that the benefits of drugs have been much overrated and the harms underrated." They also cited research indicating that comparisons of trial protocols with published papers have also shown "widespread selective reporting of favorable results." These criticisms extend beyond Europe, with the example of unnecessary cardiac deaths among individuals taking Vioxx in the United States cited as an example. Complete access to all early trial results with Vioxx, the authors suggested, might have forced regulators to give additional scrutiny to the drug and/or influenced physicians in prescribing it.

The authors detailed their own 3-y effort to secure access to unpublished reports held by the EMA on clinical trials conducted on 2 antiobesity drugs, rimonabant and orlistat. In enumerating their difficulties in accessing this information, the authors also detailed the basic principles governing citizens' access to European Union documents. Among the arguments set forth by the EMA for not releasing the documents in the 3 y during which the authors attempted to access the unpublished results were: protection of commercial interests, no overriding public interest, the administrative burden involved, and the lack of value the data would have after the EMA redacted selected documents. The EMA reversed its stance in 2010 only after a press release from an ombudsperson in the case accused the agency of "maladministration." The authors as well as the ombudsperson concluded that "the EMA put protecting the profits of the drug companies ahead of protecting the lives and welfare of patients." On November 30, 2010, the EMA announced it would widen public access to documents including trial reports and protocols.

British Medical Journal

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. We have added a special section on molecular imaging, including both radionuclide-based and other molecular imaging efforts, in recognition of the extraordinary activity and promise of diagnostic and therapeutic progress in this area. 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.

THERAPY

Long-Term Toxicity and Myeloablative RIT

In an article e-published on May 12 ahead of print in *Cancer*, Giudetti et al. from the National Cancer Institute (Milan, Italy) reported on a study evaluating hematopoietic damage and incidence of secondary myelodysplastic syndrome and acute myelogenous leukemia in patients who received myeloablative doses of the radioimmunotherapeutic ^{90}Y-ibritumomab tiuxetan. The study included 53 elderly patients with non-Hodgkin lymphoma (NHL). All patients underwent autograft after high-dose radioimmunotherapy (RIT) myeloablative conditioning with ^{90}Y-ibritumomab tiuxetan. At 49-mo follow-up after RIT, 4 patients had developed secondary myelodysplastic syndrome and/or acute myelogenous leukemia (at 6, 12, 27, and 36 mo). The 5-y cumulative incidence was 8.29%. Results from these patients were compared in a matched-pair analysis with those from 55 NHL patients who had undergone autografts after chemotherapy-based myeloablative conditioning but did not receive RIT, where the latter group was found to have an 8.05% overall incidence of secondary myelodysplastic syndrome and/or acute myelogenous leukemia. The RIT group was found to have a significant but transient decrease in bone marrow granulocyte-macrophage progenitors and a significant and persistent shortening of bone marrow telomere length. The authors concluded that the limited toxicity noted in the study patients, as well as the comparative results, indicated that "the development of secondary myelodysplastic syndrome/acute myelogenous leukemia was not influenced substantially by high-dose RIT."

Cancer

^{90}Y-hPAM4 and Pancreatic Cancer

Gulec and colleagues from the Goshen Center for Cancer Care (IN) and the Garden State Cancer Center (Belleville, NJ) reported on April 28 ahead of print in *Clinical Cancer Research* on the results of a phase 1 single-dose escalation trial assessing the utility of ^{90}Y-clivatuzumab tetraxetan (radiolabeled human antibody hPAM4, which binds a mucin glycoprotein expressed in pancreatic adenocarcinomas) in individuals with advanced pancreatic carcinoma. The study included 20 patients (4, stage 3; 16 stage 4) who underwent ^{111}In-hPAM4 imaging and serum sampling before receiving varied doses of ^{90}Y-hPAM4 (15 mCi/m^2, 7 patients; 20 mCi/m^2, 9 patients; 25 mCi/m^2, 4 patients). Among the factors assessed as part of phase 1 data were adverse events, safety, CT results, bio-

