

*Each month the editor of Newsline selects articles on diagnostic, therapeutic, research, and practice issues from a range of international publications. Most selections come from outside the standard canon of nuclear medicine and radiology journals. These briefs are offered as a monthly window on the broad arena of medical and scientific endeavor in which nuclear medicine now plays an essential role. The lines between diagnosis and therapy are sometimes blurred, as radiolabels are increasingly used as adjuncts to therapy and/or as active agents in therapeutic regimens, and these shifting lines are reflected in the briefs presented here. We have also added a small section on noteworthy reviews of the literature.*

## PET/CT and PRRT

In an article e-published on October 8 ahead of print in *Thyroid*, Versari et al. from the Arcispedale Santa Maria Nuova-IRCCS (Reggio Emilia, Italy) and the University of Pisa (Italy) reported on the utility of  $^{68}\text{Ga}$ -DOTA-TOC PET/CT in selecting appropriate patients with radioiodine-negative progressive differentiated thyroid cancer (DTC) for peptide receptor radionuclide therapy (PRRT). The study included 41 patients, each of whom underwent PET/CT with  $^{18}\text{F}$ -FDG to assess recurrent disease and with  $^{68}\text{Ga}$ -DOTATOC to assess somatostatin receptor (SSTR) expression, as well as dosimetric evaluation with  $^{111}\text{In}$ -DOTATOC scintigraphy.  $^{68}\text{Ga}$ -DOTATOC PET/CT was positive in 24 patients, 13 of whose SSTR expression levels were deemed suitable for PRRT. PRRT resulted in disease control in 7 (2 partial responses, 5 stabilizations) of these patients, with response durations of 3.5–11.5 mo. Functional volume as assessed serially by PET/CT proved to be the only parameter associated with a significant difference between lesions that did and did not respond to PRRT. Adverse events associated with PRRT were minimal and included nausea, weakness/lack of energy, and

transient hematologic toxicity, although one patient experienced permanent renal toxicity. Symptom relief was noted as an objective response in the majority of treated patients. The authors concluded that because SSTR imaging yielded positive results in more than half of the cases with radioiodine-negative DTC and identified PRRT as promising in about one third of patients, that “ $^{68}\text{Ga}$ -DOTATOC PET/CT seems a reliable tool both for patient selection and evaluation of treatment response.” They added that functional volume determination over time appears to constitute a reliable parameter for determining tumor response to PRRT.

*Thyroid*

## Biomarker “Pathways” to AD

Jack et al. from the Mayo Clinic and Foundation (Rochester, MN) reported on October 16 ahead of print in *Neurology* on a study designed to evaluate the incidence of cognitive and imaging findings associated with serial identification of amyloid PET positivity and to better characterize these findings. The retrospective study included 207 cognitively normal individuals ( $\geq 70$  y old) participating in a larger aging study who had 2 or more serial imaging assessments (amyloid PET,  $^{18}\text{F}$ -FDG PET, and/or MR imaging) at specific timepoints, as well as 12 individuals with Alzheimer disease dementia. Baseline imaging identified 123 cognitively normal participants who were amyloid- $\beta$  negative, 26 of whom met criteria for positive incident amyloid- $\beta$  PET on subsequent imaging.

When compared with the participants who remained amyloid- $\beta$  negative, these 26 showed no differences in other imaging assessment, demographics, or cognitive variables, except for task-free functional connectivity. Eleven of the 26 incident amyloid- $\beta$  positive participants were found to have abnormal hippocampal volume,  $^{18}\text{F}$ -FDG PET findings, or both at baseline. In the remaining 15, incident amyloid positivity occurred

before abnormalities on  $^{18}\text{F}$ -FDG PET and in hippocampal volume. For the 11 participants who showed evidence of neurodegeneration before incident amyloid positivity, the authors noted that combinations of preexisting non-Alzheimer pathophysiologies and  $\tau$ -mediated neurodegeneration might have played roles. The authors concluded that these findings “suggest that both ‘amyloid-first’ and ‘neurodegeneration-first’ biomarker profile pathways to preclinical Alzheimer disease exist.”

