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.

PET/CT as a Predictor in Primary Gastric Adenocarcinoma

Harada et al. from the University of Texas MD Anderson Cancer Center (Houston, TX) and Kumamoto University (Japan) reported on May 14 ahead of print in *Surgery Today* on the potential of pretreatment SUV_{max} and total lesion glycolysis as assessed on PET/CT as predictors of response to chemoradiation therapy (CRT) in patients with localized gastric adenocarcinoma. The study included data from 59 such patients who underwent preoperative CRT. Relationships between PET/CT metrics and pathologic complete response and overall survival were analyzed. Of the 59 patients, 29 (49%) had Siewert type III adenocarcinoma and 30 (51%) had tumors in the lower stomach. Disease was poorly differentiated in 41 patients, and 26 had signet ring cells. Over all, the median SUV_{max} was 7.3 (range, 0–28.2), and the median total lesion glycolysis was 56.6 (0–1,881.5). Patients with signet ring cells were found to have low pathologic complete response rates, SUV_{max}, and total lesion glycolysis. On additional analysis, high SUV_{max} was found to be a predictor of pathologic complete response, but neither SUV_{max} nor total lesion glycolysis was associated with overall survival. The authors concluded that "a high SUV_{max} was associated with sensitivity to chemoradiation and pathologic response in gastric adenocarcinoma, and signet ring cells seemed to confer resistance."

Surgery Today

^{18}F-FMISO vs ^{64}Cu-ATSM PET in Focal Cerebral Ischemia

In an article e-published on May 19 ahead of print in the *Journal of Cerebral Blood Flow and Metabolism*, Little et al. from the Karolinska Institutet/Karolinska University Hospital (Stockholm, Sweden) and the Technical University of Denmark (Roskilde) reported on a study comparing ^{18}F-FMISO and ^{64}Cu-ATSM PET as hypoxia tracers in focal cerebral ischemia in a murine M2 occlusion model with preserved collateral blood flow. Rats underwent the occlusion procedure and imaging with either ^{18}F-FMISO or ^{64}Cu-ATSM, with the latter group also undergoing MR imaging. Levels of hypoxia in neurons and astrocytes were assessed by immunofluorescence analysis, with pimonidazole as a surrogate for ^{18}F-FMISO. An increase in ^{18}F-FMISO uptake but not ^{64}Cu-ATSM uptake was found in the occluded cortex. Pimonidazole intensity in neurons and astrocytes was increased in hypoxic regions, an intensity that was higher in neurons than astrocytes. In most rats, immunofluorescence showed a loss of astrocytes in regions with increased pimonidazole uptake. The authors concluded that ^{18}F-FMISO is superior to ^{64}Cu-ATSM in detecting hypoxia in acute ischemic stroke. In addition, "^{18}F-FMISO may provide efficient diagnostic imaging beyond the hyperacute phase." They added that "results do not provide encouragement for the use of ^{64}Cu-ATSM in experimental acute ischemic stroke."

Journal of Cerebral Blood Flow and Metabolism

Understanding ^{18}F-Fluciclovine PET/CT Reports

Lowentritt, from Chesapeake Urology (Towson, MD), and Kipper, from Genesis Healthcare (San Diego, CA), provided on April 26 ahead of print in *Prostate Cancer* a helpful primer for referring physicians on understanding and interpreting results from ^{18}F-fluciclovine PET/CT in men with biochemical recurrence of prostate cancer. The authors noted that in the absence of a standardized grading system for such imaging assessment, interpretation may be challenging. They listed 6 key features of which referring physicians should be aware: (1) The attributes of the tracer as a radiolabeled synthetic amino acid targeting the amino acid transporters ASCT2 and LAT1, overexpressed in prostate cancer. (2) The fact that ^{18}F-fluciclovine PET/CT image interpretation is mainly visual and qualitative, with radiotracer uptake in suspicious lesions compared against uptake in bone marrow or blood pool. (3) ^{18}F-fluciclovine PET/CT detection rates increase as prostate-specific antigen (PSA) levels rise. (4) Detection rates may vary among centers, possibly as a result of different equipment and variations in reader experience. (5) ^{18}F-fluciclovine PET/CT data (like any imaging results) should not be used in isolation. (6) ^{18}F-fluciclovine PET/CT results have frequently led to changes in disease management plans. The authors added that communication is key to improving results: physicians and imaging physicians should collaborate to improve the quality and utility of reports. Referrers should clearly convey critical information, including prescan PSA levels, and raise pertinent clinical questions. Imaging specialists should provide complete consultative reports, including thoughts on next diagnostic steps. The article provides valuable information for distribution to referring physicians of patients with prostate cancer.

