image reconstruction methods that efficiently produce images suitable for human interpretation from source data; (2) automated image labeling and annotation methods, including information extraction from imaging reports, electronic phenotyping, and prospective structured image reporting; (3) new machine learning methods for clinical imaging data, such as tailored pretrained model architectures and distributed machine learning methods; (4) machine learning methods that can explain the advice they provide to human users (so-called explainable AI); and (5) validated methods for image deidentification and data sharing to facilitate wide availability of clinical imaging datasets.

National Institute of Biomedical Imaging and Bioengineering

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.

Amyloid PET: Semiquantification and Grading

Chincarini, from the Istituto Nazionale di Fisica Nucleare (Genova, Italy), and other members of the European Alzheimer's Disease Consortium (EADC) from Italy, Spain, Portugal, France, Belgium, Switzerland, and Germany reported on May 4 ahead of print in *Neuroimage. Clinical* on development of a model to compare and integrate visual reading of amyloid PET images using 2 independent semiquantification methods designed to yield tracer-independent multiparametric evaluation. The study included PET/CT imaging from 175 cognitively impaired patients from multiple EADC member institutions using ^{18}F-florbetaben (n = 53), ^{18}F-flutemetamol (n = 62), and ^{18}F-florbetapir (n = 60). Scans were first classified visually as positive or negative according to approved criteria. Additional classification by 5 independent readers unaware of clinical data assigned grades of negative, mild negative, borderline, mild positive, and positive. Scan quality was visually assessed and recorded. Semiquantified assessments were provided by SUV ratio and the ELBA method. The authors measured reader agreement and inconsistency in visual assessment as well as the relationship between discrepancies on grading and semiquantification. Their results showed that it is feasible to create a map between different tracers and different quantification methods without resorting to ad hoc acquired cases. The visual scale, combined with the mathematical model, delivered cutoffs and transition regions on all fluorinated tracers and were largely independent from the population. These tracers appeared to have the same contrast and discrimination ability with respect to the negative-to-positive grading. The authors concluded that validating the integration of both visual reading and different quantifiers in a more robust framework contributes to "bridging the gap between a binary and a user-independent continuous scale."

Neuroimage. Clinical

^{18}F-NaF PET/CT vs MR or CT in Spondyloarthritis

In an article published on May 14 in *Arthritis Research and Therapy* (2019; 21:119), Raynal et al. from the Centre Hospitalier Régional Universitaire Nancy (Vandóuvre-lès-Nancy, France) and the University of Alberta (Edmonton, Canada) reported on a study intended to assess increased sacroiliac joint uptake on ^{18}F-NaF PET/CT and compare data acquired to MR imaging for inflammation and to CT for structural damages. The study included 23 patients (ages, 18–45 y) with axial or mixed spondyloarthritis. All patients had undergone pelvic radiography, MR imaging and CT scanning of the sacroiliac joint, and ^{18}F-NaF PET/CT within a month. Images were analyzed by 3 readers unaware of clinical records. MR images were assessed according to the Assessment of Spondyloarthritis International Society (ASAS) criteria and the Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Index for Assessment of Spinal Inflammation (SPARCC) method. Erosion and ankylosis were quantified on CT images using the same methodology. Abnormal uptake on ^{18}F-NaF PET was assessed using a qualitative method inspired by the ASAS criteria and 2 quantitative approaches (the PET activity score according to the SPARCC method and SUV_{max}). Imaging results showed structural sacroiliitis on 7 radiographs and 10 CTs. MR imaging in 10 patients showed inflammatory sacroiliitis, whereas PET imaging was positive in 20 patients. Positive PET findings were not correlated with positive MR images nor with structural sacroiliitis on CT. Interreader agreement was good for PET activity scores and good to excellent for SUV_{max}. These PET metrics were correlated with SPARCC inflammation scores but not with erosion or ankylosis scores on CT scan. The authors concluded that "further studies with a control group and a larger sample are needed to evaluate the

sensitivity and specificity" of ^{18}F-NaF PET imaging in this disease setting.

