

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.

Outcome Predictors in DAT SPECT

Jaakkola et al. from the Turku University Hospital and University of Turku (Finland) reported on December 16 ahead of print in the *Journal of Neural Transmission (Vienna)* on an analysis of predictors of outcomes in clinical brain dopamine transporter (DAT) imaging with ^{123}I -FP-CIT SPECT for evaluation of clinically uncertain parkinsonism. The study included 538 patients, with data on demographics and indications for referral to DAT SPECT imaging. Patient data were categorized by scanning results (normal, 235 patients; abnormal, 303 patients), and these results were compared with preimaging characteristics and variables. Independent variables correlated with abnormal imaging showing dopaminergic deficits included older age, asymmetry of motor symptoms, and shorter time since symptom onset. A higher probability of an abnormal scan was associated with re-evaluation for previously diagnosed Parkinson disease, and a higher probability of a normal scan was associated with suspected medication-induced parkinsonism. The authors summarized their findings that “the probability of an abnormal outcome in clinical brain DAT imaging

increases with known risk factors of neurodegenerative parkinsonism,” but “a long duration of uncertain motor symptoms and suspicion of medication-induced parkinsonism are associated with a higher probability of a normal outcome.” They noted that these findings not only shed light on epidemiologic factors in parkinsonism but point toward referral biases, the understanding of which may be used to improve clinical DAT imaging.

Journal of Neural Transmission (Vienna)

PET/CT and HNSCC of Unknown Primary

In an article e-published on December 16 ahead of print in *Laryngoscope*, Mani et al. from the Christie National Health Service Trust (Manchester, UK) reported on a retrospective study evaluating the role of ^{18}F -FDG PET/CT and subsequent panendoscopy in head and neck squamous cell carcinomas (HNSCC) of unknown primary origin. The study included 52 patients seen at a regional oncology center who presented with a metastatic neck node and unknown primary who had undergone PET/CT prior to panendoscopy. Imaging accuracy was compared with panendoscopy and histopathologic biopsy findings. Images from 27 patients indicated a primary site, and calculated diagnostic parameters were 83%, 87%, 89%, and 80% for sensitivity, specificity, and positive and negative predictive values, respectively. Three PET/CT scans were determined to be false-positives, and 3 tongue-base tumors were missed by PET/CT and identified on panendoscopy. The authors concluded that PET/CT is valuable in this setting, because it “helps direct biopsy and aids in the detection of local and distant metastases along with synchronous primary tumors.” However, given the false-positive and -negative rates, they emphasized that panendoscopy and biopsy remain essential adjuncts in investigation, regardless of PET/CT results.

Laryngoscope

PET and Therapy Response in Esophageal SCC

Chhabra et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) reported on December 10 ahead of print in the *British Journal of Cancer* on the prognostic significance of SUV on ^{18}F -FDG PET in patients with esophageal squamous cell carcinoma (SCC) treated with induction chemotherapy followed by concurrent chemoradiation (CRT). The study included 57 patients (36 men, 21 women; clinical stage T1N1 or T24N01 without evidence of metastatic disease) treated with CRT, 52 of whom received induction chemotherapy and 10 of whom underwent surgery following CRT. Patients underwent PET/CT imaging for pretreatment staging (51 patients), after induction chemotherapy (41 patients), and after CRT (40 patients). SUV_{max} and metabolic tumor volume were calculated for the index lesion and lymph node metastases in each patient. Overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were calculated over a median follow-up of 4.4 y and correlated with PET metrics. Median survival for all patients was 2.9 y, with 3-y OS, DFS, DMFS and LRFS rates of 47%, 40%, 44%, and 36%, respectively. Using a cutoff of a 35% decrease in SUV_{max} from baseline to postinduction imaging, 3-y OS for responders (25 patients) was 64%, whereas nonresponders (13 patients; <35% decrease from baseline) had a 3-y OS of 15%. The authors concluded that baseline and postinduction PET metrics can be used to provide valuable prognostic information for patients with esophageal SCC.