Prostate Cancer

FDG PET/MRI in Renal Transplant

In an article e-published on May 19 ahead of print in *Scientific Reports*, Pajenda et al. from the Medical University of Vienna (Austria) reported on the use of ^{18}F-FDG PET/MR imaging for functional graft assessment in patients after solid organ kidney transplantation with acute kidney injury. The study included 13 such patients and 24 healthy volunteers who served as controls. SUVs and time/activity curves were used to assess general kidney performance, initial flow, and renal response function. General kidney performance for the total kidney and medulla was significantly higher for the volunteers than the patients, with no difference found in the general kidney performance of the cortex. Initial flow in the patient group was found to correlate with renal recovery, defined as change in serum creatinine 10 d after PET/MR imaging. A negative correlation between renal response function and tubular damage was identified in the patient group. The authors noted several implications of their results, including the suggestion that the repair mechanism at the proximal tubules requires glucose as an energy supply, so that "higher FDG uptake might translate into higher energy turnover and cellular repair mechanisms indicating regain of kidney function." These observations, they noted, require additional investigation. The authors concluded that "parameters obtained from FDG PET/MRI showed a possible predictive feature for renal recovery in solid organ kidney transplantation patients undergoing acute kidney injury."

Scientific Reports

Hypoxia PET in HNSCC

Zschaeck et al. from the the Technische Universität Dresden (Germany), the German Cancer Research Center (DKFZ) (Heidelberg, Germany); the Charité–Universitätsmedizin Berlin (Germany), the German Cancer Consortium (DKTK) (Dresden, Germany), Eberhard Karls University Tübingen (Germany), Aarhus University Hospital (Denmark), Odense University Hospital (Denmark), and St. Luc University Hospital (Brussels, Belgium) reported on May 14 ahead of print in *Radiotherapy and Oncology* on an analysis of original hypoxia PET imaging in a large cohort of patients with head and neck squamous cell carcinoma treated at 5 institutions on 4 prospective imaging trials. The study included 102 patients who underwent ^{18}F-FMISO hypoxia imaging and 51 who underwent ^{18}F-FAZA hypoxia imaging for localized disease and who were treated with curative radiochemotherapy. Despite baseline patient characteristics that varied widely among participating centers, maximal tumor-to-muscle ratio and hypoxic volume with a 1.6 threshold on PET were found to have strong and consistent associations with locoregional control and overall survival. Not only were these findings consistent across the 2 tracers but the same cutoff values could be used. These findings and additional analyses led the authors to conclude that PET-measured hypoxia is robust and strongly associated with locoregional control and overall survival in head and neck squamous cell cancer and that "the most commonly investigated tracers, FMISO and FAZA, can probably be used equivalently in multicenter trials." Hypoxia-directed treatment, however, did not show improved outcomes in centrally categorized hypoxic tumors, leading the authors to note that "optimal strategies to improve the dismal outcome of hypoxic tumors remain elusive."

