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 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.

^{177}Lu-PSMA I&T Toxicities

Hartrampf et al. from University Hospital Würzburg (Germany), Johns Hopkins University School of Medicine (Baltimore, MD), and Okayama University (Japan) reported on January 27 in *Cancers (Basel)* (2022;14[3]:647) on a study evaluating the toxicity profiles of ^{177}Lu–prostate-specific membrane antigen (PSMA)–I&T in patients with metastatic, castrate-resistant prostate cancer. The study included 49 such patients treated with at least 3 cycles of ^{177}Lu-PSMA-I&T. Serum lab values were compared before and after radioligand therapy, and adverse events were documented. Under treatment, 11 (22%) patients were found to have nephrotoxicity of Common Terminology Criteria for Adverse Events (CTCAE) grades I or II by creatinine metrics and 33 (67%) as assessed by estimated glomerular filtration rate (eGFR). Only 13% showed reduced ^{99m}Tc-MAG3–derived tubular extraction rates. Over all renal functional metrics, absolute changes of only 2% were recorded. Recategorization based on renal parameters was infrequent. After 3 cycles of therapy, follow-up eGFR correlated negatively with age and eGFR change correlated with Gleason score at baseline. Leukocytopenia of CTCAE I and II was seen in 41% and 2% of patients, respectively. Thrombocytopenia of CTCAE I was seen in 14%, with absolute decreases of 15.2% and 16.6% for leukocyte and platelet counts, respectively. Thirty-six (73%) and 10 (20%) patients experienced CTCAE I and II anemia, respectively. The authors concluded that "after PSMA-targeted therapy using ^{177}Lu-PSMA I&T, no severe (CTCAE III/IV) toxicities occurred, thereby demonstrating that serious adverse renal or hematological events are unlikely to be a frequent phenomenon with this agent."

Cancers (Basel)

PET/MR and Lymphoma Imaging Biomarkers

In an article published on February 16 ahead of print in *Annals of Hematology*, Husby et al. from the Norwegian University of Science and Technology (Trondheim, Norway), St. Olavs Hospital/Trondheim University Hospital (Norway), University Hospital of North Norway (Tromsø), Aarhus University Hospital (Denmark), University Medical Center Groningen (The Netherlands), and the University Medical Centers Amsterdam (The Netherlands) reported on the diagnostic performance of ^{18}F-FDG PET/MR compared to that of ^{18}F-FDG PET/CT in a group of patients with Hodgkin lymphoma, diffuse large B-cell lymphoma, or high-grade B-cell lymphoma. A total of 61 patients were imaged with both modalities at baseline and again for response assessment after treatment. Images were interpreted by experienced physicians, and prognostic biomarkers (Deauville score, SUV_{max}, SUV_{peak}, and metabolic tumor volume [MTV]) were compared. Baseline PET/MR showed a sensitivity of 92.5% and specificity of 97.9% when compared with PET/CT as a reference standard for nodal sites. Corresponding PET/MR figures for extranodal sites were 80.4% and 99.5%. Concordance in expert reading was found in 57 patients, with disagreement attributed to misclassification of region rather than inaccuracy in lesion detection. For posttreatment response assessment, PET/MR showed a sensitivity of 100% and specificity of 99.9% for all sites combined compared to the PET/CT standard. Deauville scores 4 and 5 and criteria of response were found to be the same for the 2 modalities, with SUV_{max}, SUV_{peak}, and MTV values highly correlated. The authors concluded that "FDG PET/MR is a reliable alternative to PET/CT in this patient population, both in terms of lesion detection at baseline staging and response assessment, and for quantitative prognostic imaging biomarkers."