British Journal of Cancer

PET Tumor Quantification for Outcome Prediction

In the December 7 issue of *Physics in Medicine and Biology* (2015;61:227–242), Rahmim et al. from Johns Hopkins University (Baltimore, MD) introduced

a metric for tumor quantification in ^{18}F -FDG PET imaging inspired by a model of uniform dose like that used in radiation therapy. The metric is called generalized effective total uptake (gETU) and generalizes common PET metrics such as SUV_{max} , total lesion glycolysis, and metabolic tumor volume (MTV) for both homogeneous and heterogeneous tumors, using a single parameter. The authors reported on evaluation of the gETU metric for improved overall survival (OS) prediction in 2 baseline ^{18}F -FDG PET/CT datasets with: (1) 113 patients with squamous cell cancer of the oropharynx; and (2) 72 patients with locally advanced pancreatic adenocarcinoma. Using hazards ratio calculations, a gETU value of 0.25 (placing greater emphasis on volume data) enabled significantly better OS prediction than total lesion glycolysis, MTV, SUV_{max} , SUV_{mean} , or SUV_{peak} in the group with oropharyngeal cancer, as did a gETU value of 3.2 (placing greater emphasis on SUV information) in the patients with pancreatic cancer. The authors concluded that “overall, the proposed methodology allows placement of differing degrees of emphasis on tumor volume versus uptake for different types of tumors to enable enhanced clinical outcome prediction.”

Physics in Medicine and Biology

Imaging Pancreatic IPMNs

Sultana et al. from the University of Liverpool (UK) published on December 10 ahead of print in *Clinical and Translational Gastroenterology* a systematic review and metaanalysis designed to explore published data on the optimal imaging approach for identifying malignant transformation in pancreatic intraductal papillary mucinous neoplasias (IPMNs), which account for 25% of all cystic neoplasms and are precursor lesions for pancreatic ductal adenocarcinoma. The authors also looked at the sensitivity and specificity of risk features on imaging and the utility of tumor markers in serum and cyst fluid for predicting malignancy in IPMNs. The metaanalysis included 37 studies that met the inclusion criteria. The pooled sensitivity and specificity for risk fea-

tures predicting malignancy on CT/MR imaging were 0.809 and 0.762, respectively, and 0.968 and 0.911, respectively, on PET. Combining the parameters of mural nodule, cyst size, and main pancreatic duct dilation on imaging with raised serum carbohydrate antigen 19-9 levels provided a sensitivity of 0.743 and specificity of 0.906. The authors concluded from analysis of their data that “PET holds the most promise in identifying malignant transformation within an IPMN” and that combining parameters may be most effective in predicting malignancy.

Clinical and Translational Gastroenterology

PET/CT TLG and Bile Duct Cancer

In an article in the December issue of *Anticancer Research* (2015;35:6985–6981) Lee et al. from Seoul Medical Center and Konkun University School of Medicine (both in Seoul, Republic of Korea) reported on the predictive value of clinicopathologic factors, including ^{18}F -FDG PET parameters, in patients with distal bile duct adenocarcinoma after curative resection. The study included the records of 25 patients who underwent ^{18}F -FDG PET/CT before surgery. Among the variables assessed were SUV_{max} , metabolic tumor volume, total lesion glycolysis, and other clinical and pathologic data. High total lesion glycolysis, high metabolic tumor volume, and high SUV_{max} were found to be significant predictors of poor overall survival. High total lesion glycolysis and large tumor size were found to be significant predictors for shorter progression-free survival. Additional analysis showed high total lesion glycolysis to be the only independent predictor for poor overall survival. The authors concluded that “Preoperative assessment of total lesion glycolysis by FDG PET/CT might be a useful prognostic predictor in patients with a distal bile duct adenocarcinoma after curative resection.”

