

Medicine for the Royal College of Physicians and Surgeons of Canada from 1976 to 1978. In 1981 he represented Canada as a delegate to the First Congress of International

Physicians for the Prevention of Nuclear War. He was recognized by SNM in 1987 with an award and was profiled in *Newsline* (*J Nucl Med.* 1987;28:791). He was the 1990

president of the World Federation of Nuclear Medicine and Biology and hosted the group's meeting in Montreal.

SNM

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## FROM THE LITERATURE

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*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.*

### Genotype and Amyloid in AD

In an article e-published on October 1 ahead of print in *Biological Psychiatry*, Thambisetty et al. from the National Institutes of Health (NIH; Baltimore, MD) reported on the effect of complement CR1, a newly identified gene associated with risk for late-onset Alzheimer disease (AD) in cognitively normal older individuals, on brain amyloid burden in aging and its modification by APOE genotype. The study was part of a neuroimaging subarm of the Baltimore Longitudinal Study of Aging and included 57 nondemented older individuals (mean age, 78.5 y). A replication study included data from 22 cognitively normal older individuals (mean age, 77.1 y) enrolled in the AD Neuroimaging Initiative study. All participants underwent <sup>11</sup>C-Pittsburgh Compound (<sup>11</sup>C-PiB)

imaging to quantify brain amyloid burden and were characterized as APOE ε4 carriers or noncarriers and as carriers or noncarriers of the CR1 risk allele.

Brain amyloid burden was found to be lower in the group with the CR1 risk variant than in the group without it, a difference that was significant in several brain regions, suggesting that the CR1 risk factor gene, if it contributes to AD, does so in a way unrelated to increasing amyloid burden. Among noncarriers of the CR1 risk allele, APOE ε4 individuals showed significantly higher brain amyloid burden than did APOE ε4 noncarriers.

The study results provided evidence that suggest complex mechanisms underlying the interaction of CR1, APOE, and brain amyloid pathways in AD. "The findings suggest that the increased risk of AD associated with CR1 is not driven by an increase in amyloid in the brain and that we may also need to consider multiple genetic risk factors in combination," said Thambisetty in an NIH press release. "It may be possible that CR1 acts through other mechanisms, distinct from those that increase amyloid deposition in the brain. These may include influencing inflammation in the brain, but further research is needed to identify what these other mechanisms might be."

*Biological Psychiatry*

### PET Guidelines in Head and Neck Cancer

Yoo et al. from the Victoria Hospital/London Health Sciences Center (Ontario) reported on September 25 ahead of print in *Clinical Oncology* (*Royal College Radiologists*) on evi-

dence-based practice guideline recommendations for the use of <sup>18</sup>F-FDG PET for diagnosis, staging, and assessing treatment response, restaging, or recurrence of head and neck cancer. The authors updated and used a previously published systematic review of the literature (*Health Technol Assess.* 2007;11: iii-iv, xi-267) as the evidence base for recommendation development. Results of the review led the authors to recommend PET imaging in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma in which conventional imaging is equivocal or where treatment may be significantly modified. PET was also recommended in all patients after conventional imaging and in addition to or prior to diagnostic panendoscopy when the primary site is unknown. In addition, PET was recommended for staging and assessment of recurrence in patients with nasopharyngeal carcinoma when conventional imaging is equivocal and for restaging patients being considered for major salvage treatment, including neck dissection. The drafted recommendations made by Yoo et al. were reviewed, adapted, and accepted by consensus by the Ontario provincial Head and Neck Disease Site Group and a special meeting of clinical experts.

