global training opportunities in nuclear medicine and hybrid imaging. The IAEA and EANM have a long history of cooperative endeavors both in Europe and in countries undergoing technologic and economic development. "The arrangement signed today will further expand this cooperation, increasing educational opportunities for professionals in nuclear medicine and hybrid imaging," said Diana Paez, MD, MEd, head of the Nuclear Medicine and Diagnostic Imaging Section at the IAEA. Under the new agreement, EANM will provide experts and infrastructure for IAEA training courses and expert missions to low- and middle-income countries and will work closely with the IAEA on development of more no-cost and interactive educational materials for the IAEA Human Health Campus.

"The agreement is an incentive for EANM to further improve the quality of education in nuclear medicine," said EANM President Kristoff Muylle, MD. In response to rising demand for dedicated training in hybrid imaging and new therapeutic applications in nuclear medicine, EANM has recently modernized its educational offerings and founded the European School of Multimodality Imaging and Therapy, which will now be open to IAEA-nominated professionals.

To date, more than 90 nuclear medicine professionals have benefitted from ongoing cooperation between the 2 organizations. Sergei Nazarenko, MD, head of the Nuclear Medicine Department at the North Estonia Medical Centre (Tallinn), has been among the beneficiaries. "Smaller European countries like Estonia have practical challenges because of their size," he said. "In order to assure availability of knowledge and competences to our local specialists, we need extensive international cooperation like the one just signed."

International Atomic Energy Agency

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 and Nanoparticle Monitoring in Breast Cancer

In an article e-published on March 15 ahead of print in *Clinical Cancer Research*, Lee, from Merrimack Pharmaceuticals, Inc. (Cambridge, MA), and a consortium of academic and industry researchers from across the United States reported on a study using PET to assess the enhanced permeability and retention effect (EPR) of therapeutic nanoparticles in patients with HER2-positive metastatic breast cancer. The study included 19 such patients who underwent serial PET imaging after administration of ^{64}Cu-HER2-targeted PEGylated liposomal doxorubicin (^{64}Cu-MM-302) during a clinical trial of MM-302 and trastuzumab with or without cyclophosphamide. In imaging acquired at 24 and 48 h postadministration, MM-302 uptake varied 35-fold (0.52–18.5 %ID/kg), with accumulation in bone and brain lesions independent of systemic plasma exposure. Additional analyses classified patients by lesion deposition with a cutpoint comparable to response thresholds in preclinical studies. Separate retrospective analyses of patient outcomes by drug levels in tumor lesions found high ^{64}Cu-MM-302 deposition to be associated with more favorable treatment outcomes. The authors concluded that these findings "provide important evidence and quantification of the EPR effect in human metastatic tumors and support imaging nanoparticle deposition in tumors as a potential means to identify patients well-suited for treatment with therapeutic nanoparticles."

Clinical Cancer Research

MRS- and PET-Guided Biopsy and Neuronavigation

Grech-Sollars et al. from Imperial College London (UK) and Salford Royal NHS Foundation Trust (UK) reported on March 17 ahead of print in the *Journal of Neurosurgery* on a technique integrating presurgical PET and MR spectroscopy with intraoperative neuronavigation to guide surgical biopsy and tumor sampling of brain gliomas. The technique is targeted at improving intraoperative tumor-tissue characterization and imaging biomarker validation. The article described the development of the intraoperative neuronavigation tool to sample high-choline tumor components identified by multivoxel MR spectroscopy and ^{18}F-methylcholine PET/CT. Coregistered data from the 2 imaging modalities were assembled into structural datasets and loaded into the intraoperative system. The system depicted high- and low-choline uptake/metabolite regions as color-coded hollow 3D spheres to facilitate targeted stereotactic biopsy and tumor sampling. In surgical trials, the spherical targets were easily visualized on the interactive system. In one example case, areas of high uptake on PET and elevated choline ratios on MR spectroscopy identified sites of high mitotic activity in an otherwise low-grade tumor. The authors concluded that although "the technique was applied for characterizing choline metabolism using MR spectroscopy and ^{18}F PET. . .this approach provides proof of principle for using different radionuclide

tracers and other MR imaging methods, such as MR perfusion and diffusion."