markers, pharmacokinetics, radiation dosimetry, and immunogenicity (human antihuman antibody response). Initial findings were normal biodistribution and acceptable radiation doses to red marrow and solid organs, as well as successful tumor targeting in 12 patients. The treatment was well tolerated, with the only significant drug-related toxicities being grade 3–4 neutropenia and thrombocytopenia that increased with dose. Three patients who received the 25 mCi/m^2 experienced dose-limiting toxicity with grade 4 cytopenias later than d 7, which established 20 mCi/m^2 as the maximal tolerated ^{90}Y dose. Although most of the participants experienced rapid disease progression during the study, 7 remained progression-free as assessed by CT for 1.5–5.6 mo, including 3 who achieved transient partial responses (32%–52% tumor shrinkage). The authors concluded that "^{90}Y-clivatuzumab tetraxetan was well tolerated with manageable hematological toxicity at the maximal tolerated ^{90}Y dose, and is a potential new therapeutic for advanced pancreatic cancer."

Clinical Cancer Research

Chemo + RIT in NHL

In an article e-published on May 2 ahead of print in *Annals of Oncology*, Zinzani et al. from the University of Bologna (Italy) reported on a phase 2 trial of a short course of fludarabine, mitoxantrone, and rituximab (FMR) followed by ^{90}Y-ibritumomab tiuxetan in untreated intermediate-to-high-risk follicular non-Hodgkin lymphoma (NHL). The study included 55 patients who were treated on a protocol of 4 induction cycles of FMR chemotherapy, followed at 8–14 wk by a consolidating single administration of ^{90}Y-ibritumomab tiuxetan. Only patients experiencing a partial response after induction and with normal platelet and granulocyte counts and a bone marrow infiltration ≤25% were eligible for radioimmunotherapy (RIT). The overall response rate to the induction cycles was 96% (38 complete and 15 partial responses). All patients who had experienced complete responses and 13 with partial responses received RIT. At the end of RIT, a total of 49 patients achieved complete responses, with an estimated 3-y progression free survival of 81% and 3-y overall survival of 100%. The authors concluded that this study "established feasibility, tolerability, and efficacy of a regimen composed by short FMR induction with ^{90}Y-ibritumomab tiuxetan consolidation in untreated intermediate/high-risk follicular NHL patients."

Annals of Oncology

MOLECULAR IMAGING/ THERAPY

Protocol for PET Study Questioned

In a letter to the editor published in the May 11 issue of the *Journal of the American Medical Association* (*JAMA*; 2011;305:1857), the consumer advocacy organization Public Citizen took issue with an earlier *JAMA* article on the merits of ^{18}F-florbetapir PET in early Alzheimer disease. In that earlier article Clark, from Avid Radiopharmaceuticals (Philadelphia, PA), and colleagues from clinical practice reported on January 19 (2011;305:275–283) on results obtained in 35 patients near the end of their lives (6 to establish the protocol and 29 to validate) and 74 young individuals presumed free of brain β-amyloid. Results of ^{18}F-florbetapir PET in the elderly group were compared with findings at autopsy and were found to correlate with the presence and density of β-amyloid. The authors concluded that "These data provide evidence that a molecular imaging procedure can identify β-amyloid pathology in the brains of individuals during life" and that "additional studies are required to understand the appropriate use of florbetapir-PET imaging in the clinical diagnosis of Alzheimer disease and for the prediction of progression to dementia." In the May commentary, Carome and Wolfe from Public Citizen took issue with the way Clark et al. reported PET reader findings, "submitting only median values, not the critical individual reader score data" given by Avid Radiopharmaceuticals to the U.S. Food and Drug Administration (FDA) in September 2010. The 3 readers in the study were highly trained for this study, yet showed substantial inter-reader variability, so that median values could be misleading. Carome and Wolfe added that although the study used patient populations at "2 extremes of the spectra for both age and health," results were still disparate across the range of individual readers. They concluded: "If widely deployed in the real-world setting, with more variability in reader training and skill and in the patient population for whom florbetapir-PET presumably is intended, the performance of the test will most likely be worse. For these reasons, in our opinion the FDA should not approve florbetapir for diagnosis of Alzheimer's disease."