*Clinical Oncology (Royal College Radiologists)*

### PET/CT in Cholecystitis

In an article appearing in the October issue of *American Surgery* (2012;78:1109-1113), Nasseri et al. from Cedars-Sinai Medical Center (Los Angeles, CA) reported on <sup>18</sup>F-FDG PET/CT as a novel approach in

diagnosis of cholecystitis after equivocal ultrasound imaging. The study included 19 patients with suspected cholecystitis who underwent  $^{18}\text{F}$ -FDG PET/CT imaging. Ten patients had positive PET/CT results, and 9 of these proceeded to cholecystectomy. Pathology in all 9 confirmed cholecystitis. The remaining PET/CT-positive patient was managed nonoperatively because of multiple comorbidities. In the 9 patients with negative PET/CT results, 6 were managed nonoperatively and discharged, with no readmissions over a follow-up period. The remaining 3 patients with negative PET/CT underwent cholecystectomy. Pathology in 2 showed no cholecystitis, and the remaining patient had mild-to-moderate cholecystitis with focal mucosal erosion/ulceration but without gallbladder wall thickening. The authors concluded that  $^{18}\text{F}$ -FDG PET/CT “appears to be a promising, rapid, direct, and accurate test in diagnosing cholecystitis and could replace the hepatobiliary iminodiacetic acid scan in cases that remain equivocal after ultrasound.”

*American Surgery*

## PET in PTLD

Dierickx et al. from University Hospitals Leuven (Belgium) reported on October 12 ahead of print in *Haematologica* on a study assessing the sensitivity, specificity, positive and negative predictive values, and accuracy of  $^{18}\text{F}$ -FDG PET in suspected or biopsy-proven posttransplant lymphoproliferative disorder (PTLD). The study included a retrospective review of 150 organ and hematopoietic stem cell transplant recipients who had undergone  $^{18}\text{F}$ -FDG imaging for an indication of PTLD. Results from a total of 170 scans were compared with tissue biopsy when possible. In 45 patients, biopsy had already confirmed PTLD, and PET was performed for staging purposes. In the remaining 125 cases, PET was indicated to differentiate between PTLD and other diseases. The authors found an overall sensitivity of 89%, specificity of 89%, and positive and negative predic-

tive values of 91% and 87%, respectively, for PET detection of PTLD. In the subset of 125 scans performed to differentiate PTLD from other diseases, sensitivity, specificity, and positive and negative predictive values were 90%, 89%, 85%, and 93%, respectively. Tracer uptake in PTLD was generally high, with a median mean value of 9.0 and maximized standardized uptake value of 17.4. PTLD often had an atypical presentation on PET, with a high incidence of extranodal involvement. The authors concluded that  $^{18}\text{F}$ -FDG PET is “highly sensitive for detecting PTLD and has an excellent ability to differentiate PTLD from nonmalignant diseases.”

*Haematologica*

## PET/CT Hypoxia Imaging in Head and Neck Cancer

Mortensen et al. from the Aarhus University Hospital (Denmark) reported on October 16 ahead of print in *Radiotherapy and Oncology* on a study evaluating the prognostic utility of  $^{18}\text{F}$ -fluoroazomycin arabinoside ( $^{18}\text{F}$ -FAZA) PET/CT imaging of hypoxia in patients receiving radiotherapy for squamous cell carcinoma of the head and neck (HNSCC). The study included 40 patients with HNSCC who underwent static  $^{18}\text{F}$ -FAZA PET/CT, followed by radiation therapy (66–76 Gy). The hypoxic volume on PET/CT was delineated using a tumor-to-muscle value  $\geq 1.4$ . Thirteen patients underwent a second scan during the radiation therapy treatment. PET/CT was successful in identifying a hypoxic volume (range, 0.0–30.9  $\text{cm}^3$ ; median, 0.3  $\text{cm}^3$ ) in 25 (63%) of the 40 patients. The  $T_{\text{max}}/M_{\text{med}}$  ranged from 1.1 to 2.9 (median, 1.5). Hypoxia was detected in 6 of the 13 patients scanned during radiation therapy, and in these 6 patients the hypoxia location did not change from the preliminary scan; however, the hypoxia volume decreased. In 30 of the patients a positive correlation was found between maximum tracer uptake in the primary tumor and that in the lymph node. Significant differences in disease-free survival (DFS)

were identified in patients with nonhypoxic (93% DFS) and hypoxic (60% DFS) scans over a follow-up period of 19 mo. The authors concluded that these results emphasize the role of  $^{18}\text{F}$ -FAZA PET/CT as a “a suitable assay with prognostic potential for detection of hypoxia in HNSCC.”