Journal of Neurosurgery

PET Response-Adapted Treatment in HL

In an article e-published on March 14 in the *Journal of Clinical Oncology*, André from the Université Catholique de Louvain (Yvoir, Belgium) and a consortium of researchers from France, Belgium, Italy, The Netherlands, and Denmark reported on the effect of early response evaluation by ^{18}F-FDG PET on subsequent management in patients undergoing combined modality treatment for stage I or II Hodgkin lymphoma. The study included 1,925 patients who were previously untreated and categorized as having favorable or unfavorable stage I or stage II disease, based on European Organisation for Research and Treatment of Cancer criteria. Patients underwent early PET imaging after 3 cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) and were randomly assigned to: (1) standard-of-care treatment, including ABVD followed by involved-node radiotherapy, regardless of PET findings; or (2) an experimental arm, in which PET-negative patients received ABVD only and PET-positive patients were switched to 2 cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPPesc) and involved-node radiotherapy. The authors found that among patients who were early PET-positive ($n = 361$), the 5-y progression-free survival rate improved from 77.4% for standard ABVD and radiation to 90.6% for intensification to BEACOPPesc and radiation. Among patients who were early PET-negative, slight advantages were seen with ABVD plus radiation, but these were not significant. The authors concluded that early PET imaging after only 2 cycles of chemotherapy allows more individualized management in this patient group, with significantly improved progression-free survival in patients whose treatment was changed after positive PET results.

Journal of Clinical Oncology

Imaging Response During ^{223}Ra Therapy

Keizman, from Tel Aviv University (Israel), and researchers from Copenhagen University Hospital/Rigshospitalet (Denmark), Kantonsspital St. Gallen (Switzerland), Rambam Medical Center (Haifa, Israel), Rabin Medical Center (Petah Tikva, Israel), Kantonsspital Chur (Switzerland), Tel Aviv Sourasky Medical Center (Israel), and the Soroka Medical Center (Beer-Sheva, Israel) reported on February 28 ahead of print in *Prostate Cancer and Prostatic Diseases* on a study characterizing imaging results in patients during and after ^{223}Ra therapy for castration-resistant prostate cancer with bone metastases. The study included 130 patients from 8 centers in 3 countries, most of whom (65%) underwent ^{223}Ra therapy after receiving docetaxel. Imaging records, including CT and bone scintigraphy, documenting response to therapy were retrospectively evaluated. Seventy patients (54%) completed the prescribed 6 injections of ^{223}Ra. Among 124 patients with available data, transient increases in bone pain were seen in 33 (27%) and an improvement in bone metastases–related pain during ^{223}Ra treatment was seen in 61 (27%). Bone scintigraphy showed stable disease in 74% and 94% of patients with available data at 3 and 6 mo, respectively, after ^{223}Ra treatment. A 26% increase in the number of bone lesions over baseline was seen at 3-mo imaging, whereas this increase was only 6% when comparing 6- with 3-mo imaging results. Extraskeletal disease progression was seen on CT in 46% of patients with available data at 3 and/or 6 mo. The authors concluded that although "bone flare (pain and/or radiological) may be noted during the first 3 months" after ^{223}Ra treatment, this should not be confused with progression. In fact, "progression of bone metastases during ^{223}Ra therapy is uncommon." They recommended that CT imaging be considered after 3 and 6 doses of ^{223}Ra to rule out extraskeletal progression.

