

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.

⁶⁸Ga-PSMA-11 vs ¹³¹I in Thyroid Cancer

Pitalua-Cortes et al. from the National Cancer Institute (Mexico City, Mexico) and the Universidad Autónoma de Bucaramanga (Colombia) reported in the December 22 issue of *Frontiers in Endocrinology (Lausanne)* (2021;12:794759) on a comparison of ⁶⁸Ga-prostate-specific membrane antigen (PSMA)-11 and ¹³¹I in the follow-up of well-differentiated metastatic thyroid cancer. The retrospective study included 10 patients (8 women, 2 men; mean age, 58 ± 11.6 y) who underwent posttherapeutic ¹³¹I whole-body scanning and SPECT/CT, as well as ⁶⁸Ga-PSMA-11 PET/CT imaging. A total of 64 metastatic lesions were analyzed (67% papillary, 33% follicular), with 58% of metastatic lesions in bone, 17% in lung, 8% in lymph nodes, 5% in the postoperative thyroid bed, 5% in brain, and 7% in other sites. ⁶⁸Ga PSMA-11 PET/CT identified all 64 lesions, whereas ¹³¹I SPECT/CT identified only 55. Lesions not detected by ¹³¹I SPECT/CT were in the lung (44.4%), brain (22.2%), postoperative thyroid bed (11.1%), lymph nodes (11.1%), and bone (11.1%). Although observer agreement was high for both tracers, it was almost 100% for ⁶⁸Ga

PSMA-11 PET/CT. The authors concluded that the superior performance of ⁶⁸Ga-PSMA PET/CT for metastatic lesion detection when compared with ¹³¹I SPECT/CT suggests that PSMA-based imaging could possibly be used for early identification of radioiodine refractory disease. They added that, in addition to avoiding some of the challenges of ¹³¹I-based follow-up, PSMA uptake values may both expedite diagnoses and provide a rationale for development of theranostic applications.

Frontiers in Endocrinology (Lausanne)

Integrating PSMA PET in NCTN Trials

In an article published on January 11 ahead of print in the *Journal of Clinical Oncology*, Schöder and members of the National Cancer Institute (NCI) Clinical Imaging Steering Committee (CISC) Prostate-Specific Membrane Antigen (PSMA) PET Working Group reported on the results of an expert review and survey of challenges to clinical use of PSMA. The working group was tasked with identification of these challenges across various clinical scenarios and development of consensus recommendations on most effectively integrating PSMA PET into National Clinical Trials Network (NCTN) studies. In this article, the group identified challenges in stage migration, response assessment, trial logistics, and statistical analysis and offered proposed solutions. The report was also informed by the results of an anonymous, open-ended survey about these challenges, as well as serial overviews of related clinical trials. The authors discussed implications for patient selection and definition of study end points and provided guidance and potential solutions for different clinical scenarios, particularly with regard to best practices in defining eligibility criteria and outcome measures.

Journal of Clinical Oncology

PET + MRI in Symptomatic Carotid Stenosis

Gianotti, from University College Dublin, and colleagues from Mater Misericordiae University Hospital, St. Vincent's University Hospital, Connolly Hospital, St. James Hospital, Trinity College Dublin, and Beaumont Hospital and Royal College Surgeons Ireland (all in Dublin, Ireland) reported on December 23 in *Frontiers in Neurology* (2021; 12:731744) on a study investigating the association of selected imaging characteristics of plaque vulnerability measured with ¹⁸F-FDG PET and MRI in patients with symptomatic carotid stenosis. The study included 25 patients (≥50 y old, mean age, 65 y; 72% men, 28% women) from a larger clinical trial who had experienced an ischemic stroke or motor/speech/vision transient ischemic attack within the last 30 d, had ipsilateral internal carotid artery stenosis (≥5.0% lumen narrowing); and had undergone carotid PET/CT angiography and MRI. MRI imaging quantified morphologic features of plaque instability. In addition to inflammation-related metabolism as represented by SUV_{max} on PET, data from CT- and MRI-assessed plaque volume were compared. Plaque volume was greater in men (1,708–1,286 mm³), patients who had experienced strokes (1,856–1,440 mm³), and non-statin users (1,325–1,797 mm³). PET SUV_{max} values were directly associated with MRI-measured plaque lipid-rich necrotic cores in the corresponding axial slices and inversely associated with whole-plaque fibrous cap thickness and calcium volume. The authors concluded that these novel correlations of noninvasive imaging biomarkers of inflammation-related plaque metabolism and morphologic MRI markers of plaque instability “may support the application of combined MRI and PET to detect vulnerable plaque in future clinical practice and randomized trials.”