Annals of Hematology

Presurgical PET in Epilepsy

Steinbrenner et al. from the Charité-Universitätsmedizin Berlin (Germany), National Hospital for Neurology and Neurosurgery (London, UK), University College London Hospitals (UK), Smt. B. K. Shah (SBKS) Medical College (Vandodara, India), Evangelische Krankenhaus Königin Elisabeth Herzberge (Berlin, Germany), the Johns Hopkins School of Medicine (Baltimore, MD), and the Sree Chitra Tirunal Institute for Medical Sciences and Technology (Trivandrum, India) reported on February 15 ahead of print in *Epilepsia* on a multicenter retrospective study assessing the utility of ^{18}F-FDG PET as part of the management decision-making process in patients with drug-resistant focal epilepsy. The study included the records of 951 patients with epilepsy (temporal lobe [TLE], 479; extratemporal [ETLE], 219; and uncertain lobar origin, 253) who had undergone PET imaging as part of presurgical workups. PET indicated distinct hypometabolism in 62% and was concordant with ictal EEG in 74% of patients with TLE and 56% with ETLE. PET was determined to be useful in presurgical decision making in 396 (47%) patients, contributing to recommended resection in 78 (20%) and intracranial EEG in 187 cases (47%).

In a third of patients, PET led to the conclusion that surgery was not feasible. For patients with TLE, rates of freedom from seizures at 1 y after surgery did not differ between patients with negative MR and EEG–PET concordance (n = 30) and those with positive MR and concordant EEG (n = 46). Half of patients with ETLE with negative MR and EEG–PET concordance and three-fourths of those with positive MR and concordant EEG were seizure free at 1 y. The authors noted that this is by far the largest reported study of presurgical PET in patients with drug-resistant focal epilepsy and that their findings "confirm the significance of FDG PET in presurgical epilepsy diagnostics."

Epilepsia

^{177}Lu-PSMA-617 RLT After Failed ^{223}Ra-Dichloride

In an article in the January 22 issue of *Cancers (Basel)* (2022;14[3]:557), Baumgarten et al. from University Hospital Frankfurt (Germany) reported on the safety and efficacy of ^{177}Lu-prostate-specific membrane antigen (PSMA)–617 in patients with metastatic castrate-resistant prostate cancer and progressive bone involvement under treatment with ^{223}Ra-dichloride. The study included 28 such men (median age, 73 y; range, 63–89 y) with progressive disease who started ^{177}Lu-PSMA-617 within 8 wk after the last ^{223}Ra administration. Patients had received a median of 4 and a group total of 120 cycles of ^{223}Ra and then received a median of 4 cycles of ^{177}Lu-PSMA-617 with a mean treatment activity of 6.5 ± 1.2 GBq per cycle (mean cumulative activity of 30.7 ± 23.4 GBq). Serum responses (≥50% decline in prostate-specific antigen 12 wk after the first ^{177}Lu-PSMA-617) were observed in 18 (64.3%) patients. Imaging-based partial remission was seen in 11 (39.3%) patients. The median imaging-based progression-free survival was 10 mo and median overall survival (OS) was 18 mo. Patients with fewer bone lesions (2–20) had significantly longer OS (28 mo) than those with higher tumor burdens (14 mo). Six patients experienced grade ≥3 hematologic toxicities after their last treatment cycle, including anemia, leukopenia, and thrombocytopenia. The authors concluded that "in progressive bone-metastatic castrate-resistant prostate cancer patients, prompt initiation of ^{177}Lu-PSMA-617 after failing ^{223}Ra is effective with an acceptable toxicity profile."

Cancers (Basel)

Automated Image-Based Diagnosis in Parkinsonism

Papathoma et al. from the Karolinska Institutet (Stockholm, Sweden), Danderyd's Hospital (Stockholm, Sweden), the Academic Specialist Center (Stockholm, Sweden), and the Feinstein Institute for Medical Research (Manhasset, NY) reported in the February 17 issue of *Scientific Reports* (2002;12[1]: 2763) on a systematic assessment of the accuracy of a previously developed ^{18}F-FDG PET–based automated algorithm in the diagnosis of parkinsonian syndromes, including unpublished data from a prospective cohort. The study included first a series of 35 patients in which the automated image-based classification method showed excellent sensitivity and specificity for discriminating Parkinson disease from atypical parkinsonian syndromes. A systematic literature review and metaanalysis showed similar results (pooled sensitivity and specificity of 84% and 96%, respectively). The authors concluded that this ^{18}F-FDG PET automated analysis has excellent diagnostic potential early in the disease course and "may be a valuable tool in clinical routine as well as in research applications."