Journal of the American Medical Association

Imaging DNA Damage in Real Time

In an article e-published on May 17 ahead of print in *Cancer Research*, Cornelissen et al. from the University of Oxford (UK) reported on a real-time method to image DNA damage during oncogenesis and therapeutic responses to cytotoxic drugs using γ-H2AX-targeted immunoconjugates. One of the most well-validated markers of the generation of a DNA double-strand break and DNA damage response activation is the phosphorylation of the histone H2AX. The modified phosphorylated form, γH2AX, labels the sites of DNA damage, and its detection is a reliable indicator of the cellular events associated with DNA damage generation. The authors developed fluorophore- and radioisotope-labeled immunoconjugates to target γH2AX, and anti-γH2AX antibodies were modified with diethylenetriaminepentaacetic acid to allow ^{111}In radiolabeling or fluorophore Cy3 tagging. A cell-penetrating peptide

was added to aid nuclear translocation. In vitro studies were conducted in irradiated breast cancer cells and confirmed colocalization of the anti-γH2AX peptide with γH2AX foci as well as retention in cells. In a mouse xenograft model of human breast cancer, the tracer was detectable with both fluorescence imaging and SPECT in amounts proportionate to the radiolabel and amounts of γH2AX present The authors concluded that these findings "establish the use of radioimmunoconjugates that target γH2AX as a noninvasive imaging method to monitor DNA damage with many potential applications in preclinical and clinical settings."

Cancer Research

Cerenkov Luminescence and Thyroid Imaging

In an article e-published on May 7 ahead of print in *Endocrine Journal*, Jeong et al. from the Kyungpook National University School of Medicine (Daegu, Korea) reported on feasibility studies of Cerenkov luminescence imaging (CLI) of radioiodine in the thyroid gland and human anaplastic thyroid carcinoma cells expressing the sodium iodide symporter (NIS) gene. In in vitro optical studies, Cerenkov luminescence was confirmed in cells incubated with radioiodine. In vivo CLI of the thyroid gland was performed in mice after injection of radioiodine with and without thyroid blocking. Mice were then implanted with human anaplastic thyroid carcinoma cells expressing the NIS gene, and CLI was performed after injection of ^{124}I. Animals also underwent PET or γ-camera imaging, and CLI intensity results were compared with those from nuclear imaging. CLI clearly demonstrated radioiodine uptake in the thyroid gland and xenografted cells in mice, which was further confirmed by nuclear imaging, with a strong correlation between CLI and nuclear imaging results. The authors concluded that "CLI can provide a new optical imaging strategy in preclinical thyroid studies."

Endocrine Journal

DIAGNOSIS

Disparities in Referral to PET

Gould et al. from the Veterans Affairs (VA) Palo Alto Health Care System (CA) reported in the May 1 issue of the *Journal of Thoracic Oncology* (2011;6:875–883) on a study of racial and economic disparities in lung cancer staging with PET as part of the Cancer Care Outcomes Research and Surveillance study. Their analysis included the records of 3,638 patients with newly diagnosed non–small cell lung cancer from 4 large, geographically disparate regions, including 5 integrated health care systems and 13 VA health care facilities. The median age of patients was 69 y (62% men, 38% women), and 26% of participants were Hispanic or nonwhite. After adjusting for other factors, PET use was 13% lower among nonwhites and Hispanics than in non-Hispanic whites, 13% lower among those with Medicare than those with private insurance, and 24% lower among those with an elementary school education than those with a graduate degree. Disparities in education and insurance levels associated with referral to PET were not observed among patients who received care in an integrated health care setting, but the association between race/ethnicity and PET use was similar in magnitude across all other subgroups. Additional analyses confirmed that income, education, insurance, and health care setting do not explain the association between race/ethnicity and PET use.