Frontiers in Neurology

COVID-19, Myocardial Injury, and PET + MRI

In an article in the January 12 issue of *JAMA Cardiology*, Hanneman et al. from the University of Toronto (Canada) and the University of Cologne (Germany) reported on a study investigating myocardial metabolic changes early after recovery from COVID-19 using ^{18}F -FDG PET and correlating these changes with abnormalities in cardiac MRI-based function and tissue characterization measures and with inflammatory blood markers. The study, which took place between November 2020 and June 2021, included 47 patients (24 women, 23 men; mean age 43 y), who were an average of 67 d (± 16 d) post-COVID 19 diagnoses at the time of combined PET/MRI imaging and blood marker evaluation. Most patients (85%) had not been hospitalized during acute stages of infection. Eight patients (17%) were found to have focal ^{18}F -FDG uptake on PET consistent with myocardial inflammation and were asked to return for repeat assessment 2 mo later. Patients with focal ^{18}F -FDG uptake were found on combined imaging to have higher regional T2, T1, and extracellular volume, higher prevalence of late gadolinium enhancement, lower left ventricular ejection fraction, worse global longitudinal and circumferential strain, and higher systemic inflammatory blood markers, including interleukin 6, interleukin 8, and high-sensitivity C-reactive protein. In these patients, PET/MRI findings and inflammatory blood markers resolved or improved at 2-mo follow-up assessment. The authors concluded that these “imaging findings are generally consistent with an imaging phenotype with good prognosis; however, it does emphasize the importance of studies examining the longer-term effects of COVID-19 on the heart.”

JAMA Cardiology

^{11}C -PABA PET in Bacterial Infection

Ordonez et al. from the Johns Hopkins University School of Medicine

(Baltimore, MD) and the University of California San Francisco reported on January 11 in *JCI Insight* (2022;7[1]:e154117) on the use of ^{11}C -paraaminobenzoic acid (^{11}C -PABA) PET imaging for detection and monitoring of pyogenic bacterial infections in a range of clinically relevant animal models and healthy human participants. In a rabbit model of experimentally induced myositis with *E. coli* or *S. aureus*, ^{11}C -PABA PET was able to selectively localize sites of infection and differentiate these from sterile inflammation. In a prosthetic joint model in rabbits, ^{11}C -PABA PET successfully detected prosthetic-related methicillin-resistant *S. aureus* infection. ^{11}C -PABA PET also correctly detected involved sites in bone in rats infected with *S. aureus*. No adverse or clinically detectable pharmacologic effects were noted in biodistribution and radiation dosimetry studies in 5 healthy human volunteers, and the tracer was rapidly cleared from most organs. The authors concluded that “ ^{11}C -PABA has the potential for clinical translation to detect and localize a broad range of bacteria” and called for additional clinical studies in patients with confirmed infections to evaluate the role of ^{11}C -PABA PET imaging in diagnosing and monitoring bacterial infections.”