Scientific Reports

PET/CT and MALT Lymphoma Staging

In an article in the January 31 issue of *Cancers (Basel)* (2022;14[3]:750), Cohen et al. from the Tel Aviv Sourasky Medical Center and Tel Aviv University (Israel) reported on the role of ^{18}F-FDG PET/CT in staging and prediction of progression-free survival (PFS) in patients with newly diagnosed mucosa-associated lymphoid tissue (MALT) lymphoma. The retrospective study included 66 such patients. PET detected extranodal lesions in 38 (57.6%) patients and accompanying nodal disease in 13 (19.7%). The detection rate for extranodal lesions was higher in those located in tissues with low/homogeneous tracer uptake than in those with high/heterogeneous uptake (100% and 40.4%, respectively). Nodal lesions were found to have significantly lower SUV_{max}, metabolic tumor volume, and total lesion glycolysis than extranodal lesions in the same patients. The rates of detection and tracer avidity of extranodal lesions were higher in patients with advanced bulky disease and associated marrow/nodal involvement. Higher SUV_{max} in extranodal lesions predicted shorter PFS. Higher SUV_{max} and total lesion glycolysis trended toward shorter PFS in patients with localized disease. The authors concluded that "SUV_{max} of extranodal lesions may predict PFS" in patients with newly diagnosed MALT.

Cancers (Basel)

PSMA PET/CT and Prostate Cancer Outcomes

Bodar et al. from Amsterdam University Medical Center/VU University (The Netherlands) and the Prostate Cancer Network/The Netherlands Cancer Institute (Amsterdam) reported on February 15 ahead of print in *BJU International* on a study investigating associations between intraprostatic, intratumoral SUV_{max} on prostate-specific membrane antigen (PSMA) PET/CT in patients with prostate cancer before robot-assisted radical prostatectomy and pathology outcomes, including International Society of Urological Pathology score (pISUP) and lymph node status. The study drew data from 318 patients from 2 previous studies with biopsy-proven prostate cancer who were scheduled for robot-assisted radical prostatectomy. Patients underwent either ^{68}Ga-PSMA-11 (59%) or ^{18}F-DCFPyL (41%) PET/CT before surgery. Associations between the primary tumor SUV_{max} and pre- and postoperative variables were assessed.

Patients with pISUP ≤2 showed significantly lower SUV_{max} than patients with pISUP >2 for both tracers. Patients with tumor grades pN1 had significantly higher median SUV_{max} than those with pN0/pNx grades with both tracers. Additional analyses showed intraprostatic SUV_{max} to be an independent predictor of pN1 for both ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL. The authors concluded that "intraprostatic, intratumoral PSMA intensity on PET/CT, as semiquantitatively expressed by SUV_{max}, may be a valuable innovative biomarker in patients with localized prostate cancer, as it is highly associated with known conventional prognostic factors, such as pISUP and lymph node status."

BJU International

First-Line ^{90}Y-Ibritumomab Tiuxetan in Follicular Lymphoma

In article published online on February 12 ahead of print in the *Annals of Hematology*, Rieger et al. from the Charité–Universitätsmedizin Berlin (Germany), the Universita degli Studi di Napoli Federico II (Italy), the National Cancer Institute (Bethesda, MD), Fondazione G. Pascale IRCCS (Naples, Italy), Lund University Hospital (Sweden), University Ulm (Germany), Johannes-Gutenberg University (Mainz, Germany), the Medical University Graz (Austria), the Technische Universität München (Germany), Max-Delbrück-Center for Molecular Medicine in the Helmholtz Association (Berlin, Germany), and the Vivantes Klinikum Am Urban (Berlin, Germany) reported on long-term follow-up of patients treated with ^{90}Y-ibritumomab tiuxetan as first-line therapy for follicular lymphoma. Previous studies have shown complete remission rates of 56% and a median progression-free survival (PFS) rate of 26 mo over a follow-up period of 30.6 mo with this radioimmunotherapeutic approach. The current study included 59 patients originally treated for grade 1–3A disease in stages II–IV. Patients with complete response and no evidence of minimal residual disease, partial response, or stable disease at 6 mo after treatment had been observed with no additional treatment. Patients with complete response but persistent minimal residual disease had received consolidation therapy with rituximab. After a median follow-up of 9.6 y, median overall PFS was 3.6 y, and 8-y PFS was 38.3%. The median overall survival (OS) was not reached during this follow-up, and 8-y OS was 69.2%. Shorter OS was associated with age (≥65 y) and disease progression within 24 mo of treatment. No increases in secondary malignancies or transformation into aggressive lymphoma were observed when compared to trials with similar follow-up periods. The authors concluded that ^{90}Y-ibritumomab tiuxetan as first-line treatment "demonstrates a favorable safety profile and long-term clinical activity in a substantial fraction of follicular lymphoma patients in need of therapy."