Anticancer Research

SUV_{max} and Nodal Mets in Oral SCC

Kitajima et al. from Kobe University Graduate School of Medicine and

Kobe University Hospital (Japan) reported in the November 4 issue of *Springerplus* (2015;4:718) on a study comparing the diagnostic accuracy of ^{18}F -FDG PET/CT with that of CT for detection of cervical node metastases in patients with oral squamous cell carcinoma (OSCC). The study included 36 patients who underwent PET/CT imaging, followed by neck dissection (4 bilateral, 32 unilateral; 250 nodal levels). Lesion size and SUV_{max} of cervical nodes visible on imaging were compared with pathology findings. Nodal metastases were identified at histopathology in 13 of 36 patients (36.1%) and 28 of 250 nodal levels (11.2%). With an SUV_{max} nodal cutoff of 3.5, the sensitivity, specificity, and accuracy of PET/CT for identification of nodal metastases on a level-by-level basis were 67.9%, 94.6%, and 91.6%, respectively. For CT, these respective percentages were 42.9%, 96.8%, and 90.8%. Modification of the SUV_{max} cutoff yielded even higher respective figures for PET/CT at 71.4%, 95.9%, and 93.2%. The authors concluded that “FDG PET/CT with SUV_{max} is a useful modality for preoperative evaluation of cervical neck lymph node metastases in patients with OSCC.”

Springerplus

PET and GIST Treatment Response

In an article e-published on December 7 ahead of print in the *Journal of Gastroenterology and Hepatology*, Hassanzadeh-Rad et al. from the Tehran University of Medical Sciences (Iran) and Bushehr University of Medical Sciences (Iran) provided a systematic review and metaanalysis of the value of ^{18}F -FDG PET for predicting therapeutic response to systematic treatment in patients with gastrointestinal stromal tumors (GISTs). A total of 21 relevant articles met the study’s inclusion criteria. Across the studies covered in these articles, the pooled sensitivity and specificity of PET in evaluation of response to treatment of GISTs were 90% and 62%, respectively. The pooled prognostic odds ratio of ^{18}F -FDG PET was 14.99. Additional analyses showed that

the sensitivity of PET was higher when the study sample size was ≥ 30 individuals and when PET was used in combination with CT (PET/CT). The authors concluded that their data suggest that “ ^{18}F -FDG PET has a significant value in predicting treatment response in GIST patients.”

Journal of Gastroenterology and Hepatology

Gut ^{18}F -FDG Uptake in Lung Cancer

Vella-Boucaud and colleagues from the Hôpital Maison Blanche, CHU de Reims; Centre de Lutte Contre le Cancer à Reims; and the Hôpital Robert Debré, CHU de Reims (all in Reims, France) reported in the December 2 issue of *BMC Pulmonary Medicine* (2015;15:152) on a study assessing the significance of incidental ^{18}F -FDG uptake in the gastrointestinal tract observed on PET/CT in patients with lung cancer. The retrospective study included 230 consecutive ^{18}F -FDG PET/CT scans acquired for lung cancer assessment. Of this group, 52 patients (23%) were found to have incidental gastrointestinal tract tracer uptake. Of these, 33 (63.5%) were found to have diffuse uptake (esophagus, 2; colon, 31) and 19 (36.5%) were found to have focal uptake (esophagus, 1; small bowel, 1; ascending colon, 5; descending colon, 4; sigmoid, 4; rectum, 3; anal margin, 1). Twelve of the 52 patients were referred to additional investigative studies, with a resulting diagnosis of malignancy in 4 patients with focal ^{18}F -FDG uptake. Patients with benign or malignant disease did not show significant differences in mean SUV_{max} . The authors concluded that because a high incidence of ^{18}F -FDG uptake in the gastrointestinal tract is associated with lung cancer imaging and because focal gastrointestinal uptake is often associated with malignant disease, “further gastrointestinal tract investigations should be performed in patients with focal gastrointestinal tract uptake.”

