

PCORI released its draft priorities in: (1) assessment of prevention, diagnosis, and treatment options; (2) improving health care systems; (3) communication and dissemination; (4) addressing disparities; and (5) accelerating patient-centered and methodologic research. Comments from the public and medical professionals were solicited.

In its comment letter, SNM encouraged PCORI to further engage smaller medical specialty societies that may lack resources to develop competitive proposals for comparative effectiveness research funding, but whose members are uniquely qualified to design and conduct such studies. In addition, SNM recommended that PCORI use changes in treatment decisions as one type of endpoint in studies and that it incorporate separate methodologies for therapeutic and diagnostics into its research designs and those conducted by other groups.

SNM

### International Workshop on Interim PET

An article appearing on March 20 ahead of print in *Leukemia and Lymphoma* provided an overview of and report on consensus findings from the Third International Workshop on Interim PET in Lymphoma, held in Men-

ton, France, September 26 and 27, 2011. The 2-d meeting was attended by 193 hemato-oncologists and nuclear medicine specialists from 23 countries. In the summary article, Meignan et al. reported on final results of international validation studies of the Deauville criteria and  $\Delta\text{SUV}_{\text{max}}$  analyses in Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). These studies confirmed the prognostic value of interim PET in 261 patients with advanced HL after 2 cycles of adreomycin, bleomycin, vinblastine, and dacarazine when reported with a 5-point scale and in 120 patients with diffuse large B-cell lymphoma after 2 cycles of a rituximab-based immunochemotherapy regimen when using the  $\Delta\text{SUV}$  analysis. At the meeting, a preliminary consensus on interim PET was established on assessment of marrow response, refining of grade 4 and 5 of the 5-point scale, the need to focus on interim PET results for different types of NHL, and methods to compute and factors affecting measurement of SUV change. The next meeting, scheduled for October 2012, will include aspects of PET in lymphoma beyond interim PET findings. The 2011 presentations are available on <http://eitti.free.fr>.

*Leukemia and Lymphoma*

### NRC Proposed Fee Schedule

On March 15, the Nuclear Regulatory Commission (NRC) released the proposed FY 2012 fee schedule, detailing licensing, inspection, and annual fees charged to its applicants and licensees. Included is an estimated fee-relief budget of \$91.1 million, which NRC proposes to use to decrease all licensees' annual fees based on their percentage share of the fee-recoverable budget authority. The fee relief budget is higher than FY 2011 because of decreased international activities and educational budgets. The NRC has included medical isotope production under fee relief categories to capture program activity for medical isotope production facilities for regulatory basis development. The FY 2012 NRC medical isotope budget of approximately \$3 million is not attributable to existing NRC licensees. The funding for this activity along with other activities not attributable to existing NRC licensees will be offset by the agency's 10% appropriation. The entire fee schedule announcement is available at: [www.gpo.gov/fdsys/pkg/FR-2012-03-15/html/2012-6153.htm](http://www.gpo.gov/fdsys/pkg/FR-2012-03-15/html/2012-6153.htm).

*Nuclear Regulatory Commission*

## FROM THE LITERATURE

*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 also added a small section on noteworthy reviews of the literature.*

### 4D PET/CT + MR in Radiotherapy

Bundschuh et al. from the Technischen Universität München (Germany) reported on March 24 ahead of print in *Strahlentherapie und Onkologie* on a study of the utility of 4D  $^{18}\text{F}$ -FDG PET/CT in combination with respiratory gated MR imaging for target vol-

ume definition in stereotactic radiation of liver metastases. The study included 18 patients scheduled for radiation therapy who underwent respiration-gated PET/CT and MR imaging. Resulting data were coregistered, and the quality of coregistration was rated on a 1 to 5 (excellent to poor) scale, including both gated and nongated PET results. Three imaging experts delineated gross tumor volumes (GTVs) for each modality, and interobserver variability was calculated for the entire group of patients and for subgroups with and without previous

treatment for liver metastases. MR and nongated PET coregistration was rated at an average of 3.3, and gated PET improved coregistration with MR to a 2.1 average. With CT, the average GTV was 51.5 mL; with MR and PET these averages were 51.8 and 48.1 mL, respectively. Differences between GTVs were more pronounced in patients with previous treatment, with more interobserver variability in MR (47.9% over all; 84.1% and 26.2% with and without previous treatment, respectively). PET GTV assessments showed the least variability, at 21%, independent of previous treatment. The authors concluded that  $^{18}\text{F}$ -FDG PET can “distinguish vital tumor tissue and scar tissue, and therefore alters the GTV especially in patients with previous local treatment,” with the added benefit of reducing interobserver variability significantly compared with MR. They noted that respiratory-gated PET appears to be necessary for good coregistration of PET and MR images in this setting.