Prostate Cancer and Prostatic Diseases

PET/CT and Noninfected Prosthetic Valves

In an article e-published in March ahead of print in *Circulation. Cardiovascular Imaging,* Mathieu et al. from the Bichat Hospital, Assistance Publique–Hôpitaux de Paris, Paris-Diderot University, and Inserm Unité Mixte de Recherche (all in Paris, France) reported on a retrospective study characterizing ^{18}F-FDG uptake patterns in noninfected prosthetic heart valves, in an effort to differentiate these findings from those associated with prosthetic valve endocarditis. The study included the records of 51 patients with prosthetic heart valves (total of 54 valves, 32 of which were of biologic materials) referred for PET/CT for oncologic indications ($n = 26$), to exclude valve endocarditis ($n = 17$), or because of a history of vasculitis ($n = 11$). Patterns of ^{18}F-FDG uptake were categorized as absent, homogeneous, or heterogeneous. Uptake was seen in the area of the valve in 47 (87%) and 30 (56%) prosthetic valves, with and without attenuation correction, respectively. The pattern was homogeneous in almost all valves. SUV_{max} was greater in mechanical than in biologic valves (4.0 [range, 2.4–8.0] and 3.3 [2.1–6.1], respectively), with the highest SUV_{max} in patients referred for vasculitis. The authors concluded from these and other results that "caution is, therefore, needed when interpreting FDG PET/CT in suspected prosthetic valve endocarditis, with specific attention to uptake pattern."

Circulation. Cardiovascular Imaging

PET/CT SLN Biopsy

Piñero-Madrona et al. from the Instituto Murciano de Investigación Biosanitaria/Hospital Clínico Universitario "Virgen de la Arrixaca" (Murcia, Spain) reported on March 8 ahead of print in *Tumori* on the development of a combined gamma probe and ^{18}F-FDG PET/CT approach in combination with sentinel lymph node biopsy for detection of nonpalpable lymph nodes in cases of suspected cancer relapse. In this technique, the gamma probe detected

signal from ^{18}F rather than ^{99m}Tc. PET/CT imaging to identify the location of suspected pathologic lymph nodes was followed by transcutaneous localization of highest tracer uptake. Short incisions were made in these areas, and nodes with the highest uptake registered by the gamma probe were removed. These excised tissues were found to be positive for disease, with the result that lymph node involvement was successfully diagnosed before clinical or other indications. The authors concluded that "this methodology confirms new horizons for the surgical approach of lymph node biopsies in patients with previous tumors with ^{18}F-FDG avidity and suspicion of relapse."

Tumori

PET/CT and Treatment Management in Lung Cancer

In an article e-published on March 8 ahead of print in *Radiotherapy and Oncology*, Hallqvist et al. from Sahlgrenska University Hospital and HTA-Centrum of Region Västra Götaland (both in Göteborg, Sweden) reported on a systematic review and metaanalysis of the effect of dose-planning PET/CT imaging on management in lung cancer patients undergoing high-dose radiochemotherapy. After a systematic literature search, 1 observational and 35 cross-sectional studies were identified that fit the inclusion criteria. None were randomized trials, and no associated clinical endpoints were included. The overall estimate of change in target definition was 36% in patients who had undergone former staging PET in addition to dose-planning PET/CT. In patients with no staging PET but only dose-planning PET/CT, estimates of change in target definition were 43% and 26% for non–small and small cell lung cancer, respectively. Changes in treatment intent from curative to palliative were 20% in patients who underwent both staging and dose-planning imaging and 22% and 9% for patients with non–small and small cell lung cancer, respectively, who underwent dose-planning PET/CT only. The authors concluded that "PET/CT for dose planning improves target definition and patient selection."

