

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.

### PET in Recurrent Thyroid Cancer

In a study e-published on April 17 ahead of print in *Endocrine*, Treglia et al. from the Catholic University of the Sacred Heart (Rome, Italy) reported on the results of a meta-analysis of published reports on the utility of  $^{18}\text{F}$ -FDG PET and PET/CT in detecting recurrent medullary thyroid carcinoma (MTC). Reports of PET or PET/CT in suspected recurrent MTC were drawn from large international databases, with selection criteria that yielded an analysis group of 24 studies with a total of 538 patients. Diagnostic performance of PET and PET/CT were evaluated on the basis of per-patient pooled detection rates. Other variables assessed were types of imaging devices, serum calcitonin and carcinoembryonic antigen (CEA) values, calcitonin doubling times, and CEA doubling times. The detection rate for  $^{18}\text{F}$ -FDG PET or PET/CT in suspected recurrent MTC on a per patient-based analysis was 59%, with significant heterogeneity among the studies. The detection rates increased in patients with serum calcitonin  $\geq 1,000$  ng/L (75% of patients), CEA  $\geq 5$

ng/mL (69%), calcitonin doubling times  $< 12$  mo (76%), and CEA doubling times  $< 24$  mo (91%). The authors noted that the 59% overall nondetection rate indicates that PET and PET/CT may be nonoptimal for recurrence screening. However, PET and PET/CT “could modify the patient management in a certain number of recurrent MTCs because these methods are often performed after negative conventional imaging studies.” The fact that the detection rate increases in patients with higher calcitonin and CEA values and lower calcitonin doubling time and CEA doubling time values suggests that “these imaging methods could be very helpful in patients with more aggressive disease.”

*Endocrine*

### PET and Pheochromocytomas/Paragangliomas

Timmers and colleagues, from the Radboud University Nijmegen Medical Centre (The Netherlands), and a consortium of researchers from the United States and Germany reported on April 18 ahead of print in the *Journal of the National Cancer Institute* on a study comparing the sensitivity and specificity of  $^{18}\text{F}$ -FDG PET/CT staging and functional characterization of pheochromocytomas and paragangliomas with that of conventional imaging with  $^{123}\text{I}$ -metaiodobenzylguanidine ( $^{123}\text{I}$ -MIBG) SPECT, CT, or MR. The study included 216 individuals (106 men, 110 women; ages,  $45.2 \pm 14.9$  y) with suspected pheochromocytomas or paragangliomas. All participants underwent CT or MR imaging, as well as  $^{18}\text{F}$ -FDG PET/CT and  $^{123}\text{I}$ -MIBG SPECT/CT. Resulting review showed that 60 (28%) patients in the study group had nonmetastatic pheochromocytomas or paragangliomas, 95 (44%) had metastatic pheochromocytomas or paragangliomas, and 61 (28%) were negative for the imaging indications.

Imaging specificity was 90.2% for PET, 91.8% for SPECT, and 90.2% for CT/MR imaging. PET and SPECT sensitivities (76.8% and 75.0%, respectively) were inferior to that of CT/MR imaging (95.7%) for nonmetastatic tumors. Tracer uptake on PET was higher in succinate dehydrogenase complex- and von Hippel-Lindau syndrome-related tumors than in multiple endocrine neoplasia type 2-related tumors. PET and CT/MR imaging were more sensitive (82.5% and 74.4%, respectively) than was SPECT (50.0%) for metastases. PET was more sensitive for bone metastases than CT/MR imaging (93.7% and 76.7%, respectively). The authors concluded that despite the current assessment of  $^{123}\text{I}$ -MIBG SPECT and CT/MR imaging as gold standards in this setting, “ $^{18}\text{F}$ -FDG PET provides a high specificity in patients with a biochemically established diagnosis” of pheochromocytoma or paraganglioma.

