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.

## Radiation Dose to NM Techs from PET/MR and PET/CT

Soret et al. from the Hôpital Universitaire Pitié Salpêtrière (Paris, France) reported on March 16 ahead of print in the Journal of Radiological Protection on a study comparing nuclear medicine technologists' radiation doses when performing routine PET/MR and PET/CT acquisitions in the same department. Over 13 mo, daily radiation doses received by technologists were collected with electronic personal dosimeters. Factors included in the retrospective analyses were the total numbers of PET/MR and PET/CT acquisitions, type of study (brain or whole-body PET), <sup>18</sup>F-FDG injected activity per day and per patient, and time spent with patients after injection. The researchers found that technologists' whole-body exposure for PET/ MR averaged  $10.3 \pm 3.5$  nSv per MBq injected <sup>18</sup>F-labeled tracer, compared to only  $4.7 \pm 1.2$  nSv per MBq injected for PET/CT. The additional exposure with PET/MR was attributed to additional time spent in patient positioning and MR coil placement, particularly in wholebody studies. They concluded that "for an equal injected activity, PET technologist radiation exposure for PET/ MR was 2-fold that of PET/CT. To minimize radiation dose to staff, efforts should be made to optimize patient positioning, even in departments with extensive PET/CT experience."

Journal of Radiological Protection

## Monoclonal Antibodies in Alzheimer Disease

In a study published on March 5 ahead of print in the Journal of Alzheimer's Disease, Lacorte et al. from the Italian National Institute of Health (Rome), Sapienza University (Rome), Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan), and the Casa Cura Policlinico (Milan, all in Italy) provided a systematic review and metaanalysis of published and unpublished clinical trials on the safety and efficacy of monoclonal-based antibody therapies in Alzheimer disease (AD). After a systematized search of clinical trial and literature databases, 101 studies were identified, using a total of 27 monoclonal antibodies. Trial results were available on 50 of these investigations (18 with data from published and unpublished sources, 21 with data from published sources only, and 11 with only unpublished data) using a total of 12 monoclonal antibodies. Assessment of reported amyloid-related imaging abnormalities (ARIAs) in these studies showed overall risk ratios of 10.65 for ARIA-E (MR signal alterations thought to represent vasogenic edema and related extravasated fluid phenomena) and 1.75 for ARIA-H (MR signal alterations attributable to microhemorrhages and hemosiderosis). Metaanalyses of PET SUV ratios indicated an overall significant effect of monoclonal antibodies in reducing amyloid burden. Although data from administration of Clinical Dementia Rating Scale-Sorting Box evaluations showed statistically significant lower rates of worsening in treated patients, these were "clinically nonrelevant." The authors concluded that these results suggested that the risks/benefits of monoclonal antibodies remain unclear. They advised that "research should focus on clarifying the effect of amyloid on cognitive decline, providing data on treatment

response rate, and accounting for minimal clinically important differences." In addition, research should investigate the possible long-term impact of ARIA events, including potential predictors of onset.

Journal of Alzheimer's Disease

## CTA vs SPECT/CT V/Q in Pulmonary Embolism

Martins et al. from the University of Campinas (Brazil) reported on February 27 ahead of print in Perfusion on a direct comparison of multidetector CT angiography (CTA) and ventilation/ perfusion (V/Q) SPECT/CT in detection of acute pulmonary emboli (PE) in routine practice. The study included 28 patients (15 men, 13 women; median age, 51.5 v) with suspected acute PE who underwent both imaging procedures. The median duration of symptoms from onset to imaging was 4 d (range, 1-14 d), with a median Wells score of 3.5 (range, 1.5-6). Final diagnoses were determined by clinician consensus (general radiologists and/or nuclear medicine physicians) and supporting clinical, laboratory, and follow-up data. The sensitivity, specificity, positive and negative predictive values, and accuracy for SPECT/CT V/Q in identifying PEs were 84.6%, 80.0%, 78.6%, 85.7%, and 82.1%, respectively. For CTA, the corresponding percentages were 46.1%, 100%, 100%, 68.2%, and 75.0%, with overall agreement between the methods at 57.1%. Ten of the 22 patients with negative CTA findings were positive on SPECT/CT V/O, and 7 of these were determined to be true-positives. The authors concluded that these results suggested that SPECT/CT V/Q "is more sensitive and accurate than CTA when interpreted by general radiologists and nuclear medicine physicians." Perfusion