Radiotherapy and Oncology

^{18}F-FDG PET/CT and Indolent Lymphoma

Metser et al. from the University of Toronto, the Cancer Centre of Southeastern Ontario/Queen's University (Kingston), Princess Margaret Hospital (Toronto), and Cancer Care Ontario (Toronto) (all in Canada) reported on March 13 ahead of print in *Cancer* on a study designed to assess the clinical impact of pretreatment ^{18}F-FDG PET/CT imaging on staging and management of patients with apparent limited-stage lymphoma under consideration for curative radiation therapy. The registry study included 197 such patients who underwent PET/CT before initiation of treatment, with a pre-PET/CT stage determined by clinical and CT data and/or a referring oncologist opinion based on clinical judgment. Changes in stage and management plans after PET/CT acquisition and analysis were compared with data on actual treatment records available from 155 patients. PET/CT imaging resulted in the upstaging of 47 (23.9%) patients from presumed limited-stage disease (stage I–II) to advanced disease (stage III–IV). Ten (5.1%) patients were downstaged, 4 of whom were downstaged from advanced- to limited-stage disease. Equivocal PET/CT results in 28 (14.2%) patients required further evaluation. After undergoing PET/CT, 95 (61.3%) patients were scheduled to receive active treatment, with 59 planned for radiotherapy alone. Of these, 34 (57.6%) received treatment and almost 80% (n = 27) had confirmed limited-stage disease. The authors concluded that "PET/CT has a significant impact on staging and management in patients with apparent limited-stage indolent lymphoma who are being considered for curative radiotherapy. PET/CT should be routinely incorporated into the workup of these patients."

Cancer

NET Biomarkers and ^{68}Ga-DOTATATE PET/CT

In an article slated to appear in the May issue of the *European Journal of Endocrinology* (2017;176:575–582), Tirosh et al. from the National Institutes of Health (Bethesda, MD), Tel Aviv University (Israel), the Foundation for Research and Technology Hellas (Crete, Greece), University Hospitals of Geneva (Switzerland), Rush University Medical Center (Chicago, IL), and the George Washington University School of Medicine and Health Sciences (Washington, DC) reported on an exploration of the association between neuroendocrine tumor (NET) biomarker levels and extent of disease as assessed by ^{68}Ga-DOTATATE PET/CT imaging. The study included 232 patients (112 with pancreatic NETs, 39 with multiple endocrine neoplasia type 1, 24 with von Hippel–Landau syndrome, 74 with small intestine NETs, 16 with NETs of unknown primary, and 30 with NETs of other prime locations). Biomarkers, including fasting plasma chromogranin A, neuron-specific enolase, gastrin, glucagon, vasoactive intestinal peptide, and pancreatic polypeptide, as well as 24-h urinary 5-hydroxyindoleacetic acid (5-HIAA) levels, were measured. Correlations between these metrics and total ^{68}Ga-DOTATATE–avid tumor volume were analyzed. Multiple specific associations were found between individual biomarkers, uptake, and type of NETs. In 1 example, ^{68}Ga-DOTATATE tumor volume in small intestine NETs was highly correlated with 5-HIAA levels. Five-HIAA $\geq$ 8.1 mg/24 h was associated with metastatic disease, with high positive (81.8%) and negative (85.7%) predictive values. The authors concluded that these "data support the use of specific NET biomarkers based on the site of the primary NET and the presence of hereditary syndrome-associated NET."

European Journal of Endocrinology

^{18}F-Fluoride or ^{18}F-FDG PET After Ischemic Event

Vesey et al. from the University of Edinburgh and the University of

Cambridge (both in the UK) reported on March 10 ahead of print in *Circulation. Cardiovascular Imaging* on a study investigating whether ^{18}F-fluoride or ^{18}F-FDG PET can better identify culprit and high-risk carotid plaque. The study included 26 patients who underwent imaging with both tracers after recent transient ischemic attack or minor ischemic stroke. Eighteen patients had been identified as having symptomatic carotid stenosis and were awaiting carotid endarterectomy, and 8 controls had no symptomatic carotid atheroma. SUVs were compared in the clinically identified culprit and the contralateral asymptomatic artery, and the relationship between radiotracer uptake and plaque phenotype or predicted cardiovascular risk was assessed. The Assessing Cardiovascular Risk Using SIGN Guidelines to Assign Preventive Treatment were used to predict risk. Excised plaque was studied with histology and a microPET/CT. ^{18}F-fluoride selectively highlighted microcalcification on both histology and microPET/CT. ^{18}F-fluoride uptake was increased in clinically identified culprit plaques compared with asymptomatic contralateral arteries ^{18}F-fluoride uptake also correlated with high-risk plaque features and predicted cardiovascular risk. Although ^{18}F-FDG uptake was somewhat increased in 7 of 16 culprit plaques, no overall statistical differences were observed in culprit and contralateral plaques or control patients. ^{18}F-FDG uptake was correlated with predicted cardiovascular risk but not with plaque phenotype. The authors concluded that "^{18}F-fluoride PET/CT highlights culprit and phenotypically high-risk carotid plaque," with the "potential to improve risk stratification and selection of patients who may benefit from intervention."