*Radiotherapy and Oncology*

## PET and SPECT in Epilepsy

In a study e-published on October 2 ahead of print in *Epilepsia*, Desai et al. from Dartmouth–Hitchcock Medical Center (Lebanon, NH), Massachusetts General Hospital (Boston, MA), and the University of Washington (Seattle) reported on the relative value and sensitivity of interictal PET and ictal subtraction SPECT in detection of seizure foci in patients with medically intractable epilepsy. The study database included 53 patients (average age, 32.7 y; range, 1–60 y) who had undergone intracranial electroencephalography (EEG) as well as preoperative interictal PET and ictal subtraction SPECT imaging. The sensitivity of seizure foci detection for PET and SPECT were compared with results from intracranial EEG monitoring. Only 27 patients had PET findings of reduced metabolism, but all 53 patients showed a region of relative hyperperfusion suggestive of an epileptogenic zone on SPECT. EEG monitoring identified a single seizure focus in 45 patients. PET identified the same region in 25 cases (56% sensitivity), and SPECT identified the same region as EEG in 39 patients (87% sensitivity). Intracranial EEG was concordant with either PET or SPECT in 41 patients (91%) and with both studies in 23 patients (51%). In 16 (80%) of 20 patients in whom PET did not correlate with intracranial EEG, the SPECT study agreed with EEG results. PET and intracranial EEG were concordant in 2 (33%) of the 6 cases in which SPECT did not agree with EEG. The authors concluded that although both “interictal PET and ictal subtraction SPECT studies can provide important information in the preoperative evaluation of medically intractable

epilepsy... ictal subtraction SPECT appears to be the more sensitive.” They added that when the 2 studies are used together they can provide complementary information.

*Epilepsia*

### SPECT/CCTA vs Conventional Angiography in Angina

Schaap et al. from St. Antonius Hospital (Nieuwegein, The Netherlands) reported on October 19 ahead of print in *Heart* on a study comparing the effect of hybrid myocardial perfusion SPECT/CT coronary angiography (SPECT/CCTA) with that of SPECT alone plus invasive coronary angiography in treatment and management decisions for patients with stable angina pectoris. The study included 107 patients (mean age,  $62.8 \pm 10.0$  y; 69% men, 31% women) with stable anginal complaints and an intermediate-to-high pretest likelihood for coronary artery disease. Hybrid SPECT/CCTA imaging was performed before conventional angiography in all patients. Treatment outcomes were classified as no revascularization, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Treatment decisions were made by 2 interventional cardiologists and a cardiothoracic surgeon based first on the results of hybrid SPECT/CCTA and second on results from SPECT alone plus conventional angiography. Revascularization (either PCI or CABG) was indicated in 54 (50%) patients using data from SPECT and CA. SPECT/CCTA agreed with SPECT and conventional angiography on the need for revascularization in 92% of patients. The percentage agreements of treatment decisions in patients with matched, unmatched, and normal hybrid SPECT/CCTA findings was 95%, 84%, and 100%, respectively. The authors concluded that “that patients could be accurately indicated for and deferred from revascularization based on hybrid SPECT/CCTA.”

*Heart*

### $^{18}\text{F}$ -Flutemetamol PET and Hydrocephalus

In an article e-published on October 10 ahead of print in *Acta Neuropathologica*, Rinne et al. from the University of Turku and Turku University Hospital (Finland) reported on a pooled analysis of 4 studies to determine the level of association between uptake of  $^{18}\text{F}$ -flutemetamol, the fibrillar amyloid- $\beta$  PET imaging agent, and neuritic plaques and fibrillar amyloid  $\beta$  measured by pathologic staining of cortical region biopsy samples. The studies included 52 patients with suspected normal pressure hydrocephalus who underwent prospective ( $n = 30$ ) or retrospective ( $n = 22$ ) PET imaging for detection of cerebral cortical fibrillar amyloid  $\beta$  and also underwent cortical brain biopsy during intracranial pressure measurement or ventriculoperitoneal shunting. The authors found that biopsy site and contralateral  $^{18}\text{F}$ -flutemetamol standardized uptake value ratios were significantly associated with neuritic plaque burden as assessed by histologic staining. The composite standardized uptake value ratios were also significantly associated with biopsy pathology. The overall sensitivity and specificity of PET imaging, as assessed by a consensus of readers, were 93% and 100%, respectively. The authors concluded that “noninvasive in vivo  $^{18}\text{F}$ -flutemetamol PET imaging demonstrates strong concordance with histopathology for brain fibrillar amyloid  $\beta$ , supporting its promise as a tool to assist physicians with earlier detection of the disease process and making diagnostic decisions about concomitant Alzheimer disease and other diseases associated with brain amyloidosis.”