Arthritis Research and Therapy

PET/CT and Complications After Abdominal Aortic Aneurysm Repair

Courtois et al. from the University of Liège (Belgium), the Karolinska University Hospital (Stockholm, Sweden), and the Clinique Geoffroy Saint-Hilaire (Paris, France) reported on May 10 ahead of print in the *Journal of Endovascular Therapy* on a study designed to determine whether aortic ^{18}F-FDG uptake on PET/CT could play a role in predicting complications after endovascular aneurysm repair. The study included 51 men (ages, 69–81 y) whose abdominal aneurysms had been surgically repaired: 17 of whom underwent PET/CT imaging before repair and 34 of whom underwent PET/CT during postsurgical follow-up (≤5 y for the 2 groups, with a median follow-up of 3 y). The D-dimer marker of fibrinolysis was assessed in blood samples acquired at the time of PET/CT imaging. PET/CT was negative in 11 patients before surgery, but significant ^{18}F-FDG uptake was seen in the aneurysm wall in 6 patients. During the first year after repair surgery, type II endoleaks developed in 5 of these patients whose presurgical PET imaging was positive but only 3 whose PET imaging had been negative. Two of the PET-positive patients had continued sac growth and required conversion to open repair. The authors noted a significant association between sac growth rate, SUV, and the presence of endoleak in the 34 patients who underwent PET/CT after the original repair surgery. Serum studies also found that D-dimer was significantly increased in patients with both endoleak and positive PET/CT imaging in the postrepair group. The authors concluded that "PET/CT may offer a double benefit as a predictor and detector of complications such as type II endoleaks" and that D-dimer could point toward potential new biomarkers to detect the presence of type II endoleaks and postrepair negative outcomes. They called for a larger prospective study to confirm the positive predictive value of PET/CT.

Journal of Endovascular Therapy

Longitudinal TSPO PET and Pain

In an article e-published on May 8 ahead of print in *Pain*, Cropper et al. from Stanford University (CA) reported on the potential utility of translocator protein-18kDa (TSPO) PET imaging in elucidating the temporal dynamics of peripheral and central inflammatory responses in a mouse model of complex regional pain syndrome (CRPS). The model was created in C57BL/6 wild-type mice by tibial fracture and casting, with ^{18}F-GE-180 imaging serially from baseline through 20 weeks postinjury. PET was assessed for its ability to noninvasively track inflammation associated with CRPS, including activation and recruitment of innate immune cells (both macrophages and microglia). PET showed increased peripheral inflammation in mouse tibia as early as 2 d after injury, lasting for 7 wk. Centralized inflammation was also visualized in the spinal cord and brain at 7 and 21 days after injury. TSPO expression was seen on spinal cord tissue immunofluorescent staining in microglia at 7 d but was restricted mainly to endothelial cells at baseline and 7 wk. These data suggested that early and persistent peripheral myeloid cell activation and transient central microglial activation are limited to the acute phase of CRPS. The authors concluded that "TSPO PET provides critical information on the spatiotemporal dynamics of the innate immune system response to injury and can be exploited for therapeutic decision making." They added that these and translated studies in humans "not only have the potential to focus treatment efforts on disease stage but may also highlight pain generators that were previously unrecognized."