*Neurology*

## $^{18}\text{F}$ -FCH PET and HCC

In an article e-published on October 9 ahead of print in *Hepatology*, Bieze et al. from the University of Amsterdam Academic Medical Center (The Netherlands) reported on the diagnostic accuracy of  $^{18}\text{F}$ -fluorocholine ( $^{18}\text{F}$ -FCH) PET in detection of hepatocellular carcinoma (HCC) and evaluation of disease extent. The study included 29 patients with HCC lesions  $>1$  cm, with diagnoses based on American Association for the Study of Liver Diseases criteria. All patients underwent  $^{18}\text{F}$ -FCH PET/CT imaging at baseline (before treatment), with 6 patients undergoing PET/CT immediately after treatment. A single patient received a third follow-up image. A total of 53 intrahepatic lesions were identified in these patients, with 48  $^{18}\text{F}$ -FCH PET-positive findings (sensitivity 88%, specificity 100%). PET/CT was also positive in 18 extrahepatic lesions, with no uptake in 3 lesions confirmed to be non-HCC (accuracy 100%). In all, PET/CT identified additional lesions not identified with other methods in 17 patients, with implications for treatment and management in 15 of these. The authors concluded that these results demonstrate the added value of  $^{18}\text{F}$ -FCH PET in patients with HCC, with “implications for staging, management, and treatment evaluation because of accurate assessment of extrahepatic disease.”

*Hepatology*

## **<sup>99m</sup>Tc-Mebrofenin SPECT for RT Planning**

Shen et al. from the University of Alabama at Birmingham reported on October 3 ahead of print in *Medical Dosimetry* on a procedure using <sup>99m</sup>Tc-mebrofenin SPECT for optimizing radiation therapy treatment planning in liver cancers and metastases. Because both conventional radiotherapy and stereotactic body radiosurgery require sufficient functional liver volumes, functional imaging is a logical and accessible approach for radiotherapy planning in liver cancer and metastases. With this technique, patients are immobilized and imaged in position with a SPECT/CT system and a radiotherapy-simulation CT system. The <sup>99m</sup>Tc-mebrofenin SPECT images were coregistered with the planning CT using the noncontrast CT from SPECT/CT. Voxels indicating higher uptake of tracer on SPECT were transferred to the planning CT to constitute an avoidance structure in optimizing a plan for stereotactic body radiosurgery therapy delivery. In a preliminary patient, the authors achieved excellent dose coverage to the target, with sparing of healthy remnant liver volume.

*Medical Dosimetry*

## **SPECT/CT and the Patellofemoral Joint**

In an article e-published on October 11 ahead of print in *Knee Surgery, Sports Traumatology, Arthroscopy*, Schön et al. from the Kantonsspital Baselland–Bruderholz (Switzerland) looked at the question of whether patella height/tilt and/or leg alignment affect <sup>99m</sup>Tc-HDP SPECT/CT uptake and distribution in the patellofemoral joint. The retrospective study looked at SPECT/CT and radiographic records in 84 knees. Radiographs were analyzed for patellar height and patellofemoral angle, with mechanical leg alignment classified as varus, valgus, or neutral. SPECT/CT results were analyzed for each anatomic region imaged. An abnormally low-lying patella (patella baja) was found to correlate significantly with higher uptake on SPECT/CT in all patellar and lateral femoral regions, whereas a higher lateral patellar

tilt correlated significantly with higher <sup>99m</sup>Tc-HDP uptake in the superior lateral femoral areas and the tibial tubercle. Significantly higher SPECT/CT tracer uptake was identified on the medial and patellofemoral joint in mechanically varus and valgus aligned knees, respectively. The authors concluded that because “the intensity and distribution of the SPECT/CT significantly correlated with patella baja and patellar tilt, SPECT/CT might be considered as an imaging modality for evaluating patients with patellofemoral disorders and for follow-up of patients after patellofemoral realignment procedures.”

*Knee Surgery, Sports Traumatology,  
Arthroscopy*

## **Multimodal SN Guidance in Vulvar Cancer**

Mathéron et al. from The Netherlands Cancer Institute and Antoni van Leeuwenhoek Hospital (Amsterdam) reported on September 17 ahead of print in *Gynecologic Oncology* on a study using a hybrid radioactive/fluorescent tracer to evaluate multimodal-based sentinel node (SN) biopsy in vulvar cancer. The study included 15 patients (29 groins) scheduled for SN biopsy. Each patient was injected peritumorally with an indocyanine green-<sup>99m</sup>Tc-nanocolloid before lymphoscintigraphy and SPECT/CT imaging. In 13 patients, blue dye was injected around the identified lesions and SNs were resected using a combination of radiotracing, fluorescence imaging, and optical blue dye detection. Excision of the SNs was confirmed with portable  $\gamma$  camera imaging before and after the procedure. Preoperative lymphoscintigraphy and SPECT/CT imaging accurately visualized drainage to 39 SNs in 28 groins. In the procedure, 98% of SNs were radioactive, with 96% visible on fluorescence imaging and 65% of the SNs stained blue at time of excision. The authors concluded that indocyanine green-<sup>99m</sup>Tc-nanocolloid “can be used for preoperative SN identification and enables multimodal (radioactive and fluorescent) surgical guidance in patients with vulvar cancer.” They added that the addition of fluorescence-based optical guidance in this

setting is more effective in SN visualization than blue dye.