*Journal of the National Cancer Institute*

### Interim PET in Hodgkin Lymphoma

In a study e-published on April 18 ahead of print in *Leukemia & Lymphoma*, Ziakas et al. from the National University of Athens (Greece) reported on a meta-analysis of published studies on interim  $^{18}\text{F}$ -FDG PET imaging in newly diagnosed Hodgkin lymphoma and resulting effects on outcomes. After excluding studies in which management decisions were based on the results of interim PET imaging, the authors included 14 studies with a total of 1,328 evaluable patients. The predefined outcome on which interim PET imaging results were determined was treatment failure at or by the end of the follow-up period. Interim PET had a sensitivity of 67% and specificity of 89%, with a negative predictive value of 93%. The diagnostic accuracy of

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interim PET was found to be influenced by a number of factors, including but not limited to age, duration of follow-up, and timing of interim PET imaging. The authors noted that widespread adoption of interim PET as a surrogate marker is challenged by inconsistent interpretation criteria as well as heterogeneous populations (and resulting difficulties in cross-study comparisons) in the published literature. They added that “the high negative predictive value may permit a treatment stratification based on a negative outcome” using interim PET.

*Leukemia & Lymphoma*

### **PET/CT in High-Risk Prostate Cancer**

Kjölhede et al. from Lund University (Sweden) reported on April 13 online in *BJU International* on a study designed to investigate the degree to which PET/CT, with both  $^{18}\text{F}$ -fluorocholine and  $^{18}\text{F}$ -fluoride as tracers, adds clinically relevant information in the assessment of patients with prostate cancer and high-risk tumors or inconclusive planar bone scans. The study included 90 patients with prostate cancer and prostate-specific antigen levels of 20–99 ng/mL and/or Gleason score 8–10 tumors who had been planned for curative treatment approaches based on routine staging with a negative or inconclusive bone scan. Each patient underwent both  $^{18}\text{F}$ -fluorocholine and  $^{18}\text{F}$ -fluoride PET/CT. One or both scans were positive for metastases in 50 patients.  $^{18}\text{F}$ -fluoride indicated bone metastases in 37 patients, whereas  $^{18}\text{F}$ -fluorocholine was positive for lymph node and/or bone metastases in 35 patients. In the 18 patients in whom PET/CT of either type showed widespread metastases, imaging led to a change in therapy intent from curative to noncurative. Among patients with positive scans using either tracer, 74% had Gleason score 8–10 tumors; conversely, 64% of patients with Gleason score 8–10 tumors had positive scans. The authors concluded that “PET/CT scans with  $^{18}\text{F}$ -fluorocholine and  $^{18}\text{F}$ -fluoride commonly detect me-

tastases in patients with high-risk prostate cancer and a negative or inconclusive bone scan.”

*BJU International*

### **Impact of DaTscan SPECT**

In an article e-published on April 6 ahead of print in the *Journal of Neurology, Neurosurgery, and Psychiatry*, Kupsch et al. from University Medicine Berlin (Germany) reported on an investigation of the effect of DaTscan on clinical management, diagnosis, diagnostic confidence, quality of life, health resource utilization, and safety during a 1-y follow-up in patients with clinically uncertain parkinsonian syndromes. DaTscan (GE Healthcare; Waukesha, WI) is a  $^{123}\text{I}$ -ioflupane agent approved in early 2011 in the United States for use with SPECT in the diagnosis of Parkinson disease and differential diagnosis from other disorders with similar clinical symptoms and characteristics. The study included results from 19 academic hospital centers in Europe and the United States. The open-label, single-dose, prospective, clinical trial included 273 patients (135 who underwent DaTscan imaging and 138 controls who were not imaged) with clinically uncertain parkinsonian syndromes. The effect of the multiple variables was assessed at 1-y follow-up. Significantly more patients in the DaTscan group had changed diagnoses with increased confidence in diagnosis at 4 wk, 12 wk, and 1 y than patients in the control group. No significant differences in quality of life or health resource utilization were noted. DaTscan was determined to be safe and well tolerated, although 1 patient in the imaging group experienced a headache believed to be related to the imaging agent. The authors concluded that with its safety and significant impact on clinical management, diagnosis, and diagnostic confidence, “DaTscan is a useful adjunct to differentiate a diagnosis of clinically uncertain parkinsonian syndromes.”