Radiotherapy and Oncology

PET/CT in Suspected PCNSL

In an article e-published on May 13 ahead of print in the *Journal of Neuro-Oncology*, Bertaux et al. from the Hôpital Pitié-Salpêtrière (Paris), the Sorbonne Université (Paris), Institut Curie (Saint-Cloud), and the Université Paris (all in France) reported on a study assessing the potential utility of pre-chemotherapy whole-body ^{18}FDG-PET/CT in suspected primary central nervous system lymphoma (PCNSL). The retrospective study included initial PET/CT and contrast-enhanced CT imaging, bone marrow biopsy, and pathology results in 130 immunocompetent patients. Pathology analysis of central nervous system lesions determined that 95% of patients had large B-cell lymphoma, including 11 with primary vitroretinal lymphoma. Ten of the 130 patients (8%) went on to be diagnosed with systemic lymphoma involvement, including 5 confirmed on pathology, all of which were detected by PET/CT. PET/CT also showed incidental systemic findings unrelated to lymphoma in 14% of patients. The authors reported that an SUV_{max} threshold of 9 was sufficient for discrimination between systemic lymphoma and other lesions, with a sensitivity of 92% and specificity of 89%. Contrast-enhanced CT and bone marrow biopsy were inferior in detecting systemic disease. They summarized their findings: "All of our patients ultimately diagnosed with concomitant systemic involvement had positive ^{18}FDG-PET/CT. We believe it constitutes a safe one-stop shop evaluation for the systemic pretreatment imaging of suspected PCNSL."

Journal of Neuro-Oncology

PET/CT in Inflammatory Breast Cancer Staging

van Uden et al. from the Rijnstate Hospital (Arnhem), the University of Twente (Enschede), and Radboud University Medical Center Nijmegen (all in The Netherlands) reported on May 7 online ahead of print in *Critical Reviews in Oncology/Hematology* on a systematic review of the utility of ^{18}F-FDG PET/CT for initial staging in patients with inflammatory breast cancer. Their results from a broad survey of available literature showed that in 10.3% of patients PET/CT detected additional locoregional lymph node metastases and distant metastases not identified on standard staging imaging. They concluded that ^{18}F-FDG PET/CT should be used as part of the standard diagnostic work-up in inflammatory breast cancer, particularly because as many as 78% of such patients present with axillary lymph node involvement and as many as 40% with distant metastases.

Critical Reviews in Oncology/Hematology

Measuring Amyloid in Down Syndrome

In an article e-published on April 16 ahead of print in *Alzheimer's & Dementia*, Zammit et al. from the University of Wisconsin–Madison, the University of Pittsburgh (PA), the Cleveland Clinic Nevada (Las Vegas), and the University of Cambridge (UK) reported on the application of a new PET index of amyloid load, developed as an alternative to SUV ratios to quantify amyloid burden, in individuals with Down syndrome. The study included 169 such individuals (mean age, 39.6 ± 8.7 y) who underwent ^{11}C-Pittsburgh compound B PET imaging and in whom amyloid load was calculated using syndrome-specific templates for the tracer created for amyloid-carrying capacity and nonspecific binding. Longitudinal changes in the amyloid load index were less variable than SUV ratios, with the highest values of amyloid load identified in the striatum and precuneus. Rates of amyloid accumulation in Down syndrome were similar to those seen in late-onset Alzheimer disease, which suggested to the authors that Alzheimer disease progression in Down syndrome "is of earlier onset but not accelerated." They noted the utility of the PET amyloid load index for characterizing and monitoring amyloid in Down syndrome.

Alzheimer's & Dementia

^{123}I-FP-CIT SPECT in PD

Nicastro et al. from the University of Cambridge (UK) and the University of Geneva/Geneva University Hospitals (Switzerland) reported on May 16 ahead of print in *BMC Neurology* on a case-controlled analysis of ^{123}I-FP-CIT SPECT images in Parkinson disease (PD) to measure extrastriatal serotonergic transporters. Patient and control data were drawn from the Parkinson's Progression Markers Initiative cohort, a multinational observational study to identify biomarkers of disease progression. This analysis included 154 patients with PD (mean age, 61.6 y; 62% men, 38% women; average disease duration, 26 mo) and 62 control subjects who had undergone both ^{123}I-FP-CIT SPECT imaging and coregistered high-resolution T1-weighted MR imaging, as well as multiple other assessments. PD patients showed reduced uptake in the bilateral caudate nucleus, putamen, insula, amygdala, and right pallidum compared with controls. After advanced image analysis, the researchers identified a trend associating higher geriatric depression scale and lower pallidum uptake in PD, as well as associating higher Scales for Outcomes in Parkinson's Disease–Autonomic Dysfunction (SCOPA-AUT) gastrointestinal subscores with lower uptake in mean putamen and caudate nucleus. Urologic SCOPA-AUT subscores were inversely correlated with mean caudate nucleus, putamen, and pallidum uptake in PD. Other findings correlated changes on PET with reported sleep behavior. The authors concluded that "in addition to the well-established striatal deficit, this study provides evidence of a major extrastriatal ^{123}I-FP-CIT impairment, and therefore of an altered serotonergic transmission in early PD."