# Thyroidectomy Without <sup>131</sup>I in DTC

In an article published on March 10 in the *New England Journal of Medicine* (2022;386[10]:923–932) Leboulleux and a consortium of nuclear medicine, endocrinology, and thyroid cancer experts from throughout France reported on a study using results from a prospective phase 3 trial to compare radioiodine therapy (1.1 GBq 131I after injections of recombinant human thyrotropin) with no radioiodine therapy in patients with lowrisk differentiated thyroid cancer after thyroidectomy. The primary objective was to determine whether, in the 2 randomly assigned groups of patients, no radioiodine therapy was "noninferior" to radioiodine therapy, taking into account functional, structural, and biologic abnormalities at 3 v. Noninferiority was defined as between-group differences of <5 percentage points in the presence of abnormal foci of <sup>131</sup>I uptake on whole-body imaging that required subsequent treatment (in the radioiodine group only), abnormal findings on neck ultrasound, or elevated levels of thyroglobulin or thyroglobulin antibodies. The researchers also looked at molecular characterization and prognostic factors. The trial included 730 patients (mean age, 52 y; 606 women, 124 men; 367 in the no-radioiodine group and 363 in the radioiodine group) with tumors  $\leq 2$  cm in diameter. At 3-y follow-up, the percentages of patients in the no-radioiodine group without an event was 95.6%. The corresponding percentage in the group that received radioiodine therapy was 95.9%. Documented events in both groups included structural or functional abnormalities in 8 patients and biologic abnormalities in 23 patients. Events were found to be more frequent in patients with postoperative serum thyroglobulin levels >1 ng/mL during thyroid hormone treatment. No differences in molecular alterations were noted in the 2 groups, and no treatment-related adverse events were reported. The authors concluded that "in patients with low-risk thyroid cancer undergoing thyroidectomy, a followup strategy that did not involve the use of radioiodine was noninferior to an ablation strategy with radioiodine regarding the occurrence of functional, structural, and biologic events at 3 years." The article received wide

coverage in the public media and professional literature. In a commentary accompanying the article (*N Engl J Med.* 2022;386[10]:990–991), David S. Cooper, MD (Johns Hopkins University School of Medicine, Baltimore, MD) praised the study's focus and noted that other trial results may soon provide additional data on this subject, adding "it is noteworthy that although radioiodine therapy for differentiated thyroid cancer was introduced in the 1940s and 1950s, we will finally have definitive evidence to enable clinicians to maximize its benefits and minimize its risks."

New England Journal of Medicine

#### Dynamic SLN Biopsy Technique in Penile Cancer

O'Brien et al. from the Peter Mac-Callum Cancer Centre, the Royal Melbourne Hospital, the Young Urology Researchers Organisation, MURAC Health, and the EJ Whitten Prostate Cancer Research Centre at Epworth Healthcare (all in Melbourne, Australia) presented on March 11 ahead of print in Urology a narrated video of an operative standard for dynamic sentinel lymph node biopsy (DSLNB) in penile cancer and a retrospective clinical analysis and discussion of the accuracy of this approach. The study included 64 patients (127 groins) who underwent DSLNB for inguinal lymph node staging of histologically proven penile squamous cell carcinoma. Data analyzed included primary tumor histology, DSLNB pathology, progression to radical inguinal lymph node dissection (RILND), and recurrence patterns. Of the total 64 patients, 53 (82.8%) underwent penile-sparing surgery. Tumor histology in 56 (88%) patients showed pT1-pT2 disease. Of the total 127 groins explored with DSLNB, 19 were positive for malignancy and 108 were negative. Over a mean follow-up of 29 mo, 36 groins progressed to RILND. Only 2 previously negative DSLNB findings were positive on RILND (1 in the groin, 1 in the pelvis). DSLNB was found to have a false-negative rate of 1.9% and a sensitivity of 90.5%, allowing 71.7%

of groins to proceed for surveillance instead of prophylactic RILND. The authors concluded that "DSLNB is a safe and accurate method for assessing inguinal lymphadenopathy in men with intermediate- to high-risk penile squamous cell carcinoma and impalpable groins." Their video study was intended to establish an operative standard in this setting consistent with international guidelines and expectations. They added that "standardized use of DSLNB by an experienced team will reduce morbidity while maintaining oncological safety for men with intermediate- to high-risk penile cancer and cN0 disease."