*Acta Neuropathologica*

### PET vs SPECT in CAD

Parker et al. from the University of Connecticut School of Medicine (Farmington) and Hartford Hospital (CT) reported on October 10 ahead of print in *Circulation. Cardiovascular Imaging* on a meta-analysis of the lit-

erature designed to compare the sensitivity and specificity of cardiac PET with that of SPECT stress myocardial perfusion imaging (MPI) for  $\geq 50\%$  stenosis of any epicardial coronary artery in patients with known or suspected coronary artery disease. The searched databases contained 117 relevant studies (11,862 patients), with 108 assessing SPECT MPI, 4 assessing PET MPI, and 5 assessing both. Pooled analyses showed a significantly higher mean sensitivity with PET (92.6%) than SPECT (88.3%). No significant difference in specificity was seen. Only a few studies investigated coronary angiography with PET.

*Circulation. Cardiovascular Imaging*

### FDG Uptake and Extremity Fat in HIV

In an article e-published on October 5 in *Antiviral Therapy*, Torriani et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) reported on a study assessing the relationship between  $^{18}\text{F}$ -FDG uptake in various fat depots and metabolic/immune parameters in individuals with HIV lipodystrophy. HIV lipodystrophy is characterized by peripheral lipoatrophy, with or without central fat accumulation, and confers increased metabolic risk. The study included 13 lipodystrophic men on antiretroviral therapy who underwent whole-body  $^{18}\text{F}$ -FDG PET/CT scans and detailed metabolic/immune phenotyping. Tracer uptake in subcutaneous adipose tissue (SAT) of the extremities was found to correlate with the degree of peripheral lipoatrophy. Extremity SAT FDG uptake was also positively associated with Homeostasis Model of Assessment: Insulin Resistance scores and fasting hyperinsulinemia, whereas fat percentage of extremities was not. Extremity SAT FDG uptake was also significantly associated with CD4 count. The authors concluded that in patients with HIV lipodystrophy “SAT FDG uptake is increased in association with reduced extremity fat and may contribute to

insulin resistance” and that “noninvasive assessments of in situ inflammation using FDG PET may usefully complement histological and gene expression analyses of metabolic dysregulation in peripheral fat among HIV+ patients.”

*Antiviral Therapy*

## PET/CT and Target Volume in Gynecologic Cancer

Vees et al. from Geneva University Hospital (Switzerland) reported in the October 22 issue of *Radiation Oncology (London)* (2012;7:176) on a study designed to assess the impact of  $^{18}\text{F}$ -FDG PET/CT on target volume delineation for radiation therapy in gynecologic cancer. The study included 10 women with locally recurrent ( $n = 5$ ) or postsurgical residual ( $n = 5$ ) gynecologic cancer. Each underwent  $^{18}\text{F}$ -FDG PET/CT-based RT treatment planning. Gross tumor volumes (GTVs) were defined by 4 experienced radiation oncologists, first using contrast-enhanced CT and then the fused  $^{18}\text{F}$ -FDG PET/CT datasets. In addition, GTVs were delineated using the signal-to-background (SBR) ratio-based adaptive thresholding technique. Mismatches were analyzed, as was inter- and intra-observer variability. The mean GTV on CT (43.65 cm<sup>3</sup>) was larger than the mean GTV on PET/CT (33.06 cm<sup>3</sup>). In 6 patients, the GTV on PET/CT added substantial tumor extension outside the GTV delineated on CT. Inter- and intra-observer variability was not significantly reduced with inclusion of PET. The SBR-calculated GTV was smaller than either the CT or PET/CT volumes. The authors concluded that “the use of  $^{18}\text{F}$ -FDG PET/CT images for target volume delineation of recurrent or postsurgical residual gynecological cancer alters the GTV in the majority of patients compared to standard CT definition” and “may improve the accuracy of radiation therapy treatment planning in gynecologic cancer.”