JCI Insight

PET MTV and Rhabdomyosarcoma Prognosis

In an article published on January 14 in *PLoS One* (2022;17[1]:e0261565), Fayolle et al. from Toulouse Purpan University Hospital, Curie Institute/PSL Research University (Paris), the Léon Bérard Cancer Centre (Lyon), and the Toulouse Paul Sabatier University–INSERM (all in France) reported on a multicenter study of the utility of pretreatment ^{18}F -FDG PET–derived metabolic tumor volumes (MTVs) in providing prognostic information in pediatric patients with rhabdomyosarcoma. MTV in the study was defined as the sum of the primary tumor and the largest metastasis (where relevant) with a 40% threshold of the primary

tumor SUV_{max} . The prognostic values of SUV_{max} , SUV_{peak} , and bone lysis were also evaluated. The study included 101 patients (62 boys, 39 girls; median age, 7.4 y) with localized disease ($n = 35$), regional nodal spread ($n = 43$), or distant metastases ($n = 23$). A total of 44 patients had alveolar subtypes. The researchers found that an MTV $> 200 \text{ cm}^3$ was associated with a 2.5-factor increased risk of death or disease progression. SUV_{max} , SUV_{peak} , and bone lysis also were correlated with both overall and progression-free survival. The authors concluded that “given the therapeutic challenges in a pediatric population, with the risk of developing secondary toxicities, our study brings an additional argument to include metabolic PET parameters in the decision-making trees for the management of rhabdomyosarcoma. And it could help to adapt patients’ therapeutic management.”

PLoS One

Consensus Statement: Postoperative ^{131}I in DTC

Pacini et al. from the University of Siena (Italy), University Hospital Essen/University Duisburg-Essen (Germany), University of Pisa (Italy), Maria Skłodowska-Curie National Research Institute of Oncology (Gliwice, Poland), Gustave Roussy Cancer Campus and University Paris-Saclay (Villejuif, France), University Hospital Marburg (Germany), and Radboud University Medical Center (Nijmegen, The Netherlands) provided on January 1 in the *European Thyroid Journal* (2022;11[1]:e210046) a European Thyroid Association Consensus Statement intended to deliver rational recommendations for indications for postoperative radioiodine therapy in differentiated thyroid cancer tailored to the specific goals of these indications and the needs of each patient. The 8 recommendations addressed the questions of which patients are candidates for which form of radioiodine therapy, appropriate activities of radioiodine for specific scenarios, and optimal preparation methods. The authors recommended individual risk-based assessment of candidates for postoperative ^{131}I treatment.

They added that because this consensus statement was based largely on retrospective studies in which biases could not be excluded, “the only way to scientifically compare 2 treatment modalities and to exclude biases is to perform randomized prospective studies,” which they termed “clearly feasible.”

European Thyroid Journal

PET and Immunotherapy Discontinuation in Melanoma

In an article published online on January 9 ahead of print in the *International Journal of Cancer*, Ellebaek et al. from Copenhagen University Hospital (Herlev, Denmark) reported on a study of the clinical value of routine ¹⁸F-FDG PET imaging as a decision-assisting tool for early immunotherapy discontinuation in advanced melanoma. The retrospective study included data from 140 patients in the Danish Metastatic Melanoma Database. Patients treated with an anti-PD-1–based regimen for <18 mo and who had experienced ≥4 mo without disease progression after stopping treatment were included. Serial ¹⁸F-FDG PET/CT had evaluated these patients as having partial or complete responses. Patients were divided into “elective” and “toxicity” groups, depending on the reasons for which their treatment had been discontinued. Over a median 29.3-mo follow-up, a higher percentage of patients remained alive in the elective group (93%) than in the toxicity group (75%), with improved melanoma-specific survival. Patients without ¹⁸F-FDG–avid lesions when treatment was discontinued showed improved melanoma-specific survival. In multivariate analysis, the absence of lesions was the only independent predictive feature of improved melanoma-specific survival. The authors concluded that patients with metastatic melanoma who obtain an early response and discontinue immunotherapy early “have an excellent prognosis, especially in the absence of ¹⁸F-FDG PET–avid lesions when discontinuing treatment.” They added that “these data support the option of early

discontinuation, limiting possible over-treatment and thereby toxicity, health, and economic expenses and improving logistics.”

