

*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. 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. 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.*

## Dopamine in Addiction and Obesity

In an article e-published ahead of print on July 18 in the *Philosophical Transactions of the Royal Society B: Biological Sciences*, Volkow and colleagues from the National Institute on Drug Abuse (Bethesda, MD) and the Brookhaven National Laboratory (Upton, NY) reported on the integration of PET imaging results into a common model for systems pathology in the role of dopamine in neuronal mechanisms of drug abuse/addiction and obesity. They described similarities in these conditions: “an enhanced value of 1 type of reinforcer (drugs and food, respectively) at the expense of other reinforcers, which is a consequence of conditioned learning and resetting of reward thresholds secondary to repeated stimulation by drugs (abuse/addiction) and by large quantities of palatable food (obesity) in vulnerable individuals (i.e., genetic factors).” In the proposed model,

during exposure to the reinforcer or to conditioned cues, the expected reward, as processed by memory circuits, overactivates the reward and motivation circuits while inhibiting the cognitive control circuit, resulting in an inability to inhibit the drive to consume the drug or food—despite attempts to do so. These neuronal circuits are modulated by dopamine and interact with 1 another so that disruption in 1 circuit can be buffered by another. These interactions and the role of dopamine can be documented and explored with PET. The authors concluded that the mechanisms outlined in this proposed common model highlight the need for multiple approaches in the treatment of addiction and obesity.

*Philosophical Transactions of the Royal Society B: Biological Sciences*

## PET and GABA(A) Receptor Binding in Epilepsy

Juhász et al. from the Children’s Hospital of Michigan, Harper University Hospital, Detroit Medical Center, and Wayne State University School of Medicine (all of Detroit) reported on July 14 ahead of print in *Epilepsia* on a PET study designed to determine the clinical significance and histopathologic correlates of cortical  $\gamma$ -aminobutyric acid(A) (GABA[A]) receptor abnormalities detected in and remote from human neocortical epileptic foci. The study included 20 patients (mean age, 9.9 y) with intractable partial epilepsy of neocortical origin and non-localizing MR imaging results. Patients underwent  $^{11}\text{C}$ -flumazenil ( $^{11}\text{C}$ -FMZ) PET imaging, and cortical areas with decreased tracer binding were correlated with intracranial electroencephalography (EEG) findings, clinical seizure variables, histology findings, and surgical outcomes. Focal decreases in cortical  $^{11}\text{C}$ -FMZ binding were detected in the lobe of seizure onset in 17 (85%) patients. Eleven patients (55%) had 17 remote cortical areas

with decreased tracer binding outside the lobe of seizure onset. Sixteen (81%) of these 17 remote cortical regions were covered by subdural EEG, and 13 of these were around cortex showing rapid seizure spread on intracranial EEG. Remote PET abnormalities were associated with high seizure frequency and, in all 6 cases in which histology was available at resection, showed gliosis. A higher number of unresected cortical regions with decreased tracer binding was associated with less positive surgical outcome. The authors concluded that “focal decreases of cortical GABA(A) receptor binding on PET may include cortical regions remote from the primary focus, particularly in patients with high seizure frequency, and that these regions are commonly involved in rapid seizure propagation.” They recommended a careful intracranial EEG evaluation of cortex with decreased GABA(A) receptor binding before resection, an approach that “may facilitate optimal surgical outcome in patients with intractable neocortical epilepsy.”

*Epilepsia*

## $^{18}\text{F}$ -MPPF PET and Anorexia Nervosa

In an article published on July 17 ahead of print in *Biological Psychiatry*, Galusca et al. from the Centre Hospitalier Universitaire–Saint Etienne (France) described the results of a study using  $^{18}\text{F}$ -4-(2-methoxyphenyl)-1-[2-(N-2-pyridinyl)-p-fluorobenzamido]ethylpiperazine ( $^{18}\text{F}$ -MPPF) to demonstrate serotonin (5-HT) pathway abnormalities in individuals with anorexia nervosa. The study included 24 individuals: 8 lean restrictive-type anorexia nervosa patients, 9 recovered patients, and 7 age-matched controls. All participants underwent  $^{18}\text{F}$ -MPPF PET imaging and an assessment of eating-related psychopathologic traits. Patients with anorexia nervosa were found to have increased tracer binding

in a selective area of the right cortex, including parts of the superior temporal gyrus, inferior frontal gyrus, parietal operculum, and temporoparietal junction when compared with control participants. Regional similarities of increased tracer binding were found in recovered participants. Patients with anorexia nervosa had increased scores on most of the psychopathologic traits associated with the disease, and elevated perfectionism and interpersonal distrust scores were noted in participants who had recovered. The authors concluded that persistent increased 5-HT<sub>1A</sub> receptor binding in the frontotemporal regions of patients who have recovered from anorexia nervosa, together with specific psychopathologic traits, supports the hypothesis of "an organic dysfunction of this area and corroborates with previous literature reports of anorexia nervosa cases induced by temporal lesions."