*Journal of Neurology, Neurosurgery, and Psychiatry*

### **Nodal Dissection and Lung Cancer Staging**

Kirmani et al. from the Papworth Hospital (Cambridge, UK) reported on April 23 ahead of print in the *European Journal of Cardio-Thoracic Surgery* on a retrospective study designed to assess the effect of lymph node dissections performed at the time of surgical resection on management of patients with lung cancer, particularly in the context of the growing number of imaging approaches in the disease. The study included 312 patients (mean age, 68 y; range, 42–86 y) with lung cancer scheduled for curative treatment. Each patient underwent staging CT, PET/CT, and brain imaging. Enlarged or PET-positive nodes were evaluated using ultrasound guidance, endobronchial or endoesophageal ultrasound with needle biopsy; mediastinoscopy; mediastinotomy; and/or video-assisted or open surgery. After lung resection and lymph node dissection, a change in nodal status was made in 25.3%, of whom 20.8% were upstaged. Occult N2 disease was identified in 9.9% of the entire study population, and 12.3% of those with cT1 tumors were upstaged at nodal dissection compared with 25.3% with cT2 tumors. Pointing to the high rate of nodal status change after surgical resection and lymph node dissection despite technologically intensive and systematic preoperative staging, the authors concluded “if considering non-surgical treatments for the early stage lung cancer, the impact of this discrepancy should be considered. If not, errors in prognosis and in determining correct adjuvant treatment may arise.”

*European Journal of Cardio-Thoracic Surgery*

### **$^{18}\text{F}$ -FCH PET/CT Staging in Prostate Cancer**

In a study published online on April 23 in *BJU International*, Poulsen et al. from the University of Southern Denmark (Odense) and Freiburg University Medical Center (Germany) reported on a prospective study of

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the efficacy of  $^{18}\text{F}$ -fluoromethylcholine ( $^{18}\text{F}$ -FCH) PET/CT for lymph node staging in prostate cancer. Specifically, the authors asked whether  $^{18}\text{F}$ -FCH PET/CT is sufficiently accurate in identifying lymph node involvement to replace lymph node dissection for staging of prostate cancer. The study included 210 intermediate- ( $n = 76$ ) or high-risk ( $n = 134$ ) prostate cancer patients who underwent  $^{18}\text{F}$ -FCH PET/CT imaging before regional lymph node dissection. Imaging results were determined by physicians unaware of histologic results. The sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) of PET/CT were compared against the results of dissection. Histologic analysis identified metastases in 41 patients. For  $^{18}\text{F}$ -FCH PET/CT, sensitivity, specificity, PPV, and NPV for lymph node staging were 73.2%, 87.6%, 58.8%, and 93.1%, respectively. Corresponding results for lymph node dissection and histologic examination were 56.2%, 94.0%, 40.2%, and 96.8%, respectively. However, PET/CT identified high focal bone uptake consistent with bone metastases in 18 patients, 12 of whom had histologically negative lymph nodes. The authors concluded that although  $^{18}\text{F}$ -FCH PET/CT is “not ideal for primary lymph node staging in patients with prostate cancer,” this imaging approach “does convey important additional information otherwise not recognized, especially for bone metastases.”

*BJU International*

### PET/CT in Metastatic Breast Cancer

Morris et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) reported on April 19 ahead of print in *Cancer* on a study assessing the prognostic value of maximum standardized uptake value ( $\text{SUV}_{\text{max}}$ ) from PET/CT images in patients with newly diagnosed metastatic breast cancer. The study included 253 patients (median age, 57 y; range, 27–90 y) with 1 or more metastatic

lesions identified on PET/CT acquired within 60 d of their metastatic breast cancer diagnoses. Patients with recent chemotherapy were excluded. Overall survival and site-specific  $\text{SUV}_{\text{max}}$  were analyzed. Over a mean follow-up of 40 mo, 152 patients (60%) died. Site-specific  $\text{SUV}_{\text{max}}$  was found to be strongly correlated with overall survival in patients with bone metastases. Positive but not statistically significant correlations were identified between survival and uptake in the liver, lymph nodes, and lung. The authors concluded that “the current results indicate that PET/CT has value as a prognostic tool in patients with newly diagnosed metastatic breast cancer to bone.”