*Radiation Oncology (London)*

## $^{99\text{m}}\text{Tc}$ -HMPAO SPECT in Mitochondrial Disease Treatment

In an article e-published on September 28 ahead of print in *Molecular Genetics and Metabolism*, Blankenberg et al. from Lucile Packard Children’s Hospital (Stanford, CA) reported on a study assessing the potential for  $^{99\text{m}}\text{Tc}$ -HMPAO, a SPECT imaging marker of cerebral blood flow and glutathione/protein thiol content, in monitoring the effects of EPI-743, an oral redox modulating, parabenzoquinone-based therapeutic for mitochondrial disease. The study included 22 patients with mitochondrial disease (Leigh disease,  $n = 7$ ; polymerase  $\gamma$  deficiency,  $n = 5$ ; mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes syndrome [MELAS],  $n = 5$ ; Friedreich ataxia,  $n = 2$ ; Kearns-Sayre syndrome,  $n = 1$ ; Pearson syndrome,  $n = 1$ ; and mtDNA depletion syndrome,  $n = 1$ ) were treated with EPI-743. Each underwent  $^{99\text{m}}\text{Tc}$ -HMPAO SPECT scanning at baseline and at 3 mo, as well as clinical/neurologic evaluations. Results found a significant linear correlation between change in cerebellar uptake of HMPAO and improvement in clinical/neurologic evaluation scores in all 22 patients. The MELAS subgroup showed a significant correlation between whole-brain tracer uptake and improvement in these scores. The authors concluded that  $^{99\text{m}}\text{Tc}$ -HMPAO SPECT “has promise as a general marker of the oxidative state of the brain and its response to redox modulating therapies.”

*Molecular Genetics and Metabolism*

## 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 Newline editor recommends several reviews accessioned into the PubMed database in Sep-

tember and October. In an article e-published on September 23 ahead of print in *Applied Radiation and Isotopes* Zimmerman, from the National Institute of Standards and Technology (Gaithersburg, MD), detailed the “Current status and future needs for standards of radionuclides used in positron emission tomography.” Mountz et al. from the University of Pittsburgh (PA) and the University of Pennsylvania (Philadelphia) described “Emerging optical and nuclear medicine imaging methods in rheumatoid arthritis” on September 25 ahead of print in *Nature Reviews. Rheumatology*. In an article e-published on October 22 ahead of print in *Pediatric Research*, Gilsanz et al. from Children’s Hospital Los Angeles (CA) reviewed the “Relevance of brown adipose tissue in infancy and adolescence.” Phinikaridou et al. from King’s College London (UK) reported on October 12 ahead of print in the *American Journal of Physiology. Heart and Circulatory Physiology* on “Advances in molecular imaging of atherosclerosis and myocardial infarction: shedding new light on in vivo cardiovascular biology.” In an article e-published on October 16 ahead of print in *Physics in Medicine and Biology*, Erlandsson et al. from University College London (UK) provided “A review of partial volume correction techniques for emission tomography and their applications in neurology, cardiology, and oncology.” Evangelista et al. from the Istituto Oncologico Veneto (Padua, Italy) reported on September 25 ahead of print in *European Radiology* on “Utility of choline positron emission tomography/computed tomography for lymph node involvement identification in intermediate-to-high-risk prostate cancer: a systematic literature review and meta-analysis.” In an article e-published on October 2 ahead of print in *European Archives of Oto-Rhino-Laryngology*, Treglia et al. from Catholic University of the Sacred Heart (Rome, Italy) outlined “The role of positron emission tomography and positron emission tomography/computed tomography in thyroid tumours: an overview.”