BMC Neurology

MTV as Local Recurrence Predictor in NSCLC

In a study e-published on May 19 ahead of print in *Radiation Oncology*, Binkley et al. from the Stanford University School of Medicine/Stanford Cancer Institute (CA) and the Indiana University School of Medicine (Indianapolis) reported on a study assessing ^{18}F-FDG PET/CT pre- and midtreatment metabolic tumor volume (MTV) prediction of per-lesion local recurrence in patients treated with definitive radiation therapy for locally advanced non–small cell lung cancer (NSCLC). The retrospective study included the records of 111 patients (median age, 68 y; 69% men, 31% women) with stage III NSCLC (387 lesions; 112 lung tumors and 275 lymph nodes; 46.8% of patients with adenocarcinoma and 39.6% with squamous cell carcinoma) who had undergone PET/CT imaging before and during radiation therapy. MTVs were measured and compared on sequential PET images, including a per-lesion analysis of local recurrence. Over a median follow-up of 38.7 mo, 3-y overall survival was 42.3% and the 3-y cumulative incidence of local recurrence was 26.8% per patient and 11.9% per lesion. MTVs at both timepoints were found to be predictive of local recurrence, and the results led the authors to conclude that midtreatment MTV "may hold higher predictive utility, particularly in the setting of small lesions." They suggested that "this may be the basis for designing adaptive dose painting strategies to maximize therapeutic index" and called for additional studies.

Radiation Oncology

Repeated PSMA PET-Directed Radiotherapy

Henkenberens et al. from the Hannover Medical School and the University of Lübeck (both in Germany) reported on May 12 ahead of print in *Strahlentherapie und Onkologie* on a study assessing outcomes in hormonenaïve patients with oligorecurrent prostate cancer after curative therapy treated with a first and second ^{68}Ga-prostate-specific membrane antigen (^{68}Ga-PSMA) PET–directed course of radiation therapy (RT). The retrospective study included 32 patients who received their first PSMA PET-directed RT of all identified metastases after relapse and their second after biochemical progression. Over a median follow-up of 39.5 mo (range, 18–60 mo), biochemical progression-free survival and androgen deprivation therapy–free survival were analyzed in relation to changes in prostate-specific antigen (PSA) levels over the survival and treatment intervals. All patients showed biochemical responses after the first PSMA PET-directed RT, and the median PSA level decreased significantly (from 1.70 ng/mL before RT to 0.39 ng/mL after). The median PSA level at biochemical progression after the first PSMA PET-directed RT was 2.9 ng/mL and at last follow-up after the second PSMA PET-directed therapy was not significantly different from the median PSMA before the first PSMA PET-directed RT. Median biochemical progression-free survival was 16.0 mo after the first PSMA PET-directed RT and was significantly shorter (8 mo) after the second. Median androgen deprivation therapy–free survival was 31.0 mo, and patients with bone metastases at

first PSMA PET-directed RT had significantly higher chances of requiring androgen deprivation therapy by the last follow-up visit. The authors concluded that "if patients are followed up closely, including PSMA PET scans, a second PSMA PET-directed RT represents a viable treatment option for well-informed and well-selected patients."