Journal of Thoracic Oncology

Incidental Pancreatic Endocrine Tumors

Haynes et al. from the Massachusetts General Hospital (Boston) reported in the May issue of *Archives of Surgery* (2011; 146:534–538) on the characteristics, implications, and short- and long-term outcomes after resection of nonfunctioning pancreatic endocrine tumors identified on PET. The study included a total of 139 patients (median age, 56 y) who underwent resection of incidentally identified tumors (median size, 3.0 cm; range 0.4–17.0 cm; 21 [18.7%] benign; 39 [28.1%] malignant; 72 [51.8%] uncertain; 2 unclassified). Complete follow-up data were available for 112 patients (80.6%) over a median of 34.2 mo, with 5-y actuarial survival rates calculated at 88.8% for patients with benign disease, 92.5% for patients with tumors of uncertain biology, and 49.8% for those with malignant tumors. Late metastasis, tumor recurrence, or disease progression were seen in 1 patient (3.8%) with a tumor initially classified as benign, 8 patients (11.1%) with uncertain tumors, and 15 patients (38.5%) with tumors classified as malignant. When compared with patients with symptomatic PET results, no large difference was observed in tumor size, patient age, disease, or survival. The authors concluded that "patients with incidentally discovered, nonfunctioning pancreatic endocrine tumors should undergo tumor resection and careful postoperative surveillance, even if surgical pathologic findings suggest benign disease."

Archives of Surgery

Thyroid Cancer and Risk for Lung Mets

In an article e-published on May 7 ahead of print in *Annals of Surgical Oncology*, Lee et al. from the Pusan National University School of Medicine and Medical Research Institute (Republic of Korea) reported on a retrospective study designed to clarify the clinical implications of cervical lymph node metastasis in papillary thyroid cancer (PTC), focusing on risk factors for lung metastasis. The study included 977 patients (829 women, 148 men; median age, 49 y) with PTC who received radioablation therapy followed by a radioiodine whole-body scan or PET/CT to screen for lung metastasis. Positive results were confirmed with chest CT. Among the factors considered in risk analysis were age, gender, extrathyroidal extension, central lymph node metastasis, lateral lymph node metastasis, and bilateral lateral cervical lymph node metastasis. Lung metastases were found in 20 (2.1%) patients. Bilateral lateral cervical lymph node metastases were found in 4.4% (43

patients) of patients. Male sex, older age, large tumors, extrathyroidal extension, lymph node metastasis, lateral lymph node metastasis, and bilateral lateral cervical lymph node metastases were significantly correlated with lung metastasis, with bilateral lateral cervical lymph node metastasis as the only significant risk factor in a multivariate analysis. The authors concluded that "careful examinations, including chest CT and PET, are recommended during the follow-up period when bilateral lateral cervical lymph node metastases is suspected" in patients with PTC.

Annals of Surgical Oncology

^{99m}Tc-ECD SPECT and Carotid Endarterectomy

Nocuń et al. from the Medical University of Lublin (Poland) reported in the May 2 issue of *Medical Science Monitor* (2011;17:CR297–CR303) on the utility of ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) brain SPECT with voxel-based analysis in the evaluation of perfusion changes after carotid endarterectomy. The study group included 30 patients (mean age, 67.4 ± 9.6 y) with internal carotid artery stenosis who underwent carotid endarterectomy. Infarction was shown on CT in 12 patients. All patients underwent ^{99m}Tc-ECD brain SPECT imaging twice: at 1–3 d before endarterectomy and again at 3–5 d after surgery. Voxel-based analysis was carried out, the percentage asymmetry index (AI) was calculated, and the percentage relative difference (RD) in perfusion before and after surgery was computed. Before surgery, cerebral hypoperfusion was seen in 26 patients, including 15 with normal CT. After surgery, perfusion increased in 18 patients (ipsilateral and bilateral), decreased in 1, was mixed in 2, and showed no change in 9. In those patients with both preoperative ipsilateral hypoperfusion and perfusion increase after surgery, AI correlated significantly with RD. The authors concluded that these results suggest that "evaluation of preoperative AI may help to identify patients in whom rapid reperfusion is more likely."