*Biological Psychiatry*

## PET and Dopamine Release Modulation

Egerton et al. from the Imperial College London (UK) reported on July 3 ahead of print in *Psychopharmacology (Berlin)* on a small animal study designed to demonstrate the feasibility of monitoring serotonin 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptor-mediated modulation of dopamine systems using PET. The study was performed in rats that were injected with either a combined 5-HT<sub>2A/2C</sub> antagonist or a more selective 5-HT<sub>2C</sub> antagonist 30 min before administration of <sup>11</sup>C-raclopride. Animals underwent PET scanning for 60 min in a quad-high-density avalanche chamber. Using the same technique, modulation of amphetamine-induced decreases in <sup>11</sup>C-raclopride binding by 5-HT<sub>2A</sub> antagonism was also determined. The authors found that 5-HT<sub>2C</sub> antagonism markedly reduced striatal <sup>11</sup>C-raclopride binding, whereas amphetamine-induced reductions in striatal <sup>11</sup>C-raclopride binding were attenuated by 5-HT<sub>2A</sub> antagonist administration. These results were consistent with serologic findings in other studies. The authors concluded that

these results support the use of PET to assess serotonin receptor-mediated modulation of dopamine systems, especially in monitoring the effectiveness of new dopamine modulators in attenuating stimulated dopamine release.

*Psychopharmacology (Berlin)*

## SLN Technique and Endometriosis

In an article e-published on July 16 ahead of print in *Human Reproduction*, Mechsner et al. from the Charité-Universitätsmedizin Berlin (Germany) reported on a pilot study to investigate the occurrence of endometriosis in pelvic sentinel lymph nodes (SLNs) in patients with deep infiltrating endometriosis. The study included 14 patients who underwent primary surgery for symptomatic deep infiltrating endometriosis. Surgery included combined vaginal laparoscopic-assisted resection of the rectovaginal septum and dye injection and removal of SLNs from the iliac region. Immunohistochemical analyses of estrogen and progesterone receptors, CD10, and cytokeratin were performed on the SLNs. SLNs were detected in 12 of the 14 patients. Typical endometriotic lesions were detected in the lymph nodes of 3 patients, and 10 of 12 SLNs were found on immunohistochemical analysis to have disseminated estrogen- and/or progesterone-positive cells. The authors concluded that the identification of endometriotic lesions and endometriotic-like cells in pelvic SLNs of patients with deep infiltrating endometriosis suggests the potential for lymphatic spread of the disease as well as the possibility of developing protocols for identifying such spread with advanced imaging techniques.

*Human Reproduction*

## Histopathology of <sup>131</sup>I-Refractory PET+ Thyroid Ca

In the July 1 issue of *Cancer* (2008;113:48–56), Rivera et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) reported on studies designed to characterize the histopathology of <sup>18</sup>F-FDG PET-

positive radioactive iodine-refractory thyroid carcinomas. The study included 70 patients for whom imaging results and biopsied metastatic tissue corresponding to PET-positive lesions were available along with clinical outcomes. All metastatic deposits and available primary tumors ( $n = 43$ ) were examined with microscopy for histopathology and classified as poorly differentiated thyroid carcinomas (PDTC) (on the basis of mitotic activity  $\geq 5$  mitoses/10 high-power fields and/or tumor necrosis), tall cell variant (TCV) of papillary thyroid carcinoma, well-differentiated papillary thyroid carcinoma (WDPTC), Hurthle cell carcinoma (HCC), or anaplastic carcinoma. Disease-specific survival statistics were the designated endpoints. Histologic analysis characterized the metastases/recurrence types as PDTC in 33 patients (47.1%), TCV in 14 patients (20%), WDPTC in 16 patients (22.9%), HCC in 6 patients (8.6%), and anaplastic carcinoma in 1 patient (1.4%). In 16 patients (37%), the histology in the primary tumor differed from that in the metastases, with the majority of these ( $n = 10$ ; 63%) transformed to a higher grade. Of patients in this group with primary tumors classified as PTC, 70% progressed to more aggressive histotypes in the metastases. Tumor necrosis and extensive extrathyroid extension in the primary tumor were independent predictors of poorer survival in this group of patients. The authors concluded that despite the fact that the majority of metastases in patients with radioiodine-refractory PET-positive thyroid cancer are of a histologically aggressive subtype, well-differentiated radioiodine-refractory metastatic disease is observable. They noted that poorly differentiated disease may be underrecognized in many cases, particularly when defined by architectural and nuclear features alone. Tumor necrosis was found to be a strong predictor of aggressive growth, even in this group of clinically aggressive tumors. They added that the significant histologic plasticity between primary tumors and metastases may reflect the genetic instability of these tumors.