Strahlentherapie und Onkologie

^{123}I-FP-CIT SPECT in Progressive Apraxia

Seckin et al. from the Mayo Clinic/Mayo Clinic College of Medicine and Science (Rochester, MN) reported on May 9 ahead of print in the *Journal of Neurology* on a study describing ^{123}I-FP-CIT (DAT scan) SPECT findings in patients with progressive apraxia of speech and comparing these findings with those from patients with progressive supranuclear palsy and corticobasal syndrome. The study included 17 patients with apraxia of speech who underwent ^{123}I-FP-CIT SPECT, with quantitative analyses of uptake in the left and right caudate and anterior/posterior putamen, including striatum-to-background ratios. The results were compared with those from previous imaging in 15 patients with progressive supranuclear palsy and 8 with corticobasal syndrome. Five (29%) patients with progressive apraxia were found to have abnormalities in at least 1 striatal region. These 5 patients' images showed lower uptake in the posterior putamen than did patients with progressive supranuclear palsy or corticobasal syndrome. No other differences were observed. The authors concluded that an "abnormal DAT scan is observed early in the disease course in approximately 30% of progressive apraxia of speech patients, with striatal abnormalities similar to those in progressive supranuclear palsy and corticobasal syndrome."

Journal of Neurology

PET/CT and Regional LN Metastases in ESCC

In an article e-published on May 19 ahead of print in *Strahlentherapie und Onkologie*, Münch et al. from the Technical University Munich, the German Cancer Consortium (DKTK) (Munich), the Helmholtz Zentrum München (Oberschleißheim), and the Universitätsklinikum Jena (all in Germany) reported on the use of ^{18}F-FDG PET imaging to analyze patterns of regional lymph node metastasis in esophageal squamous cell carcinoma (ESCC) and their correlation with the primary tumor. The goal of the study was to evaluate the potential utility of PET/CT in guiding elective nodal irradiation. The retrospective study included 102 patients with ESCC who had undergone pretreatment PET/CT. A total of 76 patients with PET-positive lymph node metastases were included in the final analysis. All lymph node metastases were assigned to 16 predefined anatomic regions and classified according to their position relative to the primary tumor. The longitudinal distance to the primary tumor was measured for each metastasis above or below the primary tumor. The length of the primary tumor was measured using PET data and separately using all other available clinical and imaging data. Significantly more lymph node metastases were identified with PET/CT than CT alone (177 and 131, respectively). The most common lymph node metastasis sites were paraesophageal (63% of patients, 37% of metastases) and paratracheal (33% of patients, 20% of metastases), and $<$5% of patients were found to have supraclavicular, subaortic, diaphragmatic, or hilar lymph node metastases. Fifty-one percent of these metastases were at the same height as, 25% were above, and 24% were below the primary tumor. For 33 (19%) of these metastases, the distance to the primary tumor was $>$4 cm. The authors concluded that "^{18}F-FDG PET can help to identify subclinical lymph node metastases which are located outside of recommended radiation fields" and that "PET-based involved-field irradiation might be the ideal compromise between small treatment volumes and decreasing the risk of undertreatment of subclinical metastatic lymph nodes and should be further evaluated."

Strahlentherapie und Onkologie

Reviews

Review articles provide an important way to stay up to date on the latest topics and approaches through valuable summaries of pertinent literature. The Newsline editor recommends several general reviews accessioned into the PubMed database in May. Gallegos and Miller from the Yale University School of Medicine (New Haven, CT) summarized "Advances in PET-based cardiac amyloid radiotracers" on May 19 ahead of print in *Current Cardiology Reports*. On May 17 ahead of print in the *Journal of Clinical Medicine*, Lauri et al. from the Sapienza University of Rome (Italy), the University of Groningen (The Netherlands), the Università Cattolica del Sacro Cuore (Rome, Italy), and the University of Pisa (Italy) published "Imaging modalities for the diagnosis of vascular graft infections: A consensus paper amongst different specialists." Evans et al. from Macquarie University (Sydney), the Royal Prince Alfred Hospital (Camperdown), and the Australian Nuclear Science and Technology Organisation (Lucas Heights, all in Australia) reviewed "Methods to enhance the metabolic stability of peptide-based PET radiopharmaceuticals" on May 14 ahead of print in *Molecules*. On the same day in *Molecules*, Becker et al. from the University of Liège (Belgium) described "The rise of synaptic density PET imaging." On May 20 ahead of print in *Molecular Pharmaceutics*, Allott and Aboagye from Imperial College (London, UK) detailed "Chemistry considerations for the clinical translation of oncology PET radiopharmaceuticals."