Annals of Hematology

Tracer-Specific Reference Tissue Selection and PET in AD

Li et al. from United Imaging Healthcare Group Co., Ltd. (Shanghai, China), University of Sydney (Australia), the Harvard Medical School (Boston, MA), University College Cork (Ireland), Zhengzhou University of Light Industry (China), and Xuanwu Hospital/Capital Medical University (Beijing, China) reported on February 15 ahead of print in *Human Brain Mapping* on a reference tissue–based quantification approach for improving change detection in brain glucose metabolism, amyloid, and tau deposition in PET imaging of Alzheimer disease (AD). Study data included large groups of PET images acquired with ^{18}F-FDG (794 scans), ^{18}F-florbetapir (906 scans), and ^{18}F-flortaucipir (903 scans) as well as T1-weighted MR images from the Alzheimer's Disease Neuroimaging Initiative database. The researchers calculated the statistical power of reference tissues in detecting longitudinal SUV ratio (SUVR) changes in cerebellum gray matter, centrum semiovale, and pons at both region-of-interest (ROI) and voxel levels, with results compared between cognitively normal and impaired individuals. The average ROI values for the pons were higher than those of the centrum semiovale and cerebellum gray matter in detecting glucose metabolism decreases, whereas the centrum semiovale reference tissue–based SUVRs provided higher values for detection of amyloid and tau deposition increases. The 3 reference tissue areas generated comparable images for the 3 tracers, although the pons-based map showed superior performance for ^{18}F-FDG. The authors concluded that "tracer-specific reference tissue improved the detection of ^{18}F-FDG, ^{18}F-florbetapir, and ^{18}F-flortaucipir PET SUVR changes, which helps the early diagnosis, monitoring of disease progression, and therapeutic response in AD."

Human Brain Mapping

^{18}F-Fluciclovine PET Amino Acid Imaging in Glioblastoma

In an article in the January 31 issue of *Frontiers in Oncology* (2022;12: 829050), Scarpelli et al. from Purdue University (West Lafayette, IN) and the Barrow Neurological Institute (Phoenix, AZ) reported on a study designed to characterize the biologic bases of enhanced fluciclovine uptake on PET in brain tumors by correlating multiple biologic factors with fluciclovine uptake across a range of human glioblastoma xenograft models. The investigation was performed in rats that underwent orthotopic implantation with 1 of 5 different human glioblastoma cell lines, followed by ^{18}F-fluciclovine PET (for tumor-to-normal uptake ratios) and MR imaging (for tumor volume and gadolinium enhancement assessment) of established tumors. Excised tumors underwent histologic analysis. Fluciclovine uptake ratios on PET were found to be most strongly correlated with tumor amino acid transporter ASCT2 levels and also significantly associated with tumor volume and tumor enhancement status on MR imaging. Both enhancing and nonenhancing tumors were visualized on PET, with a median tumor-to-normal uptake ratio across the 5 tumor lines of 2.4 (range, 1.1–8.9). The authors concluded that these data

suggest that "fluciclovine PET may be useful for assessing brain tumor amino acid metabolism" but noted that variables such as size of tumors and enhancement status could be confounding if not accounted for in fluciclovine-based metabolic measurements.