International Journal of Cancer

PET/CT in Untreated Multiple Myeloma

Li et al. from the Second Hospital of Anhui Medical University (Hefei, People’s Republic of China) reported on January 9 ahead of print in *Clinical and Experimental Medicine* on a systematic review and metaanalysis of the prognostic value of ¹⁸F-FDG PET/CT at diagnosis and before treatment in patients with multiple myeloma. The researchers systematically reviewed the major medical literature databases for relevant articles, with a resulting study set of 16 qualifying articles including 2,589 patients. Statistical analyses indicated that PET/CT has an excellent prognostic role in multiple myeloma and that higher SUV_{max}, more focal lesions, and extramedullary disease at the time of diagnosis were associated with poor overall and progression-free survival. Similar results were seen in most subgroup analyses. The authors concluded that “pretreatment ¹⁸F-FDG PET/CT examination has prognostic value for myeloma patients and has guiding significance for clinical treatment.”

Clinical and Experimental Medicine

Predicting Chemoimmunotherapy Outcomes in NSCLC

In an article in the January 9 issue of *Therapeutic Advances in Medical Oncology* (2022;14:17588359211068732), Kim et al. from Yonsei University College of Medicine (Seoul and other sites in the Republic of Korea) evaluated whether imaging biomarkers of ¹⁸F-FDG PET/CT and routinely assessed clinical and laboratory values were associated with clinical outcomes in patients with advanced non–small cell lung cancer (NSCLC) receiving pembrolizumab plus platinum-doublet chemotherapy as first-line treatment.

The retrospective study included 52 patients with advanced disease who underwent ¹⁸F-FDG PET/CT before beginning treatment. Over a median follow-up period of 16.7 mo (range, 15.7–17.7 mo), 43 (82.7%) patients experienced disease progression and 31 (59.6%) died. An objective response to treatment was seen in 23 (44.2%). After analysis, SUV_{max}, metabolic tumor volume, total lesion glycolysis, and bone marrow-to-liver uptake ratio on PET/CT, as well as neutrophil-to-lymphocyte ratio in laboratory analyses, were independently and significantly predictive of treatment response, progression-free survival, and overall survival. The authors concluded that these results suggest the potential of these variables as “effective markers for combined PD-1 blockade and chemotherapy” in patients with NSCLC.

Therapeutic Advances in Medical Oncology

SSTR Expression and PET/CT in Pancreatic NENs

Majala et al. from Turku University Hospital/University of Turku and Helsinki University Hospital/University of Helsinki (both in Finland) reported in the December 29 issue of *Cancers (Basel)* (2021;14[1]:162) on a study designed to correlate immunohistochemical tissue levels of somatostatin receptors 1–5 with receptor density as seen in ⁶⁸Ga-DOTA-NOC uptake on PET/CT in a prospective series of patients with nonfunctional pancreatic neuroendocrine neoplasms (PNENs). The study included 21 patients with a total of 35 such lesions and with 21 lymph node metastases on histologic analysis who underwent both ⁶⁸Ga-DOTANOC and ¹⁸F-FDG PET/CT imaging. Twenty patients proceeded to surgery, and 1 underwent endoscopic ultrasonography and core-needle biopsy. Histology and PET/CT findings were correlated. Expression of SSTR1 was detected in 74% of lesions, SSTR2 in 91%, SSTR3 in 80%, SSTR4 in 14%, and SSTR5 in 77%. SSTR2 immunohistochemistry significantly correlated with

^{68}Ga -DOTANOC PET/CT findings. All ^{68}Ga -DOTANOC-avid tumors expressed SSTR2, SSTR3, or SSTR5. SSTR5 expression was associated with low Ki-67 proliferation, possibly associated with better prognoses. The authors noted that “further prospective studies, in larger tumor series, are needed to study the correlation of SSTR expression profile with ^{68}Ga -labeled SST and ^{18}F -FDG PET/CT for the personalized management of PNEN patients.”