*Strahlentherapie und Onkologie*

### **PET/CT and Pancreatic Cancer Prognosis**

In an article in the March 19 issue of *Radiation Oncology* (2012;19:37), Parlak et al. from Baskent University Adana (Turkey) reported on a study designed to determine whether gross tumor volumes (GTVs), as determined by fusion of  $^{18}\text{F}$ -FDG PET and contrast-enhanced CT images, could predict outcomes in patients with locally advanced pancreatic cancer treated with definitive concurrent radiation therapy. The study included 30 such patients who underwent PET/CT as part of treatment planning. Assessment of tumor volumes in these studies provided data for dividing patients into 2 groups: those with GTVs greater or smaller than a cutoff value of 91.1  $\text{cm}^3$  as determined by receiver operating characteristic analysis (for an overall median GTV of 100.0  $\text{cm}^3$ ). Patients then received 50.4 Gy (1.8 Gy/28 fractions) of radiotherapy concurrent with continuously infused 5-fluorouracil, followed by 4–6 courses

of maintenance gemcitabine. End-points assessed were overall survival, local–regional progression-free survival, and progression-free survival. The study is ongoing, but at a median follow-up of 11.2 mo, median overall survival, local–regional progression-free survival, and progression-free survival for all participants were 10.3, 7.8, and 5.7 mo, respectively. For the group with GTVs smaller than the cutoff, these figures were 16.3, 11.0, and 9.0 mo, respectively. For those with GTVs larger than the cutoff, these figures were 9.5, 6.0, and 4.8 mo, respectively. The authors concluded that the superior results for those with lower GTVs on PET “suggests a potential for FDG PET-CT–defined GTV size in predicting outcomes of locally advanced pancreatic cancer patients” treated with definitive chemoradiotherapy.

*Radiation Oncology*

### **PET/CT and Hilar Node Mets**

Carrillo et al. from The Ohio State University Medical Center (Columbus) reported on March 17 ahead of print in the *Annals of Thoracic Surgery* on a retrospective study assessing the ability of PET/CT to identify hilar metastases in patients with resected non–small cell lung cancer (NSCLC). The authors hoped the results might provide support for an imaging evaluation method to determine the benefits of neoadjuvant therapy in patients with stage II disease. The study included the records of 119 NSCLC patients who underwent fusion PET/CT within 30 d after resection (average number of lymph nodes resected, 2.98; range, 1–12 nodes). Sensitivity, specificity, and positive and negative predictive values for PET/CT in detecting hilar nodal metastases were calculated for a range of maximum standardized uptake values ( $\text{SUV}_{\text{max}}$ ). In addition, hilar nodes from patients with false-positive PET/CT scans were investigated for the presence of histoplasmosis, and the impact of hilar node size  $>1$  cm on calculated values was assessed. Decreased sensitivity and increased specificity

were noted with higher  $\text{SUV}_{\text{max}}$  cutoff values. At a standard  $\text{SUV}_{\text{max}}$  of 2.5, sensitivity and specificity of PET/CT were only 48.5% and 80.2%, respectively. The addition of size of hilar node as assessed by CT led to a small improvement in sensitivity at all cutoff values. The authors concluded that “fusion PET/CT lacks sensitivity and specificity in identifying hilar nodal metastasis in patients with resected NSCLC,” but that additional studies are needed to compare PET/CT and alternative sampling techniques.