Frontiers in Oncology

Metabolism-Associated Gene Signatures for ^{18}F-FDG Avidity

Lee et al. from Samsung Medical Center/Sungkyunkwan University School of Medicine (Seoul, South Korea) and CHA University (Seongnam, South Korea) reported on January 31 in *Frontiers in Oncology* (2022;12:845900) on a study designed to elucidate metabolic genes and functions associated with ^{18}F-FDG uptake and to assess associated prognostic value in a sample group of patients with hepatocellular carcinoma. The study included 60 patients with Edmondson–Steiner grade II disease, who underwent ^{18}F-FDG PET/CT before initiation of treatment. RNA sequencing data were obtained from tumor and normal liver tissues, and associations between specific metabolism-associated genes and tumor tracer uptake were analyzed. The researchers applied a novel metabolic gene expression balance scoring system correlating glucose and lipid metabolism-associated gene expression. Nine genes related to glycolysis and the *HIF-1* signaling pathway were positively correlated with tumor tracer uptake, and 21 genes related to fatty acid metabolism and the *PPAR* signaling pathway were negatively associated with tumor tracer uptake. Seven potential biomarker genes were identified. Balance scoring according to dominance between glucose and lipid metabolism demonstrated good prognostic value in this patient group. The authors concluded that these data strongly support "the prognostic power of FDG PET/CT and indicate the potential usefulness of FDG PET/CT imaging biomarkers to select appropriate patients for metabolism-targeted therapy in hepatocellular carcinoma."

Frontiers in Oncology

PET/MR and SSTR2 Expression in Meningioma

In an article in the January 28 issue of *Frontiers in Oncology* (2022;11:820287), Roytman et al. from Weill Cornell Medicine/New York Presbyterian Hospital and Columbia University Medical Center (both in New York, NY) reported on a study using ^{68}Ga-DOTATATE PET/MR imaging to determine whether a relationship exists between tumor vascularity and somatostatin receptor-2 (SSTR2) expression in meningiomas. The prospective study included 36 patients with 60 meningiomas (World Health Organization [WHO]-1, 20; WHO-2, 27; and WHO-3, 13) who underwent ^{68}Ga-DOTATATE PET/MR with dynamic contrast-enhanced (DCE) perfusion. Tumor volumes were segmented and superimposed onto parametric DCE maps including multiple parameters, and PET tumor SUVs and SUV ratios to superior sagittal sinus were recorded. Results showed a strong and significant correlation between tumor vascularity and SSTR2 expression in WHO-2 and WHO-3 but not in WHO-1 meningiomas, which the authors concluded suggested "biological differences in the relationship between tumor vascularity and SSTR2 expression in higher-grade meningiomas." They called for additional work to expand on this finding.

Frontiers in Oncology

PET/CT + mpMR in Radiorecurrent Prostate Cancer

Rasing et al. from University Medical Center Utrecht and Amsterdam University Medical Center (both in The Netherlands) reported on February 3 in *Cancers (Basel)* (2022;14[3]:781) on the positive predictive value of combined multiparametric MR and prostate-specific membrane antigen (PSMA) PET/CT imaging in patients with locally recurrent prostate cancer after primary radiation therapy and on the added value of pathology verification with MR-targeted biopsies. The study included 41 patients with locally recurrent prostate cancer referred for 19-Gy single-dose MR-guided focal salvage high-dose-rate brachytherapy. All patients had undergone multiparametric MR and PSMA PET/CT before biopsy. Imaging results were used to identify lesions suspected for isolated tumor recurrence, and these were biopsied. Forty (97.6%) patients had positive biopsies for recurrent cancer. Five of these initially had negative biopsies of lesions identified on MR/PSMA PET, and recurrence was confirmed in 4 of the 5 after rebiopsy (1 patient refused a second biopsy). The positive predictive value for combined multiparametric MR and PSMA PET imaging was 97.6%. The authors concluded that biopsies can be withheld "when the results of the combined multiparametric MRI and PSMA PET/CT are conclusive, avoiding an unnecessary invasive and burdensome procedure."