Pain

^{68}Ga-PSMA PET/CT in Postoperative PCa Recurrence

De Bari et al. from the Centre Hospitalier Régional Universitaire Jean-Minjoz (Besançon, France), the Istituto Di Ricovero e Cura a Carattere Scientifico Sacro Cuore Don Calabria Hospital (Negrar-Verona, Italy), Sacred Heart University Hospital (Rome, Italy), University Hospital/LMU Munich (Germany), and the University of Brescia (Italy) reported on May 11 ahead of print in *Cancer Radiotherapie* on a study intended to define the pattern of relapse of postoperative prostate cancer by using ^{68}Ga-labeled prostate-specific membrane antigen (^{68}Ga-PSMA) PET/CT. The study included 40 men who underwent ^{68}Ga-PSMA PET/CT to assess for biochemical failure and potential radiation treatment. The pelvic clinical target volume was contoured according to Radiation Therapy Oncology Group (RTOG) guidelines, with bone metastases considered as outside the clinical target volume. The 32 patients with disease-positive results were then categorized as having relapsed inside or outside of the clinical target volume. Eight of the 32 patients (25%) had lymph node failure inside the clinical target volume, and 22 (68.75%) had nodal relapses outside, with the 2 (6.25%) remaining patients having relapses in both locations. Among all patients, 36 PET-positive lymph node lesions were identified, including 23 (63%) nodal relapses within the clinical target volume contoured according to RTOG guidelines and/or at the lomboaortic level. The authors noted that to cover 95% of these 23 relapses, a hypothetical clinical target volume for radiation should include the nodal regions of the RTOG-defined clinical target volume as well as the paraaortic lymph node level up to T12-L1, regions at risk for an occult relapse. They added that "in our experience, ^{68}Ga-PSMA PET/CT allows an early detection and definition of the pattern of recurrence in patients with prostate cancer previously treated with radical prostatectomy with or without adjuvant radiotherapy or androgen deprivation therapy," adding that modern imaging modalities can help radiation oncologists in tailoring the indications for adjuvant/salvage radiotherapy.

Cancer Radiotherapie

CRH Stimulation and ^{18}F-FDG PET in Cushing Adenoma

In an article e-published on May 6 ahead of print in *Endocrine*, Boyle et al. from the National Institute of Neurological Diseases and Stroke (Bethesda, MD), the University of Illinois College of Medicine at Peoria, the Warren Grant Magnuson Clinical Center at the National Institutes of Health (Bethesda, MD), George Washington University (Washington, DC), the University of Colorado (Denver), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Bethesda, MD), MedStar Washington Hospital Center (Washington, DC), the National Institute of Diabetes and Digestive and Kidney Diseases (Bethesda, MD), and The Ohio State University (Columbus) reported on a study evaluating the utility of corticotropin-releasing hormone (CRH) stimulation in improving ^{18}F-FDG PET detection of pituitary adenomas in Cushing disease. The study included 27 individuals (20 women, 7 men) with likely Cushing disease diagnoses who underwent ^{18}F-FDG PET imaging at baseline and at 3.6 ± 1.5 follow-up (twice at each time point, with ovine CRH stimulation and without). SUVs in the sella were calculated, and 2 neuroradiologists visually interpreted the images. Additional histopathology and genetics studies were performed. The researchers found that the mean SUV in adenomas significantly increased from baseline to follow-up with CRH administration. Visual assessments agreed that adenomas were visible on 21 scans and not visible on 26 and disagreed on 7. CRH stimulation also led to the detection of 6 additional adenomas not visible on baseline PET. Of the 5 MR-negative adenomas, 2 were detected on PET (1 only after CRH stimulation). The authors concluded that their results suggest that ovine CRH stimulation "may lead to increased ^{18}F-FDG uptake and increased rate of detection of corticotropinomas in Cushing disease. They added that "these results also suggest that some MRI-invisible adenomas may be detectable by ovine CRH–stimulated ^{18}F-FDG PET imaging."