*Gynecologic Oncology*

## **Freehand SPECT in the OR**

In an article e-published on September 17 ahead of print in the *European Journal of Surgical Oncology*, Mihaljevic et al. from the Technische Universität München (Germany) reported on the use of “freehand” SPECT in sentinel lymph node biopsy in patients with malignant melanoma. The authors characterized freehand SPECT as “a novel imaging modality combining  $\gamma$  probes, surgical navigation systems, and emission tomography algorithms, designed to overcome some of the limitations of conventional  $\gamma$  probes.” The study included 20 patients with malignant melanoma who underwent routine planar scintigraphy before surgery. In the operating room, each patient underwent a preliminary scan with freehand SPECT to identify the number and location of separable sentinel lymph nodes, with resulting data used to create a 3D-image of the target site, as well as a scan with a conventional  $\gamma$  probe. After sentinel lymph node biopsy, another conventional scan was performed to document excision of all targeted nodes. Planar scintigraphy before surgery identified 40 sentinel lymph nodes in 26 nodal basins. Preincision freehand SPECT identified 38 of these nodes and an additional node (95.0% node-based sensitivity). Freehand SPECT results were identical to those with planar scintigraphy in 25 basins, although it missed one basin (96.2% basin-based sensitivity). In comparison, the  $\gamma$  probe did not detect 7 nodes in 4 basins (82.5% node-based sensitivity, 84.6% basin-based sensitivity). Freehand SPECT detected 9 remaining radioactive spots after initial resection, 2 of which were then resected because they matched sentinel node positions identified on preoperative planar scintigraphy. The authors concluded that “freehand SPECT provides a real-time, intraoperative 3D-image of the radioactive labeled sentinel lymph nodes, facilitating their detection and resection.”

*European Journal of Surgical  
Oncology*

## Florbetapir PET in AD, MCI, and Normal Aging

Johnson et al. from the Massachusetts General Hospital and Harvard Medical School (Boston, MA) reported on October 9 ahead of print in *Alzheimer's and Dementia* on a study assessing the performance characteristics of  $^{18}\text{F}$ -florbetapir PET in patients with Alzheimer disease (AD) or mild cognitive impairment (MCI) and in healthy age-matched control individuals. The study included 184 participants (45 with AD, 60 with MCI, and 79 healthy controls) who underwent  $^{18}\text{F}$ -florbetapir PET imaging in which amyloid- $\beta$  burden was assessed both visually and quantitatively to yield classifications of positive or negative. Seventy-six percent of AD patients were rated as amyloid- $\beta$  positive, as were 38% of MCI patients and 14% of healthy controls. Amyloid-positive status and mean cortical amyloid burden were associated positively with increasing age and apolipoprotein-E  $\epsilon 4$  carrier status. The authors concluded that these data, which are consistent with expected rates of amyloid positivity among individuals with clinical diagnoses of AD and MCI, "indicate the potential value of  $^{18}\text{F}$ -florbetapir PET as an adjunct to clinical diagnosis."

*Alzheimer's and Dementia*

## Prognostic Models in Follicular Lymphoma RIT

In an article e-published on October 15 ahead of print in *Clinical Cancer Research*, Press, from the Fred Hutchinson Cancer Research Center (Seattle, WA), and colleagues from a range of research facilities reported on an analysis of prognostic factor models for follicular lymphoma, using results from a phase III trial comparing 6 cycles of CHOP-rituximab (CHOP-R) with 6 cycles of CHOP followed by  $^{131}\text{I}$ -tositumomab (CHOP-RIT) in follicular lymphoma. The goal was to compare 3 prognostic models (the Follicular Lymphoma International Prognostic Index [FLIP] 1, the FLIP 2, and the lactate dehydrogenase [LDH] + serum  $\beta 2$  microglobulin

