET

Hooker et al. from the University of California–Berkeley reported on April 25 ahead of print in *Molecular Imaging and Biology* on a modular synthetic strategy to append imaging agents to a viral capsid. The researchers labeled the inside surface of the hollow protein shell of bacteriophage MS2 (mtMS2) with ^{18}F-fluorobenzaldehyde through a multistep bioconjugation strategy. An aldehyde functional group was first attached to interior tyrosine residues through a diazonium coupling reaction. The aldehyde was further elaborated to an alkoxyamine functional group, which was then condensed with no carrier added ^{18}F-fluorobenzaldehyde. Biodistribution of the injected radioactive conjugates was evaluated in rats. ^{18}F-labeled MS2 showed prolonged blood circulation time and a significantly altered excretion profile. Additional small molecule "cargo" installed in the capsids did not alter biodistribution. The authors concluded that these studies "provide further insight into the pharmacokinetic behavior of nanomaterials and serve as a platform for the future development of targeted imaging and therapeutic agents based on mtMS2."

Molecular Imaging and Biology

US-Modulated Optical Tomography in SLNs

Kim et al. from Washington University (St. Louis, MO) reported in the March/April issue of the *Journal of Biomedical Optics* (2008;13:020507) on a study applying ultrasound-modulated optical tomography (UOT) to image ex vivo methylene blue–dyed sentinel lymph nodes embedded in chicken breast tissues. The novel UOT system used ring-shaped light illumination, intense acoustic bursts, and charge-coupled device camera-based speckle contrast detection. The authors pointed to several advantages such a system conveys, including the fact that it is nonionizing and noninvasive, portable and less expensive than photoacoustic imaging, and relatively easy to use in combination with 3 imaging techniques (such as UOT, photoacoustic imaging, and single element ultrasonic pulse-echo imaging) in a single system. On the basis of initial successful imaging results, they concluded that this technique has the potential for extension to clinical sentinel lymph node imaging.

Journal of Biomedical Optics

THERAPY

^{131}I Effects on Salivary Glands

Ish-Shalom et al. from the Rambam Medical Center (Haifa, Israel) reported in the May issue of the *European Journal of Endocrinology* (2008;158:677–681) on a study examining the effects of ^{131}I treatment on salivary gland activity, saliva composition and oxidative profile, and related oral discomfort complaints after thyroidectomy for carcinoma of the thyroid gland. The study included 40 women who had undergone thyroidectomy, including 23 who were treated with ^{131}I and 17 who were not. Saliva was analyzed for antioxidant and biochemical composition and flow rate. The researchers found that although salivary flow rates in both groups were similar, the biochemical compositions

were not. In ^{131}I-treated patients, salivary superoxide dismutase enzyme, total protein, and albumin concentrations were significantly reduced by 40%, 25%, and 18%, respectively, as were all other salivary antioxidants. Oral discomfort was reported significantly more frequently among these patients. The authors concluded that these changes "leave the oral cavity less protected against oxidative stress."

European Journal of Endocrinology

Tracking Microdistribution in RIT

In an article in the May 1 issue of *Clinical Cancer Research* (2008;14: 2639–2646), Fidarova et al. from the University College London (UK) and the Gray Cancer Institute (Northwood, UK) reported on the use of a fluorescently labeled anti–carcinoembryonic antigen (CEA) antibody to investigate the kinetics and microdistribution of a potentially useful radioimmunotherapy antibody in a mouse model of colorectal cancer using high-resolution digital microscopy. Mice bearing LS174T liver orthotopic tumors were injected with the labeled antibody and at 10 min, 1 h, or 24 h later were injected with a perfusion marker and then killed. Frozen sections were analyzed with fluorescence microscopy and image analysis techniques. Results indicated that the fluorescently labeled antibody showed rapid, selective uptake in tumor deposits, with a strong negative correlation with tumor size at 10 min and 1 h, a correlation that was no longer significant at 24 h. The antibody demonstrated a tendency to localize more uniformly in tumors at the latest time point (24 h). The authors concluded that these data "suggest that radioimmunotherapy can be highly efficient in an adjuvant or minimal residual disease setting."

Clinical Cancer Research

^{213}Bi-Antibody Targeting of Breast Cancer Metastases

Song et al. from the Johns Hopkins University (Baltimore, MD) reported in the May 15 issue of *Cancer Research* (2008;68:3873–3880) on the potential efficacy of an antibody (7.16.4) against the rat variant of HER-2/neu, labeled with the α-emitter ^{213}Bi to treat widespread metastases in a transgenic mouse model of metastatic breast carcinoma. The model features wide dissemination of tumor cells leading to osteolytic bone lesions and liver metastases. The researchers determined a maximum tolerated dose and the kinetics of marrow suppression and subsequent recovery before cardiac ventricular injection of groups of mice with 120 or 90 μCi ^{213}Bi-7.16.4 or 120 μCi ^{213}Bi-rituximab (unreactive controls). Another group of mice was injected with unradiolabeled 7.16.4. The group receiving the highest radiolabeled dose of antibody experienced increased median survival time (41 d). The corresponding survival times were 36, 31, and 33 d for the 90 μCi ^{213}Bi-7.16.4, ^{213}Bi-rituximab, and unradiolabeled 7.16.4 groups and 28 d for a group of untreated controls. The authors concluded that ^{213}Bi-labeled monoclonal antibody targeting the HER-2/neu antigen was effective in treating early-stage HER-2/neu–expressing micrometastases and that these results suggest that additional gains in efficacy "may require higher specific activity constructs or target antigens that are more highly expressed on tumor cells."

Cancer Research