Urology

## In-Transit Metastases in Distal Extremity Rhabdomyosarcoma

In an article published on March 12 ahead of print in the European Journal of Surgical Oncology, Terwisscha van Scheltinga et al. from the Princess Máxima Center for Pediatric Oncology (Utrecht, The Netherlands), the University Paris-Saclay/Hôpitaux de Paris (France), University Hospitals Bristol and Weston NHS Foundation Trust (UK), Royal Manchester Children's Hospital (UK), Hospital Universitari Infantil Vall d'Hebron (Barcelona, Spain), University of Bari (Italy), University Hospital of Padua (Italy), Great Ormond Street Hospital (London, UK), Amsterdam UMC/University Amsterdam (The Netherlands), the Royal Marsden Hospital (Sutton, UK), Institut Gustave Roussy (Villejuif, France), University Hospital of Wales (Cardiff, UK), and the University Medical Center Utrecht (The Netherlands) reported on a study evaluating the frequency, staging, and survival of pediatric patients with in-transit metastases in distal extremity rhabdomyosarcoma. In-transit metastases are defined as metastatic lymph nodes or deposits occurring between the primary tumor and proximal draining lymph node basin. The study included 109 patients (median age, 6.2 y; range, 0-21 y) with extremity rhabdomyosarcoma distal to the elbow or knee and enrolled in the European Paediatric Soft Tissue Sarcoma Group RMS 2005 trial between 2005 and 2016.

Thirty-seven patients (34%) had lymph node metastases at diagnosis, and 19 of these had in-transit metastases, most in the lower extremities. In 51 patients who underwent <sup>18</sup>F-FDG PET/CT, suspicious lymph nodes were detected in 24 (47%), with 14 of these having intransit metastases (solitary or in combination with proximal nodes). In the 58 patients not undergoing PET/CT, suspicious lymph nodes were detected in 13 (22%), with in-transit metastases in 5. At a median follow-up of 6.3 y (range, 2-12.5 y), 60 (55%) patients were in first complete remission and 9 (8%) were in remission after relapse. One patient was alive with disease, and 37 (34%) had died (2 patients lost to follow-up). The 5-y event-free survival rates for patients with in-transit metastases, proximal lymph nodes, or combined proximal/in-transit metastases were 88.9%, 21.4%, and 20%, respectively. Corresponding 5-y overall survival rates were 100%, 25.2%, and 15%. The authors summarized their findings that in-transit metastases constituted more than 50% of all lymph node metastases in this group of patients with distal extremity rhabdomyosarcoma and that <sup>18</sup>F-FDG PET/CT improved nodal staging by detecting more regional and intransit metastases. In addition, patients with proximal (axillary or inguinal) lymph node involvement appeared to have worse prognoses. The authors advised that "popliteal and epitrochlear nodes should be considered as true (distal) regional nodes, instead of in-transit metastases," recommending biopsy of these nodes especially in distal extremity rhabdomyosarcoma of the lower limb.