BMC Pulmonary Medicine

Physician Belief and Image Interpretation

In an article e-published on December 1 in *Neuro-Degenerative Diseases*

(2016;16:111–1117), Boccardi, from the University of Brescia (Italy), and colleagues from the INDIA-FBP Working Group explored the effects of individual scientific belief about disease etiology on imaging interpretation and diagnosis. Their study focused on the question of whether the beliefs of dementia experts about the pathogenic role of amyloid- β in Alzheimer disease (AD) may affect the use and interpretation of PET amyloid imaging in that setting. The study included 22 dementia experts who rated their beliefs about the pathogenesis of AD: 55% assigned a dominant role to amyloid- β and 32% assigned a shared role to amyloid- β and tau pathologies. The experts were then asked to rate the probability of a change in diagnosis based on PET imaging results in 7 sample case vignettes in which patients received an initial diagnosis based on a comprehensive workup and later underwent amyloid PET, with imaging results that were either consistent or inconsistent with the original diagnosis. The participants reported a probability of change of diagnosis of 17% for cases in which the postimaging diagnosis remained consistent with the original diagnosis to 51% for cases in which PET imaging did not agree with the original clinical data. These diagnostic changes were not biased by the physicians’ beliefs about the etiology of AD. The authors concluded that “this work supports an unbiased interpretation of amyloid PET across different beliefs about the pathogenic role of amyloid, and a belief-independent reluctance to change diagnosis in cases where change is expected and recommended.”

Neuro-Degenerative Diseases

^{18}F -FLT PET and Pelvic Bone Marrow

Wyss et al. from the University of California San Diego (La Jolla) reported on December 7 ahead of print in *Radiotherapy and Oncology* on a study comparing the utility of ^{18}F -FDG and ^{18}F -fluorothymidine (^{18}F -FLT) in identifying active pelvic bone marrow in an effort to determine which tracer is more appropriate for bone-marrow sparing in planning

for radiation therapy. The study included data from 41 patients, 25 of whom underwent ^{18}F -FDG PET/CT only, 7 of whom underwent ^{18}F -FLT PET/CT only, and 9 of whom were imaged with both tracers. Active subvolumes of the pelvic bone marrow were defined as those with the highest SUVs comprising 40%, 50%, and 60% of the total pelvic bone marrow volume. Overlap of bone marrow volumes of equal size were quantified using the Dice similarity. In patients who were imaged with both tracers, mean Dice coefficients for the 40%, 50%, and 60% subvolumes were 0.683, 0.732, and 0.781, respectively. When comparing individual active bone marrow subvolumes to the mean subvolume, Dice coefficients varied from 0.598 to 0.889 for ^{18}F -FDG and from 0.739 to 0.912 for ^{18}F -FLT. Region-Region growing analyses showed that ^{18}F -FLT PET defined more highly clustered active bone marrow subvolumes. The authors concluded that “within the limitations of a small sample size, we found significant agreement between FDG PET and FLT PET; however, FLT PET had significantly less individual variation and is likely to be superior to FDG PET for bone marrow-sparing radiotherapy.”

Radiotherapy and Oncology

Visual Hallucinations, Hypometabolism, and PD/MCI

In an article e-published on December 14 ahead of print in *Human Brain Mapping*, Gasca-Salas et al. from the University of Navarra (Pamplona, Spain), the Centro de Investigación Biomédica en Red Sobre Enfermedades Neurodegenerativas (Madrid, Spain), and the Basque Foundation for Science (Bilbao, Spain) reported on a PET study in patients with Parkinson disease with mild cognitive impairment (MCI) with or without visual hallucinations. The study included 21 patients with Parkinson disease with MCI (12 without and 9 with visual hallucinations) and 19 controls, all of whom underwent a comprehensive baseline neuropsychological examination and ^{18}F -FDG PET imaging. Regional tracer uptake was analyzed on

imaging, and the neuropsychological examination was repeated after 30 mo. Patients experiencing visual hallucinations were found to have lower tracer uptake bilaterally in the occipital and parietal cortex, right temporal lobe, and left cingulum compared with patients who were not experiencing visual hallucinations. At baseline assessments, no significant differences were found between those with and without hallucinations in terms of clinical characteristics or cognitive status. At >30-mo follow-up, 3 of the patients without and 4 of the patients with visual hallucinations had progressed to dementia. The authors concluded that “even in the absence of significant cognitive differences, Parkinson disease–MCI patients with visual hallucinations exhibit more severe cerebral hypometabolism and had a higher rate of progression to dementia than visual hallucination–negative patients, supporting the importance of visual hallucination and cerebral hypometabolism in establishing the risk of dementia in Parkinson disease–MCI.”