*Cancer*

### PET/CT and Therapy Planning in Cervical Ca

In an article e-published on April 12 ahead of print in the *International Journal of Radiation Oncology, Biology, Physics*, Nam et al. from Sungkyunkwan University School of Medicine (Seoul, South Korea) reported on the feasibility of  $^{18}\text{F}$ -FDG PET/CT-guided conformal brachytherapy treatment planning in women with cervical cancer. The study included 12 women with cervical cancer who underwent pretreatment PET/CT imaging. Brachytherapy simulation was performed after an external-beam radiation therapy median dose of 4,140 cGy. Patients underwent PET/CT scans with placement of tandem and ovoid applicators. Gross tumor volumes were determined by adjusting the window and level and outlining the edge of the enhancing area, with the guidance of a nuclear medicine physician. A standardized uptake value profile of tumor margins was made for each patient relative to the maximum uptake value of each tumor and analyzed. The plan was designed to deliver 400 cGy to point A (conventional plan) or to cover the clinical target volume (CTV) (PET/CT plan). The median dose that encompassed 95% of the target volume of the clinical target volume was 323.0 cGy for the conventional plan and 399.0 cGy for the PET/CT

plan. The maximum standardized uptake values of tumors were reduced by a median of 57%, and all except 1 patient presented with discernable residual uptake within the tumors. The median value of the thresholds of the tumors contoured by simple visual analysis was 41%. The authors concluded that the fact that the “PET/CT plan was better than the conventional point A plan in terms of target coverage without increasing the dose to the normal tissue” made “optimized 3-dimensional brachytherapy treatment planning possible.” Moreover, the combination of PET and CT provided enhanced visual target localization, although additional studies are needed to more fully characterize the potential input of metabolic activity assessed by PET in treatment planning.

*International Journal of Radiation Oncology, Biology, Physics*

### $^{13}\text{N}$ -Ammonia PET and Cardiac Outcomes

Fiechter et al. from University Hospital Zurich and the University of Zurich (Switzerland) reported on April 2 ahead of print in the *International Journal of Cardiology* on the long-term predictive value of myocardial perfusion imaging (MPI) with  $^{13}\text{N}$ -ammonia PET in patients with suspected cardiac perfusion abnormalities. The study included 943 such patients who underwent  $^{13}\text{N}$ -ammonia PET, with follow-up data available in 698 (74%). Of these, 77 who underwent early revascularization were excluded, leaving a total of 621 patients. Imaging results on these patients were categorized as normal ( $n = 152$ ) or abnormal ( $n = 469$ ) for comparison with outcomes, including hard events (cardiac death and nonfatal myocardial infarction) and all major adverse cardiac events (hard events, hospitalization for cardiac reasons, and late revascularization). During the follow-up period ( $5.7 \pm 2.5$  y), 275 patients had at least 1 cardiac event, including 102 cardiac deaths and 33 nonfatal myocardial infarctions. Abnormal perfusion was significantly associated with a higher incidence of major ad-

verse cardiac events and hard events throughout the follow-up period. The authors concluded that “cardiac perfusion findings in  $^{13}\text{N}$ -ammonia PET are strong predictors of long-term outcome.”