European Journal of Surgical Oncology

## Assessing <sup>131</sup>I Capsule Activity and Reducing Staff Exposure

Zuhayra et al. from the University Hospital of Schleswig–Holstein (Germany) reported on March 17 in *Physica Medica* (2022;96:157–165) on a method for estimating <sup>131</sup>I capsule activity by measuring the dose rate at contact of the delivered lead-closed container carrying the capsules and thereby estimating radiation exposure. This method was compared to that of conventional <sup>131</sup>I capsule measurement using a dose calibrator. The dose rate on the surface of the closed lead container was measured at 2 locations and correlated linearly with <sup>131</sup>I capsule activity measured in a dose calibrator to create calibrating curves. The hand and wholebody (effective) doses were determined with official dose meters during validation of the proposed method in clinical practice. The determination coefficients of linear calibration curves were >0.9974. The total relative uncertainty for estimating <sup>131</sup>I capsule activity with the proposed method was less than  $\pm 7.5\%$ . The reduction of the hand dose with the proposed method was 97% of the conventional measurements of the <sup>131</sup>I capsules by dose calibrators. The authors summarized their findings that "measuring dose rate on the surface of the closed lead containers enables the <sup>131</sup>I capsule activity to be estimated simply, reliably, and with sufficient accuracy" to result in significant reduction of radiation exposure for medical staff.

Physica Medica

## <sup>68</sup>Ga-PSMA-11 PET/CT and ADT Monitoring

In an article published on March 4 in Cancers (Basel) (2022;14[5]:1329), Tseng et al. from the New Taipei Municipal TuCheng Hospital, Chang Gung University School of Medicine (Taoyuan), and Linkou Chang Gung Memorial Hospital (Taoyuan, all in Taiwan) reported on a pilot study evaluating <sup>68</sup>Ga–prostate-specific membrane antigen-11 (68Ga-PSMA-11) PET/CT findings in patients with advanced or metastatic hormone-naïve prostate cancer after 3 mo of androgen-deprivation therapy. The prospective study included 30 men with untreated stage III or IV disease scheduled to receive therapy for at least 6 mo. Participants underwent <sup>68</sup>Ga-PSMA-11 PET/CT imaging before the start of therapy and at 10-14 wk. Response was assessed using a number of factors, including the modified PET Response Criteria in Solid Tumors 1.0, with a subgroup analyzed by International Society of Urological Pathology (ISUP) grade. After 3 mo of treatment, all PET/CT variables indicated significant reductions in disease, showing partial response in 24 patients, complete response in 2, stable disease in 2, and disease progression in 2. In 16 patients with ISUP grade 5, SUV<sub>max</sub> reduction was less marked, and none reached complete response. The authors concluded that these pilot results indicated that "68Ga-PSMA-11 PET/CT imaging holds promise to monitor treatment response after the first 3 mo of androgendeprivation therapy."

Cancers (Basel)

## PSMA-Guided Mets-Directed Therapy in Oligometastatic PCa

Mazzola et al. from the IRCCS Sacro Cuore Don Calabria Hospital (Verona), the Azienda Ospedaliera Universitaria Careggi (Firenzi), University of Florence, University and Spedali Civili Hospital (Brescia), University of Perugia, Humanitas University (Milan), **IRCCS** Humanitas Research Hospital (Milan), and the University of Brescia (all in Italy) reported on March 9 ahead of print in Clinical and Experimental Metastasis on a multiinstitutional study of prostate-specific membrane antigen (PSMA)-guided metastases-directed radiation therapy in patients with bone oligometastatic prostate cancer. The study included 40 men with 56 bone oligometastases detected by PSMA-based PET and with no concurrent androgendeprivation therapy. Oligometastatic disease presented as a single lesion in 28 patients, 2 lesions in 9 patients, 3 lesions in 2, and 4 lesions in 1 patient (30.3% spine metastases, 69.7% nonspine metastases). All patients underwent stereotactic body radiation therapy (SBRT) with a median dose of 30 Gv (range, 24-40 Gv) in 3-5 fractions. Over a median follow-up of 22 mo (range, 2-48 mo), 1- and 2-y local control rates were 96.3% and 93.9%, respectively, with corresponding distant progression-free survival rates of 45.3% and 27%. Additional analyses showed that the lower prostate-specific antigen values after radiation were significantly related to distant progression-free survival. Seven patients were directed to a second radiation course with concurrent androgen-deprivation therapy, and 11 patients with polymetastatic spread received androgen deprivation alone. A lower number of treated oligometastases was correlated with higher androgen-deprivation-free survival rates. The authors concluded that PSMA PET-guided SBRT "resulted in excellent results in terms of clinical outcomes, representing a helpful tool with the aim to delay the start of androgen-deprivation therapy."