[ $\beta 2\text{M}$ ] models) and to determine whether any subgroups of patients benefitted more from 1 treatment or the other. The study included results from 532 patients enrolled in the trial. Although outcomes were good in both arms of the study (5-y progression-free survival was 60% with CHOP-R and 66% with CHOP-RIT; 5-y overall survival was 92% with CHOP-R and 86% with CHOP-RIT; yielding an overall response rate of 84% for both arms), only  $\beta 2\text{M}$  was found to trend toward significance as a predictor of treatment outcomes. Patients with normal  $\beta 2\text{M}$  experienced greater progression-free survival with CHOP-RIT than with CHOP-R, a difference not seen in patients with abnormal  $\beta 2\text{M}$ . The authors concluded that although all 3 prognostic models predicted both progression-free and overall survival, the LDH +  $\beta 2\text{M}$  model was the easiest to apply and succeeded in identifying a poor-risk subset. With application of the LDH +  $\beta 2\text{M}$  model, the authors identified a statistically significant trend indicating that "low-risk patients had superior observed progression-free survival if treated with CHOP-RIT, whereas high-risk patients had a better progression-free survival with CHOP-R."

*Clinical Cancer Research*

## Surveillance Imaging and Relapse in NHL

Truong et al. from West Virginia University (Morgantown, WV) reported on October 10 ahead of print in *Clinical Lymphoma, Myeloma, and Leukemia* on a study evaluating the routine use of surveillance CT and/or PET/CT in detecting first relapse in patients with non-Hodgkin lymphoma (NHL) in complete remission after first-line therapy. The retrospective study looked at the records of 163 patients who experienced a first relapse of NHL after achieving a complete response with first-line therapy. The authors focused on the way in which relapse was detected (surveillance CT or PET/CT, patient-reported symptoms, findings at physical examination) and data on baseline histologic type, cost of surveillance PET/

CT, number of additional diagnostic imaging procedures, number of invasive procedures, and iatrogenic complications resulting from imaging. Most relapses ( $n = 127$ ; 77.9%) were detected by patient-reported symptoms or physical examination (or both), compared with only 22.1% ( $n = 36$ ) by surveillance imaging. Patient-reported symptoms led to detection of the majority of relapses in aggressive as well as indolent NHL. Surveillance PET/CT contributed to >75% of follow-up costs in the first 2 y of monitoring. No overall survival differences were noted in the 2 groups. The authors concluded that these data suggest "a limited role for surveillance imaging by CT or PET/CT in detecting first relapse in NHL."

*Clinical Lymphoma, Myeloma, and Leukemia*

## Monitoring vs Neck Dissection After CRT

In an article e-published on September 30 ahead of print in *Laryngoscope*, Khodayari et al. from the University of California Davis Comprehensive Cancer Center (Sacramento) reported on a study looking at the effect of neck dissection on outcomes in patients with residual PET-negative lymphadenopathy after chemoradiotherapy for head and neck cancer. The retrospective study included the records of 55 patients with stage III/IV squamous cell carcinoma of the head and neck with residual PET-negative lymphadenopathy (standardized uptake value <3). All patients had undergone chemoradiotherapy to a median dose of 70 Gy (range, 60–64 Gy). Over a median follow-up of 30 mo (range, 6–67 mo), 3-y overall survival, progression-free survival, and local-regional control did not differ between patients who underwent neck dissection and those who were observed. The authors concluded that "omission of neck dissection appears to be reasonable for patients with residual lymphadenopathy but negative PET after chemoradiotherapy for head and neck cancer."

*Laryngoscope*

## PET/CT and Early Response to Neoadjuvant Chemo in Breast Cancer

Andrade et al. from the Camargo Cancer Hospital (São Paul, Brazil) reported on October 2 ahead of print in the *European Journal of Surgical Oncology* on a study assessing whether  $^{18}\text{F}$ -FDG PET/CT can be used to predict early response to neoadjuvant chemotherapy in breast cancer. The study included 40 patients (mean age, 41.9 y) with invasive ductal breast carcinoma (median tumor size, 6 cm) who underwent PET/CT at baseline and after 2 cycles of neoadjuvant chemotherapy. All patients then proceeded to surgery and pathology evaluation of response. Pathologic complete response was achieved in 12 (30%) patients. Maximum standardized uptake values ( $\text{SUV}_{\text{max}}$ ) in tumors at baseline and after second-course neoadjuvant chemotherapy were 8.97 and 4.0, respectively. Patients with pathologic complete response had a significantly higher relative change in  $\text{SUV}_{\text{max}}$  in tumors between baseline and after second-course neoadjuvant therapy than patients who were not pathologic complete responders (−81.58% and −40.18%, respectively). The optimal change in SUV threshold that discriminated between pathologic complete responders and nonresponders was −71.8% (83.3% sensitivity, 78.5% specificity). The optimal change in SUV threshold to discriminate between neoadjuvant chemotherapy responders and nonresponders was −59.1% (68% sensitivity, 75.0% specificity). The authors concluded that these data “suggest that the FDG-PET/CT [change in] SUV after the second course of neoadjuvant chemotherapy can predict pathological response in ductal breast carcinomas and potentially identify a subgroup of nonresponding patients for whom ineffective chemotherapy should be avoided.”