Endocrine

^{68}Ga-DOTA-Octreotate PET/CT in SDH-Associated PPGL Surveillance

In an article e-published on April 12 ahead of print in the *Journal of Clinical Endocrinology and Metabolism*, Kong et al. from the Peter MacCallum Cancer Centre (Melbourne), the University of Melbourne (Parkville), and the Royal Melbourne Hospital (Parkville) reported on the incremental value of ^{68}Ga-DOTA-octreotate PET/CT imaging in surveillance of germline succinate dehydrogenase (SDHx) mutation carriers after treatment for or at risk of pheochromocytoma or paraganglioma (PPGL). Current recommendations include periodic whole-body MR imaging in such patients, who are at increased risk of developing additional disease. The retrospective study included 20 patients (10 men, 10 women; median age, 46 y): 14 with SDHB, 4 with SDHD, 1 with SDHC, and 1 with SDHA mutations. Fifteen of these individuals had undergone previous surgery and radiotherapy. Indications for ^{68}Ga-DOTA-octreotate PET/CT included monitoring because of previously treated disease (n = 7), for residual disease (n = 9), for asymptomatic mutations (n = 2), and for raised catecholamines (n = 2). Median time between imaging with the 2 modalities was 1.5 mo. Lesion detection results were compared between MR and CT imaging on a per-patient, per-lesion basis and were verified with results from histopathology and/or clinical follow-up. On a per-patient basis, PET/CT sensitivity and specificity were both 100%; corresponding figures for MR/CT were 85% and 50%. On a per-lesion basis, PET/CT sensitivity was 100% and specificity was 75%; corresponding figures for MR/CT were 80% and 25%. PET/CT also correctly identified additional small nodal and osseous lesions, whereas MR/CT imaging provided more false-positive findings. The addition of ^{68}Ga-DOTA-octreotate PET/CT resulted in a change in management for 8 (40%) patients: 3 underwent localized treatment instead of observation, 1 was changed to observation on the basis of extra disease detected, and 4 with metastases proceeded to radionuclide therapy. The authors concluded that incorporation of ^{68}Ga-DOTA-octreotate PET/CT as part of surveillance in individuals with SDHx-associated PPGL "seems prudent" but that additional research is needed to define optimal surveillance strategies.

Journal of Clinical Endocrinology and Metabolism

PET/CT in Left-Sided Endocarditis: Native vs Prosthetic Valves

De Camargo et al. from the University of São Paulo Hospital/Medical School (Brazil), the Hospital Israelinta Albert Einstein (São Paulo, Brazil), the Brigham and Women's Hospital/Harvard Medical School (Boston, MA), the Hospital of the University of Pennsylvania (Philadelphia), and the Northern Ireland Public Health Laboratory/Belfast City Hospital (Northern Ireland) reported on April 5 ahead of print in *Clinical Infectious Diseases* on a study of the utility of ^{18}F-FDG PET/CT in the diagnosis of native valve infective endocarditis. The study included the records of 303 episodes of left-sided suspected infective endocarditis in 188 patients with prosthetic valves/ascending aortic prostheses and 115 patients with native valves. The accuracy of ^{18}F-FDG PET/CT was evaluated in the 2 groups, as well as inflammatory patterns and tracer uptake. In the group with prosthetic valves and aortic prostheses, the sensitivity, specificity, and positive and negative predictive values of ^{18}F-FDG PET/CT focal uptake were 93%, 90%, 89%, and 94%, respectively. The corresponding figures for patients with native valves were 22%, 100%, 100%, and 66%. ^{18}F-FDG uptake classification as "abnormal" at admission, when added to current criteria, enabled a recategorization of 76% (47/62) of patients in the prosthetic valve/aortic prosthesis group from "possible" to "definite" infective endocarditis. In the separate histopathology analysis, a predominance of polymorphonuclear neutrophils in the inflammatory infiltrate and reduced fibrosis were found only in the prosthetic valve group. The authors concluded that the addition of ^{18}F-FDG PET/CT at initial presentation of patients with suspected

prosthetic valve endocarditis increases the diagnostic capability of current criteria. In patients presenting with suspected native valve endocarditis, however, ^{18}F-FDG PET/CT is less accurate and "could only be considered a complementary diagnostic tool for a specific population of patients with native valve endocarditis."