*Annals of Thoracic Surgery*

### **PET/CT and Endometrial Cancer Prognosis**

In a study e-published on March 19 ahead of print in *Gynecologic Oncology*, Lin et al. from the Chang Gung University College of Medicine (Taoyuan, Taiwan) evaluated the ability of pretreatment  $^{18}\text{F}$ -FDG PET/CT to predict outcomes in women with primary stage M1 endometrial carcinoma. The retrospective study included 15 patients, and factors assessed were standardized uptake value (SUV), total body metabolic tumor volume, and total lesion glycolysis on PET, as well as histologic type and grade, T stage, N stage, age, Eastern Cooperative Oncology Group performance status, hormone receptor status, metastatic patterns, number of involved metastatic patterns, and serum CA125 levels. Median survival for study participants was 17 mo. Total body metabolic tumor volumes and lesion glycolysis were found to be highly correlated with and significant prognosticators of overall survival. Four patients with total body metabolic tumor volume  $>450\text{mL}$  (total body tumor lesion glycolysis  $>2,700$  g) had a median survival of 2 mo, compared with a median survival of 47 mo for the other 11 participants. The authors concluded that PET parameters can provide significant prognostic information in patients with stage IVB endometrial carcinoma and that establishing a cutoff point that identifies those with poor prognoses allows more targeted consideration of aggressive therapy in those

who are likely to have more prolonged survival.

*Gynecologic Oncology*

## Nanoprobes for SLNs

Huang et al. from the National Institute of Biomedical Imaging and Bioengineering (Bethesda, MD) reported on March 15 ahead of print in *Biomaterials* on a study describing the development and use of mesoporous silica-based nanoprobes for long-term triple-modal imaging of tumor-draining sentinel lymph nodes. The nanoprobes integrate multiple functional moieties to allow near-infrared optical, MR, and PET imaging. The authors described the construction, labeling ( $^{64}\text{Cu}$  for PET), in vitro characterization, and initial in vivo applications. In in vivo studies, serial multimodal imaging was subsequently achieved to visualize tumor-draining sentinel lymph nodes up to 3 wk in a 4T1 tumor metastatic model, with clear differences between metastatic and contralateral nodes observed, including differences in uptake rate, amounts of particles, and contrast. The authors concluded that “These findings provide very helpful guidance for the design of robust multifunctional nanomaterials in sentinel lymph node mapping and tumor metastasis diagnosis.”

*Biomaterials*

## $^{99\text{m}}\text{Tc}$ -Labeled Doxorubicin Imaging

In an article e-published on March 20 ahead of print in *Cancer Biotherapy and Radiopharmaceuticals*, Kumar et al. from the Postgraduate Institute of Medical Education and Research (Chandigarh, India) reported on a study designed to radiolabel doxorubicin with  $^{99\text{m}}\text{Tc}$  as a scintigraphic marker of high DNA turnover/intercalation in malignant cells. The authors described development and labeling techniques, initial assessment of blood kinetics and biodistribution, and acquisition of scintigraphic images at 1.5, 3, and 4 h after injection in tumor-bearing mice. The radiolabeling efficiency of the  $^{99\text{m}}\text{Tc}$ -doxorubicin was estimated at >95%, with protein-binding efficiency >88% and in vitro stability

up to 24 h. Tracer clearance was by both renal and hepatic pathways. Data analyses indicated that a focal concentration of the radiotracer was seen in tumor at 1.5 h and in 3- and 4-h images. The authors concluded that this scintigraphic approach “could be a powerful tool for cancer detection at early stage.”

*Cancer Biotherapy and Radiopharmaceuticals*

## Interim PET in Hodgkin Lymphoma

Kostakoglu, from Mount Sinai School of Medicine (New York, NY), and colleagues reported on March 15 ahead of print in *Leukemia & Lymphoma* on a study designed to assess the value of combined PET and CT criteria in interim response prediction in stage I/II nonbulky Hodgkin lymphoma, to determine the extent to which these findings validate International Harmonization Project (IHP) and Deauville PET response criteria, and to compare results with diagnostic CT-based (dCT) lesion size changes. The study included 88 patients in a clinical trial for stage I and II nonbulky Hodgkin lymphoma. All patients underwent both PET and dCT at baseline and after 2 chemotherapy cycles. IHP and Deauville criteria, as well as percentage decreases in the sum of the products of lesion perpendicular diameters after 2 chemotherapy cycles, were correlated with progression-free survival. At a median follow-up of 3.3 y, 23.9% of patients relapsed/progressed and 77% were classified as progression-free survivors. IHP criteria predicted 2-y progression-free survival at 88% and 54% for those negative and positive, respectively, on PET after 2 therapy cycles. Figures were similar for the Deauville criteria. Although interim PET predicted progression-free survival better than lesion size as assessed by CT alone, in the group with positive interim PET findings a negative dCT was associated with a 27%–35% increase in progression-free survival. The authors concluded that although IHP- and Deauville criteria-based interpretation

of interim PET was strongly associated with 2-y progression-free survival, the combined analyses of interim PET with dCT, suggests a better predictive value for survival compared with either test alone.