*Cancer*

## PET and Anaplastic Thyroid Carcinoma

Bogsrød et al. from the Mayo Clinic (Rochester, MN) and the Radiumhospitalet (Oslo, Norway) reported in the July issue of *Thyroid* (2008;18:713–719) on the use of <sup>18</sup>F-FDG PET in the clinical management of patients with anaplastic thyroid carcinoma. The study included 16 patients with the disease. PET results were correlated with the results of conventional and other imaging, as available, as well as histology, clinical follow-up, and changes in management resulting from PET findings. PET was true-positive, with intense uptake for all primary tumors, in all 9 patients with lymph node metastases, in 5 of 8 patients with lung metastases, and in 2 patients with other distant metastases. Clinical management was changed on the basis of PET in 8 (50%) of patients. In 8 of the 16 patients, the medical records showed a direct effect of PET findings on clinical management. The authors concluded that “PET may improve disease detection and have an impact on the management of patients with anaplastic thyroid carcinoma relative to other imaging modalities.”

*Thyroid*

## Gene Expression Imaging and Prostate Cancer

In an article e-published on July 11 ahead of print in *Nature Medicine*, Burton et al. from the University of California at Los Angeles reported on the use of recombinant human adenoviral vectors to detect nodal metastases in a human prostate cancer model, achieved by the prostate-restricted expression of optical and PET imaging reporter genes by the viral vector coupled with the innate lymphotropic properties of adenovirus. Their results indicated that peritumoral administration of these vectors results in direct detection of reporter gene expression in metastatic lesions within sentinel lymph nodes. Direct PET visualization using this approach would eliminate the need for invasive lymphadenectomy and provide the accurate assessment of nodal involvement that is essential to

planning treatment. The authors concluded that: “These findings may lead to more effective diagnostic and therapeutic strategies for individuals with advanced-stage prostate cancer.”

*Nature Medicine*

## PET and Proliferation Monitoring

Shields et al. from Wayne State University (Detroit, MI) reported in the July 15 issue of *Clinical Cancer Research* (2008;14:4463–4468) on methods to assess the reproducibility of measurement of fluorothymidine (FLT) retention in patients with non-small cell lung cancer (NSCLC), as part of a larger effort to apply <sup>18</sup>F-FLT PET in monitoring antineoplastic therapy. The study included 9 patients with NSCLC who had not yet been treated or who had progressed after previous therapy. Each patient underwent <sup>18</sup>F-FLT PET imaging twice within a period of 2–7 d, and differences between the scans were assessed, as well as activity in the blood, fraction of unmetabolized FLT, mean SUV, and kinetic variable of FLT flux. The mean SUV obtained at 30–60 min after tracer injection had a mean error (difference) of 3.6% between the 2 scans. The 2 scans were highly correlated in each patient. Shorter imaging times (at 25–30 or 55–60 min after injection) also resulted in small error rates (8.4% and 5.7%, respectively). Both compartmental and graphical kinetic analyses were reproducible. The authors concluded that <sup>18</sup>F-FLT PET imaging of patients with NSCLC was “quite reproducible” and that the worst-case mean SUV error noted was 21% using a very short imaging time.

*Clinical Cancer Research*

## Laparoscopic Sentinel Basin Dissection in Gastric Cancer

In an article e-published on July 21 ahead of print in the *Journal of Surgical Oncology*, Lee et al. from the National Cancer Center (Goyang, Korea), reported on the feasibility of laparoscopic sentinel basin dissection as an alternative to sentinel node biopsy for

limited resection in early gastric cancer. The study included 21 patients with diagnosed CT1N0 adenocarcinoma. Using an intraoperative endoscope, <sup>99m</sup>Tc-human serum albumin and indocyanine green were injected into the submucosal layer around tumors. Stained and/or radioactive lymphatic basins were detected and defined as sentinel basins. After laparoscopic sentinel basin dissection, patients underwent laparoscopy-assisted gastrectomy and lymphadenectomy. Both sentinel and nonsentinel excised nodes underwent pathologic evaluation. The mean time for the laparoscopic sentinel basin dissection was 15.2 min, and the detection rate for sentinel basins was 95.2%. One patient has 6, 4 patients had 3, and 10 patients had 2 sentinel basins. Lymph node metastases were identified by sentinel basin dissection in 2 patients. The authors concluded that these findings suggest that laparoscopic sentinel basin dissection is technically feasible and may have better sensitivity than sentinel node biopsy.