Human Brain Mapping

¹⁸F-FDG Uptake and LN Mets in Gastric Cancer

Okumura et al. from the University of Tokyo (Japan) reported in the December 2 issue of the *World Journal of Surgical Oncology* (2015;13:327) on a study evaluating the relationship between ¹⁸F-FDG uptake on PET/CT and the presence or absence of metastasis in individual lymph nodes. The study included 21 patients with gastric cancer scheduled for gastrectomy with lymph node dissection. Patients were injected with ¹⁸F-FDG in the morning and proceeded to surgery in the afternoon. Radiation doses were measured at each lymph node using a well-type counter and compared with tracer uptake and pathology results. A total of 906 lymph nodes were analyzed, including 115 metastatic nodes. Metastatic lymph nodes showed significantly higher tracer uptake and were significantly larger than nonmetastatic nodes. The area under the receiver operating characteristic (ROC) curve was larger for ¹⁸F-FDG uptake than for the shortest lymph node

diameter, and the area under the ROC curve for intestinal-type adenocarcinoma was larger than that for the diffuse type of disease. The authors concluded that ¹⁸F-FDG uptake “is potentially a more useful variable than lymph node diameter for discriminating between lymph nodes with and without metastasis, especially in intestinal type gastric cancer cases.”

World Journal of Surgical Oncology

FUO, PET, and Children with Comorbidities

In an article e-published on December 8 ahead of print in *Pediatric Critical Care Medicine*, Chang et al. from Mackay Memorial Hospital and Mackay Junior College of Medicine, Nursing, and Management (Taipei, Taiwan), and National Taiwan University Hospital and National Taiwan University College of Medicine (Taipei) reported on preliminary experience using ¹⁸F-FDG PET/CT in evaluation of fever of unknown origin in critically ill children with complicating underlying diseases under treatment. The study included 19 critically ill children (mean age, 5.7 y) with fever of unknown origin and underlying diseases requiring intensive care support. All underwent ¹⁸F-FDG PET/CT. Fever lasted at least 7 d (mean, 21.6 d; range, 7–52 d). Imaging findings were compared with final histopathology, culture, or serology results and with follow-up imaging. A final diagnosis was made in 16 patients (84.2%), in 14 of whom ¹⁸F-FDG PET/CT accurately localized the source of fever (sensitivity of 87.5%). Two false-negative PET/CT results were later attributed to relapse of underlying disease. In the other 2 patients with negative PET/CT results, fever subsided shortly after imaging and without treatment. The authors concluded from this preliminary experience that ¹⁸F-FDG PET/CT “may be clinically beneficial in evaluating fever of unknown origin in children with complicated underlying diseases mandating intensive support in intensive care units if usual investigative methods are unsuccessful” but added that further large prospective studies are needed to validate these findings.