*Leukemia & Lymphoma*

## PET/CT and MR Lymphography

In an article e-published on March 13 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics*, Fortuin et al. from the Radboud University Nijmegen Medical Center (The Netherlands) reported on the utility of  $^{11}\text{C}$ -choline PET/CT and ferumoxtran-10-enhanced MR lymphography in treatment of prostate cancer patients with lymph node metastases. The study included 29 patients who underwent both imaging procedures for lymph node evaluation. Factors evaluated were number, size, and location (within or outside standard clinical volumes for elective pelvic irradiation) of lymph node metastases. MR lymphography visualized 738 lymph nodes, of which 151 were positive (23 patients). PET/CT visualized 132 lymph nodes, of which 34 were positive (13 patients). Suspicious lymph nodes detected on MR lymphography had a mean diameter of 4.9 mm, compared with 8.4 mm on PET/CT. Suspicious lymph nodes were found outside the clinical target volumes in 14 (61%) of 23 patients by the MR technique and in 4 (31%) of 13 patients with PET/CT. The authors concluded that both  $^{11}\text{C}$ -choline PET/CT and ferumoxtran-10-enhanced MR lymphography can detect lymph nodes suspicious for metastasis, “irrespective of the existing size and shape criteria for CT and conventional MR imaging,” and that because of their respective abilities to identify suspicious lesions outside the conventional target volume “these techniques could help to individualize treatment selection and enable image-guided radiotherapy.”

*International Journal of Radiation Oncology, Biology, Physics*

## PET after Radiotherapy in NSCLC

Bollineni et al. from the University Medical Center Groningen (The Netherlands) reported on March 13 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics* on a study designed to investigate the predictive value of  $^{18}\text{F}$ -FDG uptake on PET at 12 wk after stereotactic ablative radiotherapy for stage I non-small cell lung cancer (NSCLC). The retrospective study included data on 132 medically inoperable patients with stage I NSCLC or  $^{18}\text{F}$ -FDG-positive primary lung tumors. All patients underwent PET imaging 12 wk after completion of stereotactic ablative radiotherapy and underwent subsequent serial follow-up CT imaging. Factors correlated with standardized uptake values (SUVs) on PET after therapy included local control, mediastinal failure, distant failure, overall survival, and disease-specific survival over a median follow-up of 17 mo (range, 3–40 mo). Follow-up showed 6 local failures, 15 mediastinal failures, 15 distant failures, 13 disease-related deaths, and 16 deaths from intercurrent diseases. Glucose-corrected median  $\text{SUV}_{\text{max}}$  was 3.0 (range, 0.55–14.50). Two-year local control was 80% for  $\text{SUV}_{\text{max}} > 5.0$  and 97.7% for  $\text{SUV}_{\text{max}} < 5.0$ . Two-year disease-specific survival rates were 74% and 91%, respectively, for high and low  $\text{SUV}_{\text{max}}$  values using the 5.0 cutoff. Two-year overall survival rates were 62% and 81%, respectively, for the high- and low-uptake categories. The authors concluded that “a single FDG PET scan at 12 wk could be used to tailor further follow-up according to the risk of failure, especially in patients potentially eligible for salvage surgery.”

*International Journal of Radiation Oncology, Biology, Physics*

## PET and SPECT in ADHD Treatment

In an article published in the March 1 issue of the *American Journal of Psychiatry* (2012;169:264–272), Fusar-Poli, from King’s College (Lon-

don, UK), and colleagues reported on a metaanalysis of SPECT and PET studies of striatal dopamine transporter alterations in individuals undergoing psychostimulant treatment for attention deficit hyperactivity disorder (ADHD). The analysis included 9 studies in a total of 169 ADHD patients and 173 age-, sex-, and IQ-matched healthy volunteers. The authors found that striatal dopamine transporter density averaged 14% higher in the ADHD group, but confounding differences across studies were large and statistically significant. Additional analyses indicated that dopamine transporter density was higher in patients with previous medication exposure and lower in those patients who had never been medicated for ADHD. These findings were not affected by participant age, comorbidity, or sex or by imaging technique. The authors concluded that “striatal dopamine transporter density in ADHD appears to depend on previous psychostimulant exposure.”