*Journal of Surgical Oncology*

## THERAPY

### Theragnostic Hypoxia-Based Dose Painting

Flynn et al. from the University of Wisconsin School of Medicine and Public Health (Madison) reported in the August 7 issue of *Physics in Medicine and Biology* (2008;53:4153–4167) on the results of studies to assess the abilities of intensity-modulated x-ray therapy (IMXT) and intensity-modulated proton therapy (IMPT) to deliver boosts based on theragnostic imaging. Theragnostic imaging designates the application of functional or molecular imaging data, in this case derived from <sup>61</sup>Cu-ATSM PET imaging, for determining individualized radiation treatment dose distributions. Dose prescriptions for a hypoxic region in a patient with head and neck squamous cell cancer were designed to (1) uniformly boost the region or (2) redistribute the dose based on the results of

<sup>61</sup>Cu-ATSM PET imaging. Using these data, treatment plans were created for 4 delivery methods: IMXT with step-and-shoot and with helical tomotherapy and IMPT delivered with spot scanning and distal gradient tracking. The researchers found that IMXT and IMPT delivered comparable dose distributions within the boost region for both uniform and redistributed therapeutic boosts. The normal tissue integral dose was reduced by a factor of up to 3 for IMPT compared with IMXT. For all delivery methods, the mean dose to the nearby organs at risk differed no more than 2 Gy between redistributed and uniform boosts. Plans with the distal gradient tracking method were comparable with those of the spot scanning method.

#### *Physics in Medicine and Biology*

### Rosiglitazone in <sup>131</sup>I Treatment

Tepmongkol et al. from Chulalongkorn University (Bangkok, Thailand) reported in the July issue of *Thyroid* (2008;18:697–704) on a study designed to determine whether treatment with rosiglitazone, a peroxisome proliferator-activated receptor- $\gamma$  agonist is associated with an increase in radioactive iodine uptake in thyroid cancer patients with high serum thyroglobulin and negative total-body scans. The study included 23 patients with epithelial cell thyroid carcinoma and previously negative posttherapeutic <sup>131</sup>I total body scans who were administered rosiglitazone daily for 6 wk. All patients then received a second diagnostic whole-body scan, followed by an ablative dose of <sup>131</sup>I. All subsequently underwent repeat posttherapy total-body scanning. In addition, biopsied thyroid cancer tissues were analyzed with immunohistochemical staining of peroxisome proliferator-activated receptor- $\gamma$ . Strong staining was found in the thyroid biopsies of 7 patients, weakly positive staining was seen in the biopsies of 9 patients, and staining was negative in the remaining 7 patients. Of the 7 patients with strong staining, 5 had either positive posttherapy total body scanning or positive results at both the

postmedication and posttherapy scanning. Only 1 of 9 patients with weak staining had positive postmedication and posttherapy scanning. The authors concluded that rosiglitazone “can increase radioiodine uptake in thyroid tissue in the majority of patients with epithelial cell thyroid carcinoma whose previous posttherapeutic <sup>131</sup>I scans were negative provided they have high intensity and extent of peroxisome proliferator-activated receptor- $\gamma$  expression in thyroid tissue.”

#### *Thyroid*

### MOLECULAR IMAGING

#### Bifunctional Ligands for RIT and MR Imaging

Chong et al. from the Illinois Institute of Technology (Chicago) reported on June 20 ahead of print in *Bioconjugate Chemistry* on the preparation and initial evaluation of novel bifunctional ligands with potential for bimodal applications in radioimmuno-therapy and MR imaging. The ligands, C-NETA and C-NE3TA, each have both acyclic and macrocyclic moieties. The authors described the synthesis of the ligands, as well as preparation of gadolinium complexes for use in contrast enhancement in targeted MR imaging. Radiolabeled versions of the ligands were created with <sup>177</sup>Lu, <sup>90</sup>Y, <sup>203</sup>Pb, <sup>205/6</sup>Bi, or <sup>153</sup>Gd, and studies in human serum assessed in vitro stability. All were stable in serum, except for the <sup>203</sup>Pb-labeled complexes. C-NETA and C-NE3TA complexes radiolabeled with <sup>177</sup>Lu, <sup>90</sup>Y, or <sup>153</sup>Gd were further evaluated for in vivo stability in athymic mice, with excellent in vivo biodistribution profiles resulting. Looking ahead to future studies, the authors reported on modification of the ligands for conjugation to the monoclonal antibody trastuzumab.