Circulation. Cardiovascular Imaging

^{99m}Tc-DPD Scintigraphy in Cardiac Amyloidosis

In a study e-published on February 16 ahead of print in *Heart, Lung and Circulation*, Moore et al. from Princess Alexandra Hospital and the University of Queensland (both in Brisbane, Australia) reported on the utility of ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy in the diagnosis of cardiac amyloidosis. The study included 21 patients, 8 with AL (median age, 58 y) and 13 with familial ATTR (median age, 70 y) amyloidosis , who underwent planar whole-body imaging 5 min (soft-tissue phase) and 3 h (bone phase) after ^{99m}Tc-DPD injection. Patients also underwent myocardial SPECT and low-amperage CT imaging after the bone phase scan, as well as electrocardiography and transthoracic echocardiography, with serum tests for troponin I and brain natriuretic peptide levels. ^{99m}Tc-DPD scintigraphy was positive in 2 (25%) patients with AL and 13 (100%) patients with ATTR amyloidosis. Grade of cardiac uptake and mean heart-to-whole-body ratios were higher in ATTR patients. Other parameters assessed did not show significant correlations. The authors concluded that "^{99m}Tc-DPD scintigraphy is highly sensitive for the diagnosis of cardiac ATTR amyloid, but less so for AL amyloid."

Heart, Lung and Circulation

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 March. Emmett et al. from the University of New South Wales (Sydney), Garvan Institute of Medical Research (Darlinghurst), the University of Sydney, Peter McCallum Cancer Institute (Melbourne), and St. Vincent's Hospital (Sydney), all in Australia, reported on "Lutetium 177 PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy" in the March issue of the *Journal of Medical Radiation Sciences* (2017;64:52–60). In an article e-published on March 11 ahead of print in *Photodiagnosis and Photodynamic Therapy*, Kharroubi et al. from the University of Lille/CHU (France) described "Nuclear medicine for photodynamic therapy in cancer: planning, monitoring, and nuclear PDT." Capdevila, from the Vall d'Hebron Institute of Oncology (Barcelona, Spain) and a team of experts from across Spain released their "Consensus on the management of advanced radioactive iodine-refractory differentiated thyroid cancer on behalf of the Spanish Society of Endocrinology Thyroid Cancer Working Group (GTSEEN) and Spanish Rare Cancer Working Group (GETHI)" in the March issue of *Clinical and Translational Oncology* (2017;19:279–287). In an article in the March issue of *Current Treatment Options in Oncology* (2017;18:15), Johnson and Longley from the University of Southampton (UK) asked "Should response-adapted therapy now be the standard of care for advanced Hodgkin's lymphoma?" Alenazy et al. from the University of Ottawa (Canada) reviewed "New solid state cadmium-zinc-telluride technology for cardiac single photon emission computed tomographic myocardial perfusion imaging" in the March issue of *Expert Review of Medical Devices* (2017;14:213–222). In an article e-published on March 15 ahead of print in the *International Journal of Molecular Sciences*, Chou et al. from the Kaohsiung Chang Gung Memorial Hospital/Chang Gung University College of Medicine (Kaohsiung City, Taiwan) provided an overview of "MicroRNA-146b: a novel biomarker and therapeutic target for human papillary thyroid cancer."