*American Journal of Psychiatry*

## PET and Nodal Breast CA Spread

Pritchard and a consortium of researchers from the Ontario Clinical Oncology Group (Canada) reported on March 5 ahead of print in the *Journal of Clinical Oncology* on a prospective study of  $^{18}\text{F}$ -FDG PET in assessment of regional nodal spread of breast cancer. The study included 325 women who underwent PET imaging within 3 mo of diagnosis with operable breast cancer, followed by axillary lymph node assessment (either sentinel lymph node biopsy [SLNB] alone if sentinel lymph nodes were negative, SLNB with axillary lymph node dissection if SLNB or PET were positive, or axillary lymph node dissection alone if sentinel lymph nodes were not identified). Sentinel nodes were found in 312 (96%) study participants and were positive for tumor in 90 (29%) of these 312. Axillary lymph node dissection was positive in 7 additional women. With axillary lymph node assessment as a gold standard, PET sensitivity, specificity, and

positive and negative predictive values for PET were 23.7%, 99.6%, 95.8%, and 75.4%, respectively. Additional analyses indicated that tumor size was predictive for prevalence of tumor in the axilla and for PET sensitivity. PET indicated distant metastases in 13 patients, with 3 confirmed as metastatic disease and 10 as false-positives. The authors concluded that “PET is not sufficiently sensitive to detect positive axillary lymph nodes, nor is it sufficiently specific to appropriately identify distant metastases,” but the “very high positive predictive value (96%) suggests that PET when positive is indicative of disease in axillary nodes, which may influence surgical care.”

*Journal of Clinical Oncology*

## HyperSPECT

In an article in the March 7 issue of *Physics in Medicine and Biology* (2012;57:1617–1629), Tibbelin et al. from the AlbaNova University Center (Stockholm, Sweden) reported on HyperSPECT, a high-resolution small-animal system based not on pinhole collimation but on in-line x-ray optics. They described the development and rationale for the system, which has x-ray lenses optimized for 27 keV for low-energy imaging with  $^{125}\text{I}$ . The authors detailed 3D simulation studies, including imaging of capillary phantoms. Sensitivity was found to be uniformly 0.37% throughout the 1-cm diameter spherical field of view, and rod sizes of around 100  $\mu\text{m}$  diameter were distinguishable in phantom images. The authors concluded that these results indicate “an increase in resolution by a factor of 5 during a simultaneous increase in sensitivity by a factor of 2 compared to the current state-of-the-art small-animal SPECT systems.”

*Physics in Medicine and Biology*

## REVIEWS

Review articles offer an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent liter-

ature. The Newslines editor recommends several reviews accessioned into the PubMed database in late February and March.

In an article e-published on March 19 in *Clinical Infectious Diseases*, Haroon et al. from University College London Hospitals NHS Trust (UK) described the “Role of fluorine 18 fluorodeoxyglucose PET/CT in focal and generalized infectious and inflammatory disorders.” On March 21 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism*, Jones and Rabiner, from the PET Research

Advisory Company (Cheshire, UK), outlined “The development, past achievements, and future directions of brain PET.” Rockall et al. from St. Bartholomew’s Hospital (London, UK) reported in the March 5 issue of *Cancer Imaging* (2012;12:49–65) on “The role of FDG PET/CT in gynaecological cancers.” In an article e-published on March 26 ahead of print in *Abdominal Imaging*, Rufini et al. from the Università Cattolica del Sacro Cuore (Rome, Italy) described the “Role of PET/CT in the functional imaging of endocrine pancreatic tumors.”

Timmers et al. from Radboud University Nijmegen Medical Centre (The Netherlands) provided an overview of “Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma” on March 7 ahead of print in *Hormone and Metabolic Research*. In an article e-published on March 9 ahead of print in *Radiation Research*, Patel et al. from the University of Miami (FL) reported on “A realistic utilization of nanotechnology in molecular imaging and targeted radiotherapy of solid tumors.”