Cancers (Basel)

Interim Report on the GastroPET Study

In an article in the January 5 issue of *Therapeutic Advances in Medical Oncology* (2022;13:17588359211065153), Obermannova et al. from Masaryk Memorial Cancer Institute (Brno), Charles University and General University Hospital (Prague), University Hospital Olomouc, and University Hospital Brno (all in the Czech Republic) reported on the methodology, study design, and initial patient safety data for GastroPET, a large multicenter phase II trial assessing an ^{18}F -FDG PET/CT preoperative treatment strategy for localized esophagogastric junction adenocarcinoma, with the R0 resection rate as a primary endpoint. The report included data on the first 63 patients enrolled. Patients with locally advanced esophagogastric junction adenocarcinoma (Siewert I–III) stages Ib–IIIc underwent baseline PET/CT scanning and repeat imaging after 14 d of oxaliplatin-5FU (docetaxel) chemotherapy. Response was defined as a $\geq 35\%$ decrease in $\text{SUV}_{\text{average}}$ from baseline. Responders ($n = 35$) were then continued on the same chemotherapy for 2–3 mo before surgery. Management for nonresponders ($n = 28$) was changed to preoperative chemoradiotherapy (weekly carboplatin and paclitaxel with concurrent radiotherapy [45 Gy in 25 fractions]). In addition to initial reporting on feasibility, the study group compared local and centralized reading of imaging results. At the time of this report, 47 patients (28 responders,

19 nonresponders) had completed surgery. Grade 3 or higher postoperative complications were reported in 5 responders and 2 nonresponders (no statistical difference). Two patients died after surgery, 1 in each arm of the study. Centralized and local image interpretations of changes in SUV were 100% concordant. The authors noted that these results confirm “the accuracy of a PET response-guided treatment algorithm for locally advanced esophagogastric junction cancer in a multicenter setting” and that preoperative treatment adaption based on PET/CT appeared to be feasible and safe.

Therapeutic Advances in Medical Oncology

^{68}Ga -PSMA-11 PET/CT and Glial Tumors

Kunikowska et al. from the Medical University of Warsaw, Poznan University of Medical Sciences, National Centre for Nuclear Research (Otwock), and the Maria Skłodowska-Curie National Research Institute of Oncology (Warsaw; all in Poland) reported on January 13 in *Science Reports* (2022;12[1]:652) on a study using ^{68}Ga -prostate-specific membrane antigen-11 (^{68}Ga -PSMA-11) PET/CT to study PSMA expression in recurrent glial tumors. The study included 34 patients (ages, 44.5 ± 10.3 y) with suspected recurrence of histologically confirmed grade III ($n = 6$) and grade IV ($n = 28$) gliomas. All patients underwent both contrast-enhanced MR and ^{68}Ga -PSMA-11 PET/CT imaging. PET/CT was positive in all areas indicated as suspicious for recurrence on MR, and recurrence was confirmed by histopathology and/or follow-up imaging. Median SUV_{max} for tumors was 6.5 (range, 0.9–15.6) and SUV_{mean} was 3.5 (range, 0.9–7.5). The median target-to-background ratio was 152 (range, 15–1,400), and median target-to-liver background ratio was 1.3 (range, 0.2–2.6). No significant differences were found in PET/CT parameters between grades III and IV. The authors concluded that because treatment options in recurrent glioma are limited,

this observation may point to therapeutic innovations using radiolabeled agents targeting PSMA.