Clinical and Experimental Metastasis

# Bone Marrow Activation, Metabolic Syndrome, and Early Atherosclerosis

In an article published on March 11 ahead of print in the European Heart Journal, Devesa and a consortium of investigators from Madrid (Spain) and New York (NY) reported on a study of the associations between cardiovascular risk factors, bone marrow activation, and subclinical atherosclerosis. The study included 745 apparently healthy individuals (624 men, 121 women; median age, 50.5 y, range, 46.8-53.6 y) from the Progression of Early Subclinical Atherosclerosis study. Participants underwent whole-body vascular <sup>18</sup>F-FDG PET/MR imaging. Bone marrow activation (tracer uptake above the median SUV<sub>max</sub>) was assessed in the lumbar vertebrae (L3-L4), and systemic inflammation was evaluated from circulating biomarkers. Early atherosclerosis was assessed by <sup>18</sup>F-FDG uptake in 5 vascular territories, and late atherosclerosis was assessed by fully formed plaques on MR imaging. Men were more likely than women to have bone marrow activation (87.6% and 80.0%, respectively) and to have metabolic syndrome (22.2% and 6.7%, respectively). Bone marrow activation was significantly associated with all metabolic syndrome characteristics, with increased hematopoiesis, and with markers of systemic inflammation, including high-sensitivity C-reactive protein, ferritin, fibrinogen, P-selectin, and vascular

cell adhesion molecule-1. In a subgroup of participants with no systemic inflammation, bone marrow activation remained correlated with metabolic syndrome and increased erythropoiesis. The coexistence of bone marrow activation and arterial <sup>18</sup>F-FDG uptake on PET was associated with more advanced plaque presence on MR imaging. The authors summarized their findings that in "apparently healthy individuals, bone marrow <sup>18</sup>F-FDG uptake is associated with metabolic syndrome and its components, even in the absence of systemic inflammation, and with elevated counts of circulating leucocytes." In addition, bone marrow activation was associated with early atherosclerosis, characterized by high arterial metabolic activity on PET, and appeared to be an early phenomenon in atherosclerosis development. European Heart Journal

# Pediatric Multisystem Inflammatory Syndrome After COVID-19

Astley et al. from the University of Sao Paulo/University of Sao Paulo School of Medicine (Brazil) reported in the March issue of Physiological Reports (2022;10[5]:e15201) on a case series of 5 pediatric survivors of multisystem inflammatory syndrome after COVID-19 infection (3 girls, 2 boys; median age, 9; range, 7-18 y). The researchers evaluated the children at a mean follow-up of 1.9 mo (range, 1.3-6.2 mo) with <sup>13</sup>N-ammonia PET/CT assessment of myocardial blood flow, standard echocardiography, brachial flow-mediated dilation using Doppler ultrasound, a maximal cardiopulmonary exercise test, and blood markers (C-reactive protein, D-dimer, fibrinogen, and troponin-T). At follow-up, 2 patients showed severe perfusion defects in the left ventricular cavity, suggesting extensive myocardial ischemia (myocardial blood flow <2.0), and 1 showed persistent mild pericardial effusion. Another 2 patients showed endothelial dysfunction. None of the patients had chronic conditions predating their COVID hospitalizations. All patients had findings that indicated

impairment in cardiorespiratory and oxidative metabolism during physical exercise with consistently lower than predicted values. The authors summarized their findings that this smallgroup study suggested that previously healthy pediatric patients had impaired myocardial blood flow, endothelial dysfunction, and lower cardiopulmonary capacity at follow-up after multisystem inflammatory syndrome associated with COVID-19. They added that additional exploration of their assessment techniques might aid in clinical decision making for these patients.