Cancers (Basel)

MR and PET in Renal Cell Carcinoma Detection

In an article in the February 11 issue of *BMC Cancer* (2022;22[1]:163), Yin et al. from Wuxi No. 2 People's Hospital/Nanjing Medical University (China), the Affiliated Hospital of Jiangnan University (Wuxi, China), and Shanghai University of Medicine and Health Sciences (China) provided a systematic review and metaanalysis of the diagnostic performance of MR and PET imaging in detection of renal cell carcinoma. After a keyword search of the major scientific databases, a total of 44 articles were included for analysis. The resulting pooled sensitivities of MR, ^{18}F-FDG PET, and ^{18}F-FDG PET/CT were 80%, 83%, and 89%, respectively. The corresponding overall specificities were 90%, 86%, and 88%. The pooled sensitivity and specificity of 1.5-T MRI studies were 86% and 94%, respectively. For prospective PET studies, the pooled sensitivity, specificity and AUC were 90%, 93%, and 97%, respectively. For detection of primary renal cell carcinoma, PET as reported in the articles reviewed had a pooled sensitivity, specificity, and AUC of 77%, 80%, and 84%, respectively. For PET/CT, the corresponding percentages were 80%, 85%, and 89%.

The authors concluded that these results suggest that "MRI and PET/CT present better diagnostic value for the detection of renal cell carcinoma in comparison with PET" and that "MRI is superior in the diagnosis of primary renal cell carcinoma."

BMC Cancer

PET/CT and GEP NET Management

Magi et al. from Sant'Andrea University Hospital/ENETS Center of Excellence (Rome), Sapienza University of Rome, the University of Bologna, and the IRCCS Azienda Ospedaliero-Universitaria di Bologna (all in Italy) reported on February 11 ahead of print in *Endocrine* on a retrospective study evaluating the role of ^{18}F-FDG PET/CT in grade 1 gastroenteropancreatic neuroendocrine tumors (GEP NETs). The study included data from 55 patients (24 with pancreatic NETs, 31 with gastrointestinal NETS). At diagnosis, 28 (51%) had metastatic disease, and 50 (91%) patients had positive findings on ^{68}Ga-labeled somatostatin receptor PET/CT. All patients underwent ^{18}F-FDG PET/CT, and 27 (49%) had positive findings. ^{18}F-FDG PET/CT findings led to changes in therapeutic management in 29 (52.7%) patients. Progression-free survival (PFS) was longer in patients with negative ^{18}F-FDG PET/CT (median PFS not reached in the study period) than in those with positive findings (24 mo), particularly in the group with pancreatic NETs. The authors concluded that these data support "a more 'open' attitude toward the potential use of ^{18}F-FDG PET/CT in the diagnostic work-up of grade 1 GEP NETs, which may be used in selected cases to detect those at higher risk for an unfavorable disease course."

Endocrine

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 January and February. Parel et al. from the National Heart, Lung, and Blood Institute (Bethesda, MD) provided "Updates in the impact of chronic systemic inflammation on vascular inflammation by positron emission tomography (PET)" on February 16 in *Current Cardiology Reports*. In the same journal on February 16, Juarez et al. from University Medical Center Utrecht (The Netherlands), University of Turku/Turku University Hospital (Finland), University Medical Center Groningen (The Netherlands), King's College London/St. Thomas' Hospital (UK), and UMA-Health (Buenos Aires, Argentina) looked at the potential of "Artificial intelligence to improve risk prediction with nuclear cardiac studies." In an article on January 26 in *Nanomaterials* (Basel) (2022;12[3]:399), Murar et al. from the Barcelona Institute of Science and Technology (Spain) and the Eindhoven University of Technology (The Netherlands) reviewed "Advanced optical imaging-guided nanotheranostics towards personalized cancer drug delivery." Anan et al. from the Universiti Sains Malaysia (Pulau Pinang) and the Imam Abdulrahman Bin Faisal University (Dammam, Saudi Arabia) published "A review on advances in ^{18}F-FDG PET/CT radiomics standardisation and application in lung disease management" on February 5 ahead of print in *Insights into Imaging* (2002;13[2]:22). In an article published on January 21 online ahead of print in the *International Journal of Molecular Sciences* (2002;23[3]: 1158), Debnath et al. from the University of Texas Southwestern Medical Center (Dallas) summarized "PSMA-targeting imaging and theranostic agents—Current status and future perspective."