*International Journal of Cardiology*

## **$^{18}\text{F}$ -NaF and Plaque Biology**

In an article in the April 24 issue of the *Journal of the American College of Cardiology* (2012;59:1539–1548), Dweck et al. from the University of Edinburgh (UK) reported on an investigation of coronary arterial uptake of  $^{18}\text{F}$ -sodium fluoride ( $^{18}\text{F}$ -NaF) and  $^{18}\text{F}$ -FDG on PET/CT as markers of active plaque calcification and inflammation, respectively. The prospective study included 119 individuals (ages,  $72 \pm 8$  y; 81 men, 38 women) with and without aortic valve disease. Each patient underwent  $^{18}\text{F}$ -NaF and  $^{18}\text{F}$ -FDG PET imaging and evaluation for coronary calcium scores. Those with calcium scores of 0 were assigned as control participants and compared with those with calcific atherosclerosis (calcium score  $>0$ ). Uptake was found to be higher in patients with coronary atherosclerosis ( $n = 106$ ) than in control participants ( $n = 13$ ) and correlated with calcium scores, although 40% of those with scores  $>1,000$  showed normal uptake. Those with increased coronary  $^{18}\text{F}$ -NaF activity ( $n = 40$ ) had higher rates of previous cardiovascular events and angina, as well as higher Framingham risk scores than those without increased activity. Quantification of coronary  $^{18}\text{F}$ -FDG uptake was difficult against myocardial activity background, but this uptake was not higher in those with atherosclerosis than in those without. The authors concluded that  $^{18}\text{F}$ -NaF PET is a “promising new approach for the assessment of coronary artery plaque biology,” and that additional studies with clinical outcomes are needed to assess whether coronary  $^{18}\text{F}$ -NaF uptake “represents a novel marker of plaque vulnerability, recent

plaque rupture, and future cardiovascular risk.”

*Journal of the American College of Cardiology*

## **PET/CT Planning in SBRT**

Wang et al. from the University of Pittsburgh School of Medicine (PA) reported on April 19 ahead of print in *Head & Neck Oncology* on the effect of PET/CT treatment planning on patterns of failure in stereotactic body radiation therapy (SBRT) for recurrent head and neck cancer. The retrospective study included 96 patients with recurrent, previously irradiated squamous cell carcinoma of the head and neck (rSCCHN) treated with SBRT. Treatment was based on PET/CT planning in 45 patients and on non-PET/CT planning in the remaining 51. Over a median follow-up of 7.4 mo, 47 (49%) patients developed post-SBRT failure. Categories of failure were created from comparisons of posttreatment scans with planning target volumes (PTVs). These failure categories included: in-field ( $>75\%$  inside PTV), overlap (20%–75% inside PTV), marginal ( $<20\%$  inside PTV but closest edge within 1cm of PTV), or regional/distant ( $>1$  cm from PTV). Treatment failures in the 47 patients were determined to be 12.3% in-field, 24.6% overlap, 36.8% marginal, and 26.3% regional/distant. The authors noted a significant improvement in overall failure-free survival and combined overlap/marginal failure-free survival for those receiving PET/CT planning compared with non-PET/CT planning in the overall cohort, with analysis of the definitive SBRT cohort increasing the significance of these findings. No significant differences were noted in age, sex, time from prior radiation, dose, use of cetuximab with SBRT, tumor differentiation, or tumor volume between the PET/CT and non-PET/CT groups. The authors concluded that because “PET/CT treatment planning showed the lowest rate of overall and near miss

failures” this approach is beneficial for SBRT treatment planning.

*Head & Neck Oncology*

## **REVIEWS**

Review articles provide an important way to stay up to date on the latest topics and approaches by providing valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in late March and April. In an article published in *Theranostics* (2012;2:374–391) Yaghoubi et al. from the University of California at Los Angeles School of Medicine provided an overview of “Positron emission tomography reporter genes and reporter probes: gene and cell therapy applications.” Camici et al. from the Vita-Salute University and Scientific Institute San Raffaele (Milan, Italy), on April 16 ahead of print in the *European Heart Journal*, described “Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque.” On April 4 ahead of print in the *Journal of Pharmaceutical Sciences*, Psimadas et al. from the University Hospital of Larissa and the Technological Educational Institute of Athens (both in Greece) reviewed “Molecular nanomedicine towards cancer:  $^{111}\text{In}$ -labeled nanoparticles.” Stacy et al. from Yale University (New Haven, CT) published “Targeted molecular imaging of angiogenesis in PET and SPECT: a review” in the March issue of the *Yale Journal of Biology and Medicine* (2012;85:75–86). In an article appearing online on April 20 ahead of print in *Biomaterials*, Liu and Zhang from Shandong University (Jinan, People’s Republic of China) provided an overview of “Gadolinium-loaded nanoparticles in theranostic magnetic resonance imaging.” Alves et al. from the Centro Hospitalar de Lisboa (Portugal) described “Alzheimer’s disease: a clinical practice-oriented review” in the April issue of *Frontiers in Neurology* (2012;3:63).