Pediatric Critical Care Medicine

Occult Malignancy Screening in Venous Thromboembolism

Robin et al. from the Centre Hospitalo-Universitaire de Brest, Université de Bretagne Occidentale (France); Université Paris Descartes (France); Centre Hospitalo-Universitaire de Saint-Etienne, Université Jean Monnet (France); Centre Hospitalo-Universitaire d’Angers (France); and the Ottawa Hospital Research Institute at the University of Ottawa (Canada) reported on December 7 ahead of print in *The Lancet. Oncology* on a study comparing screening strategies with and without ¹⁸F-FDG PET/CT in detection of occult malignant disease in patients with unprovoked venous thromboembolism. The open-label, multicenter randomized study enrolled and studied 394 patients with venous thromboembolism not provoked by a major inherited or acquired risk factor. Patients were randomly assigned to a limited screening strategy (197 patients; physical examination, conventional laboratory tests, and basic radiography) or to the addition of ¹⁸F-FDG PET/CT imaging to this limited strategy (197 patients). Patients were followed for 2 y. After the initial assessment, cancer was diagnosed in 11 patients (5.6%) who underwent ¹⁸F-FDG PET/CT imaging and 4 (2.0%) in the limited screening group. Seven (64%) of the 11 cancers diagnosed in the ¹⁸F-FDG PET/CT group were early-stage, compared with 2 (50%) of the 4 cancers diagnosed in the limited screening group. One occult malignancy was detected among the 186 patients who had initial negative PET results, compared with 9 of the 193 patients with negative diagnoses in the limited screening group. Five (42%) of the 12 cancers eventually diagnosed in the ¹⁸F-FDG PET/CT group were advanced, compared with 7 (54%) of the 13 cancers eventually diagnosed in the limited screening group. Two patients in the ¹⁸F-FDG PET/CT group and 5 in the limited screening group died of cancer-related causes during follow-up. The authors concluded that “a strategy including limited screening and a ¹⁸F-FDG PET/CT was not associated with a significantly

higher rate of cancer diagnosis after unprovoked venous thromboembolism.” However, the risk of subsequent cancer diagnosis was “lower in patients who had negative initial screening that included ^{18}F -FDG PET/CT than in patients who had negative initial limited screening.” They added that “whether or not ^{18}F -FDG PET/CT might be useful in a more selected population of patients with a high risk of cancer remains to be determined.”

The Lancet. 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 Newslines editor recommends several reviews accessioned into the PubMed database in November and December. Awan et al. from the Case Comprehensive Cancer Center, University Hospitals, and Case Western Reserve University School of Medicine (Cleveland, OH) provided an overview of the “Application of positron emission tomography/computed tomography in radiation treatment planning

for head and neck cancers” in the November 28 issue of the *World Journal of Radiology* (2015;7:382–393). On December 4, ahead of print in *Nature Reviews. Neurology*, Iqbal et al. from the New York State Institute for Basic Research in Developmental Disabilities (Staten Island, NY) published “Tau and neurodegenerative disease: the story so far.” Mondello et al. from the University of Messina (Italy), Memorial Sloan-Kettering Cancer Center (New York, NY), Hospital S. Maurizio (Bolzano/Bozen, Italy), and Medical University Innsbruck (Austria) offered perspective on “ ^{90}Y -ibritumomab tiuxetan: a nearly forgotten opportunity” on December 9 ahead of print in *Oncotarget*. In an article e-published on November 28 ahead of print in *Biochimica et Biophysica Acta*, Janssen et al. from the VU University Medical Center (Amsterdam, The Netherlands) surveyed “Imaging of neuroinflammation in Alzheimer’s disease, multiple sclerosis and stroke: recent developments in positron emission tomography.” The article was part of a special issue titled “Neuroinflammation” and edited by de Vries and Schwaninger. “Antibody-mediated delivery of thera-

peutics for cancer therapy” was reviewed by Parakh et al. from the Olivia Newton-John Cancer Research Institute, La Trobe University, Austin Health, and the University of Melbourne (all in Melbourne, Australia) on December 10 ahead of print in *Expert Opinion on Drug Delivery*. In an extended article in the December 7 issue of *Annual Review of Biomedical Engineering* (2015; 17:385–414) Vaquero and Kinahan from the Universidad Carlos III de Madrid (Spain) and the University of Washington (Seattle) described “Positron emission tomography: current challenges and opportunities for technological advances in clinical and preclinical imaging systems.” England et al. from the University of Wisconsin Madison offered an overview of “Molecular imaging of pancreatic cancer with antibodies” on December 10 ahead of print in *Molecular Pharmaceutics*. On December 14, ahead of print in *ACS Chemical Neuroscience*, Zhang et al. from the Academy of Military Medical Sciences (Beijing, China) reported on “Advances of molecular imaging for monitoring the anatomical and functional architecture of the olfactory system.”