Clinical Infectious Diseases

Head Injury and Brain Amyloid Deposition

In an article e-published on April 9 ahead of print in the *Journal of Neurotrauma*, Schneider et al. from the Johns Hopkins University School of Medicine (Baltimore, MD), the Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD), the National Institute of Neurological Disorders and Stroke (Bethesda, MD), Tel Aviv University (Israel), the University of Mississippi Medical Center (Jackson), and Wake Forest University (Winston-Salem, NC) reported on results from the Atherosclerosis Risk in Communities—PET (ARIC-PET) Study of patients who underwent ^{18}F-florbetapir PET imaging with a history of head injury (defined as self-reported or by emergency department/hospitalization ICD-9 codes). The goal was to look at associations between head injury with total and regional brain amyloid deposition. The study included 329 nondemented participants (81 with prior head injury) who underwent ^{18}F-florbetapir PET imaging from 2012 to 2014. The researchers derived prevalence ratios for elevated (>1.2) global and regional SUV ratios (SUVRs). The mean age of participants was 76 y (57% women, 43% men; 43% of participants were black). Head injury was found to be correlated with increased prevalence of elevated global SUVR, as well as with elevated uptake in the orbitofrontal cortex, prefrontal cortex, superior frontal cortex, and posterior cingulate. Evidence was also found for a dose–response relationship in which a history of more than 1 head injury was associated with an SUVR >1.2 in the prefrontal and superior frontal cortices, a much greater association than in individuals with a history of only 1 head injury. The authors concluded that "head injury was associated with increased amyloid deposition globally and in the frontal cortex and posterior cingulate, with suggestion of a dose–response association of head injuries with β-amyloid deposition." They called for additional studies to determine whether increased amyloid deposition contributes to dementia in this population.

Journal of Neurotrauma

Preoperative PET/CT in Thymic Epithelial Tumors

Ishibashi et al. from Tottori University School of Medicine (Yonago, Japan) reported on March 28 in *Yonaga Acta Medica* (2019;62:146–152) on a study exploring the relationship between ^{18}F-FDG PET/CT findings and World Health Organization (WHO) classification or Masaoka staging of thymic epithelial tumors. The retrospective review included 32 patients with histologically proven thymic epithelial tumors (17 low-risk thymomas [1 type A, 9 type AB, and 7 type B1], 8 high-risk thymomas [4 type B2 and 4 type B3], and 7 thymic carcinomas [squamous cell carcinoma]). Masaoka staging system categorization included 24 as early stage (stages I and II) and 8 as advanced stage (stage III). All patients underwent ^{18}F-FDG PET/CT imaging before surgery. Multiple PET parameters were compared with Masaoka staging and WHO classification to identify PET parameter cutoff values for accurate differentiation of early and advanced stages. The researchers found that only SUV_{max} was a meaningful differentiator in the WHO classification system, whereas all analyzed PET parameters were significantly higher in the advanced stage than the early stage in Masaoka classification. Among the PET parameters, total lesion glycolytic activity was best correlated in predicting early and advanced stages in thymic epithelial tumors with maximal sensitivity and specificity, and with a cutoff value of 30.735. The authors concluded that although a significant correlation between SUV_{max} and the WHO classification was noted in this setting, volumetric PET parameters may achieve more precise staging in the Masaoka system than SUV_{max}.

Yonaga Acta Medica

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 systematic and general reviews accessioned into the PubMed database in May. Kiuchi et al. from the University of Western Australia/Royal Perth Hospital the Universidade Federal Fluminense (Niterói, Rio de Janeiro, Brazil), and the Baker Heart and Diabetes Institute (Melbourne, Australia) described "New approaches in the management of sudden cardiac death in patients with heart failure: Targeting the sympathetic nervous system" on May 16 ahead of print in the *International Journal of Molecular Sciences*. In an article in the May 1 issue of the *Journal of the National Comprehensive Cancer Network* (2019; 17:506–513), Mason et al. from the Washington University School of Medicine (St. Louis, MO), Memorial Sloan Kettering Cancer Center (New York, NY), the Mayo Clinic (Rochester, MN), the University of Colorado (Denver), and Harvard Medical School (Boston, MA) provided an overview of the "Current status of MRI and PET in the NCCN Guidelines for Prostate Cancer." Hellwig and Domschke, from the University of Freiburg (Germany) provided an "Update on PET imaging biomarkers in the diagnosis of neuropsychiatric disorders" on May 6 ahead of print in *Current Opinion in Neurology.*