#### *Bioconjugate Chemistry*

#### Imaging STAT3 Signaling Pathways

In an article e-published on June 24 ahead of print in *Stem Cells Development*, Xie et al. from Stanford University

(CA) reported on their work in developing methods for imaging signal transducers and activators of transcription 3 (STAT3) signaling pathways during mouse embryonic stem cell differentiation. STAT3 mediates the expression of a variety of genes in response to cell stimuli, and in mouse embryonic stem cells plays a role in cell growth and differentiation. The authors described the process of building a lentiviral construct with a STAT3 binding sequence (enhancer) and promoter driving renilla luciferase and monomeric red fluorescence protein, followed by a constitutive cytomegalovirus promoter driving green fluorescence protein as a selection marker. After in vitro confirmation of specificity, the authors isolated a mouse embryonic cell line stably transduced with the STAT3 reporter construct. This cell line was selected as a developmental model for the STAT3 functional study in mice, using serial noninvasive bioluminescence imaging. The authors found that the onset of embryoid body formation involved inhibition of STAT3 activity and that, during differentiation, STAT3 activity steadily increased from d 5 to 14. They concluded that this first study monitoring real-time STAT3 activity during embryonic stem cell differentiation provided evidence that this “genetically modified line can be used to study the biological role of STAT3 during embryonic stem cell differentiation into different derivatives.”

#### *Stem Cells Development*

#### Subcellular Localization of Elements and Molecules

Wittig et al. from University Hospital Essen (Germany) reported in the July issue of *Molecular Cancer Therapeutics* (2008;7:1763–1771) on a study describing laser postionization secondary neutral mass spectrometry as a powerful tool with promise for subcellular elemental and molecular imaging in the development of targeted drugs. Using drugs currently employed in boron neutron capture therapy as an experimental example, the authors were able to follow and distinguish specific substances as the therapeutic agent was

transported into the cytoplasm and into the nucleus. They concluded that this successful example shows that laser postionization secondary neutral mass spectrometry can be combined with prompt  $\gamma$ -ray analysis in a screening technique in the early and crucial stages of new drug development or to improve the use of existing drugs.

*Molecular Cancer Therapeutics*

## Molecular Imaging of Intestinal Inflammation

Brewer et al. from the University of California at Los Angeles reported

on July 16 ahead of print in *Gastroenterology* on a study examining the biologic basis of tracer uptake in  $^{18}\text{F}$ -FDG PET molecular imaging of murine intestinal inflammation. The authors used CT isocontour analysis to standardize quantitation of uptake in longitudinal assessment of immune colitis. Intestinal FDG uptake was compared with histologic scores and with glucose transporter 1 levels in mucosal immune cells. Intestinal tracer uptake was found to be quantitatively correlated with disease activity in mild and severe murine colitis

models at all time points examined and was sufficiently sensitive to identify preclinical inflammation. When intestinal inflammation was increased by treatment with piroxicam and decreased with anti-TL1A treatment,  $^{18}\text{F}$ -FDG uptake increased and decreased correspondingly. This and other specific findings about cellular response provided a clarification of the cellular basis of  $^{18}\text{F}$ -FDG signal in intestinal inflammation, as well as a novel method for standardized quantitation of immune colitis.

*Gastroenterology*

(Continued from page 46N)

- Community Bulletin Board: A repository in which questions about PET and PET/CT can be posted for review and answered by the PET CoE community. The goal of the bulletin board is to provide communication among individuals in the PET community regarding specific PET- and PET/CT-related questions and/or needs.
- E-Library (Resource Material): A central library for PET- and PET/CT-related articles covering cost effectiveness, procedures, and references. The regularly updated library will be posted on the PET CoE Web site as well as distributed on CD to PET CoE members once each year.
- Cross-Sectional Imaging Atlas: An online PET/CT imaging atlas to help physicians accurately describe and interpret studies. The first datasets will be cross-

sectional atlases on head and neck anatomy; lymph nodes in the chest, abdomen, and pelvis; and segmental liver anatomy. They will also contain important PET and CT landmarks for reporting. The datasets will be expanded to include other anatomic regions and disease-specific examples for physicians, technologists, and students.

The work of the PET CoE is made possible by the support of its members. Scientists, physicians, technologists, and health care professionals are encouraged to join the PET CoE and become involved in the many ongoing projects to advance molecular imaging and therapy.

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