Physiological Reports

## PET/CT and Sarcopenia in Elderly Mantle Cell Lymphoma

In an article in the February 23 issue of the Journal of Clinical Medicine (2022;11(5):1210), Albano et al. from the ASST Civil Brescia, the University of Brescia, and the ASST Valcamonica Esine (all in Italy) reported on a comparative study of the prognostic roles of <sup>18</sup>F-FDG PET/CT and CT-estimated sarcopenia in elderly individuals with mantle cell lymphoma. Fifty-three patients (39 men, 14 women; average age, 72.7 y) were included. All participants underwent PET/CT before and at the end of their institutions' standard chemotherapy regimens. Metabolic response was assessed at end-of-treatment PET/CT using Deauville scores. Sarcopenia was assessed as skeletal muscle index derived from low-dose PET/CT images at the L3 level, with specified cutoffs. Thirty-two (60%) patients were defined as sarcopenic. The 3- and 5-y progression-free survival rates were 29% and 23%, respectively. The corresponding overall survival rates were 43% and 33%. At a median follow-up of 50 mo. disease progression or relapse was documented in 37 patients (70%, average time of 17.2 mo; range, 2-62 mo); 26 of those patients had died. Metabolic response, total metabolic tumor volume, total lesion glycolysis, and sarcopenia were all found to be independent prognostic factors for progression-free survival, although no variable was correlated with overall survival. The authors concluded that baseline evaluation of CT and PET may help to define sarcopenia in elderly patients with mantle cell lymphoma.

Journal of Clinical Medicine

## Apatinib in <sup>131</sup>I-Refractory DTC

In an article in the February 23 issue of Frontiers in Endocrinology (Lausanne), Du et al. from Affiliated Cancer Hospital of Zhengzhou University/Henan Cancer Hospital (Zhengzhou, China) and People's Hospital of Changshou District (Chongqing, China) described their experience using apatinib in a group of patients with radioiodine-refractory differentiated thyroid carcinoma (DTC). The study included 47 patients (19 men, 28 women; mean age, 55.8 y; range, 48-68 y) who received 500 mg of apatinib daily for a 4-wk cycle. Participants underwent CT or MR imaging at 4 and 8 wk after initiation of treatment and every 8 wk thereafter. Although no patients achieved complete response, 36 (76.6%) achieved partial response and 8 (17.0%) saw stable disease, respectively. The objective response and disease control rates were 76.6% and 93.6%, respectively. The median progression-free and overall-survival rates were 18 and 59 mo, respectively. Of the 91 adverse events documented, 21

were grade 3 or higher. The authors concluded that apatinib has distinct efficacy in radioiodine-refractory DTC in terms of objective response rates and progression-free and overall survival, with a favorable safety profile.

> Frontiers in Endocrinology (Lausanne)

#### 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 February and March. Roussel et al. from University Hospitals Leuven (Belgium), the San Raffaele Scientific Institute (Milan, Italy). Fox Chase Cancer Center/Temple University Health System (Philadelphia, PA), Radboud University Medical Center (Nijmegen, The Netherlands), University of Texas Southwestern Medical Center (Dallas, TX), the Johns Hopkins University School of Medicine (Baltimore, MD), and the University of Pittsburgh School of Medicine (PA) published "Novel imaging methods for renal mass characterization: A collaborative review" on February 22 ahead of print in European Urology.

Karapanou et al. from the General Military Hospital of Athens, Evangelismos Athens General Hospital, and Alexandra Hospital Athens University School of Medicine (all in Greece) provided an overview of "Advanced RAI-refractory thyroid cancer: An update on treatment perspectives" on March 1 ahead of print in Endocrine-Related Cancer. In an article in the February 25 issue of Frontiers in Endocrinology (Lausanne), Morris et al. from the National Institutes of Health Clinical Center (Bethesda, MD) reviewed "Parathyroid imaging: Past, present, and future." Alzghoof et al. from Amsterdam UMC/Vrije Universiteit (The Netherlands) and the University of Turku (Finland) summarized "a-Synuclein radiotracer development and in vivo imaging: Recent advancements and new perspectives" on March 15 ahead of print in Movement Disorders. Giovanella et al. from the Imaging Institute of Southern Switzerland/Ente Ospedaliero Cantonale (Bellinzona, Switzerland), the University of Turin (Italy), University Hospital of the European University (Limassol, Cyprus), the University of Messina (Italy), and the University Hospital Center Sestre Milosrdnice (Zagreb, Croatia) reported in the March 1 issue of Cancers (Basel) (2022;14[5]:1272) on "Molecular imaging and theragnostics of thyroid cancers."