Medical Science Monitor

PET/CT and Psoriasis

In an article e-published on May 16 ahead of print in *Archives of Dermatology*, Mehta et al. from the University of Pennsylvania (Philadelphia) reported on a study designed to evaluate the utility of ^{18}F-FDG PET/CT imaging in detecting and quantifying systemic inflammation in patients with psoriasis. The study included 6 patients with psoriasis affecting more than 10% of body surface area and 4 controls (age/sex matched to 4 of the patients for a nested case-control study). All participants underwent ^{18}F-FDG PET/CT, and tracer uptake in the liver, musculoskeletal structures, and aorta were assessed as a measure of uptake by macrophages and other inflammatory cells. PET/CT imaging showed numerous sites of inflammation in the skin, liver, joints, tendons, and aorta in the patient group. Joint inflammation was shown in 1 patient with arthritis and in another patient without joint pain. In the nested case-control study, PET/CT imaging showed increased vascular inflammation in multiple segments of the aorta in patients compared with controls. The authors concluded that ^{18}F-FDG PET/CT "is a sensitive tool for identifying inflammation and can be used to identify clinically observed inflammation in the skin and subclinical inflammation in the blood vessels, joints, and liver of patients with psoriasis."

Archives of Dermatology

Novel SPECT Approach in PEs

Morris et al. from the University of California San Diego reported on May 12 ahead of print in *Heart, Lung and Circulation* on a clinical study to evaluate the safety of ^{99m}Tc-DI-80B3 (radiolabeled humanized antifebrin-D diner Fab' fragments) in scintigraphic imaging of patients with pulmonary emboli (PEs) and to assess the ability of these images to localize acute PEs. The study included 14 patients with segmental or larger PEs on recent contrast-enhanced CT imaging who were administered ^{99m}Tc-DI-80B3 intravenously. Each patient underwent SPECT imaging at 15 min, 2 h, and 4 h after injection. No serious adverse events or antibody responses were noted. Focal tracer accumulations on SPECT at 4 h corresponded well with PEs on CT. Two SPECT readers unaware of the purpose of the study identified 79% and 71% of the right lungs and 79% and 64% of the left lungs in which CT scans indicated PEs. The authors concluded that ^{99m}Tc-DI-80B3 "may offer a novel approach to imaging PE in a clinically acceptable timeframe without exposure to potentially nephrotoxic radiographic contrast agents."

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 reviews accessioned into the PubMed database in late April and in May. In an article e-published on April 28 ahead of print in *Clinical Oncology (Royal College of Oncology),* Vassiliou et al. from the Bank of Cyprus Oncology Center (Nicosia) provided an overview of "Bone metastases: assessment of therapeutic response through radiological and nuclear medicine imaging modalities." On May 9, ahead of print in *Chemical Society Reviews*, Razgulin et al. from Stanford University (CA) offered "Strategies for in vivo imaging of enzyme activity: an overview and recent advances." Afaq and Akin, from the Memorial Sloan–Kettering Cancer Center (New York, NY) reported in the May issue of *Future Oncology* (2011;7:669–677) on "Imaging assessment of tumor response: past, present, and future." In an article e-published on May 15 ahead of print in the *Journal of Cardiovascular Translational Research*, Bravo and Bengel from Johns Hopkins University (Baltimore, MD) summarized "The role of cardiac PET in translating basic science into the clinical arena."