Science Reports

PET/CT in Neurofibromatosis Type 1

In an article published online on January 13 ahead of print in the *Journal of NeuroOncology*, Geitenbeek et al. from University Medical Center Utrecht, Erasmus Medical Center Cancer Institute (Rotterdam), and Maastricht University Medical Center (all in The Netherlands) reported on the diagnostic accuracy and value of ^{18}F -FDG PET/CT in detecting malignant peripheral nerve sheath tumors (MPNSTs) in adult and pediatric patients with neurofibromatosis type 1. The retrospective study included 60 patients, all of whom underwent PET/CT and in whom 70 tumors were identified (10 MPNSTs and 60 benign peripheral nerve sheath tumors [BPNSTs]; 40 in females, 30 in males; 15 in children, 55 in adults). Over a mean follow-up of 3.5 ± 1.6 y at the time of the report, 7 MPNST patients and 4 BPNST patients had died. The authors developed a diagnostic algorithm for PET/CT findings. They identified ideal threshold values of 5.8 for SUV_{max} (sensitivity 70%, specificity 92%), 5.0 for SUV_{peak} (sensitivity 70%, specificity 97%), 1.7 for maximum tumor-to-liver ratio (TL_{max}) (sensitivity 90%, specificity 86%), and 2.3 for TL_{mean} (sensitivity 90%, specificity 79%). A standard TL_{mean} threshold value of 2.0 yielded a sensitivity of 90% and specificity of 74%, and the standard SUV_{max} threshold value of 3.5 yielded a sensitivity of 80% and specificity of 63%. SUV_{max} and adjusted SUV for lean body mass were somewhat lower in children, but TL ratios were similar in the 2 groups. Using thresholds of $\text{TL}_{\text{mean}} > 2.0$ or $\text{TL}_{\text{mean}} < 2.0 + \text{SUV}_{\text{max}} > 3.5$, the authors' algorithm achieved sensitivity of 100% and specificity of 63%. They concluded that these semiquantitative PET markers “offer acceptable diagnostic accuracy for detecting malignant

transformation of peripheral nerve sheath tumors in neurofibromatosis type 1,” adding that the potential differences between uptake values of adults and children did not impact the diagnostic algorithm.

Journal of NeuroOncology

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 Newslines editor recommends several general reviews accessioned into the PubMed database in December and January. In an article e-published on January 10 in *Geburtshilfe und Frauenheilkunde* (2022;82[1]:50–58), Unger et al. from Universitätsklinikum Freiburg and the St. Vincentius Kliniken (Karlsruhe, both in

Germany) provided a structured overview of “Expression of prostate specific membrane antigen (PSMA) in breast cancer.” Taralli et al. from the Fondazione Policlinico Universitario Agostino Gemelli IRCCS (Rome), S. Orsola-Malpighi University Hospital (Bologna), Azienda Ospedaliera San Camillo Forlanini (Rome), and the Università Cattolica del Sacro Cuore (Rome, all in Italy) summarized data on “The prognostic value of ¹⁸F-FDG PET imaging in staging in patients with malignant pleural mesothelioma: A literature review” on December 22 in the *Journal of Clinical Medicine* (2021;11[1]:33). In an article published on January 17 ahead of print in the *British Journal of Haematology*, El-Galaly et al. from Aalborg University (Denmark), the BC Cancer Centre for Lymphoid Cancer/University of Brit-

ish Columbia (Vancouver, Canada), Sir Charles Gairdner Hospital (Perth, Australia), and the University of Western Australia asked “Pretreatment total metabolic tumour volumes in lymphoma: Does quantity matter?” Bidakhvidi et al. from University Hospitals Leuven (Belgium) reviewed on December 28 in *Cancers (Basel)* (2021;14[1]:129) “Peptide receptor radionuclide therapy targeting the somatostatin receptor: Basic principles, clinical applications, and optimization strategies.” In the December 31 issue of the *International Journal of Molecular Sciences* (2021;23[1]:474), Ben-Shalom et al. from Tel Aviv Sourasky Medical Center, Weizmann Institute of Science (Rehovot), and Tel Aviv University (all in Israel) reported on “The role of molecular imaging as a marker of remyelination and repair in multiple sclerosis.”