*European Journal of Surgical Oncology*

## PET/CT + MR in Arthritis

In an article appearing in the October issue of the *Chinese Medical Journal* (2013;126:3732–3738), Zhang et al. from Peking University People's

Hospital (Beijing, China) reported on a study using  $^{18}\text{F}$ -FDG PET/CT, MR imaging, and arthritis score to look at different methods for dynamic evaluation in a rat model of rheumatoid arthritis. The study included 16 healthy 8-wk-old rats, in half of whom arthritis was induced. Arthritis scores were recorded on each group, and all rats underwent PET/CT and MR imaging every 3 d. All rats were killed at 5 wk, followed by histopathologic studies. Arthritis scores and standardized uptake values (SUVs) peaked at 21 d after injection in the arthritis group after gradual progression. The arthritis scores in knee joints correlated closely with SUV changes, and MR findings were confirmed by histopathology. The authors concluded that “PET/CT can detect the earliest molecular metabolism changes of rheumatoid arthritis, and MR imaging can follow up the dynamical anatomical changes,” suggesting that PET/CT and MR may be useful for monitoring disease progression.

*Chinese Medical Journal*

## PET/CT and Oncolytic Virus Treatment

Koski et al. from the University of Helsinki (Finland) reported on October 7 ahead of print in *Human Gene Therapy* on the predictive ability of CT and  $^{18}\text{F}$ -FDG PET in oncolytic virus treatments, where inflammatory tumor swelling may confound conventional CT. The report included a laboratory study in small animals as well as results from 2 retrospective studies in patients undergoing oncolytic virus treatment. In the animal study, immunocompetent hamsters were treated with intratumoral adenovirus injections, tumor growth was measured, and  $^{18}\text{F}$ -FDG uptake was assessed. The retrospective series included 17 patients with advanced cancer treated with oncolytic adenoviruses in the Advanced Therapy Access Program (ATAP), each of whom underwent radiologic response evaluation with both contrast-enhanced CT and  $^{18}\text{F}$ -FDG PET. A third set of retrospective data on radiological response and survival included 182 patients treated with oncolytic adenoviruses in the ATAP and looked at the relative prognostic abilities of CT and PET. In all studies, responses in CT and

PET were well correlated and, in the human studies, were equally reliable in predicting survival after oncolytic adenovirus treatment. The authors noted that new  $^{18}\text{F}$ -FDG-avid lymph nodes on PET after virus treatments may represent inflammation and should not be interpreted as treatment failure when other signs of disease progression are also absent. Their data suggested that  $^{18}\text{F}$ -FDG PET is likely to be more sensitive in detection of response than in assessing tumor size.

*Human Gene Therapy*

## 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 reviews accessioned into the PubMed database in September and October. On October 7, ahead of print in *Arthritis Care and Research*, Bruijnen et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported on “The present role of positron emission tomography in diagnosis and monitoring of peripheral inflammatory arthritis: a systematic review.” Khemthongcharoen et al. from the National Electronics and Computer Technology Center (Pathum Thani, Thailand) summarized “Advances in imaging probes and optical microendoscopic imaging techniques for early in vivo cancer assessment” on October 9 ahead of print in *Advanced Drug Delivery Reviews*. In an article e-published on September 11 ahead of print in the *Journal of Controlled Release*, Oliveira et al. from Utrecht University and University Medical Center Utrecht (The Netherlands) reviewed “Targeting tumors with nanobodies for cancer imaging and therapy.” Hommet et al. from Tours University Hospital (France) provided an overview of “Neuroinflammation and  $\beta$  amyloid deposition in Alzheimer's disease: in vivo quantification with molecular imaging” in the October issue of *Dementia and Geriatric Cognitive Disorders* (2013;37: 1–18). On October 1, ahead of print in *CA: Cancer Journal for Clinicians*, Thakor and Gambhir looked at “Nanooncology: the future of cancer diagnosis and therapy.”