



Each month the editor of *Newsline* selects article on diagnostic, therapeutic, research, and practice issues from a range of international publications. Many selections come from outside the standard canon of nuclear medicine and radiology journals. This month the literature contained a remarkable number of articles on the utility of PET and other nuclear medicine techniques in predicting response to treatment in a variety of diseases. Several of these are included in this review. Note that although we have divided the articles into diagnostic and therapeutic categories, these lines are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic capabilities are now enlisted in direct support of and, often, in real-time conjunction with therapies. 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.

Therapy

RIT for Fungal Infection

In an article published in the May issue of the *Journal of Infectious Diseases* (2006;193:1427–1436), Dadachova et al. from the Albert Einstein College of Medicine (Bronx, NY) reported on a study designed to elucidate the mechanisms by which radioimmunotherapy (RIT) has been noted to be effective in treating fungal and/or bacterial infections. Investigating the actions of ^{213}Bi -labeled monoclonal antibodies in in vitro studies of *Cryptococcus neoformans*, they found that microbicidal effects resulted mainly from “direct-hit” killing, with contributions from crossfire effect. RIT also promoted apoptosis-like death in fungal cells and was associated with

changes in concentration of specific cytokines interleukin, tumor necrosis factor- α , and interferon- γ , suggesting that therapeutic effects from RIT may be tied to changes in inflammatory response. The authors concluded that their results suggest that the “antimicrobial efficacy of RIT involves killing through promotion of fungal cell apoptosis-like death, reduction in yeast capsule size, cooperation with macrophages, and modulation of the inflammatory response.”

Journal of Infectious Diseases

Surgically Treated Thyroid Cancer in Children

Demidchik and colleagues from Belarus, Germany, and Japan reported in the April issue of *Annals of Surgery* (2006;243:525–532) on a retrospective study to evaluate the results of surgical treatment for thyroid cancer in pediatric patients. The study included 740 individuals who were younger than 15 years old at the time of surgeries, which included total thyroidectomy in 426 (57.6%), lobectomy in 248 (33.5%), subtotal thyroidectomy in 58 (7.8%), and partial lobectomy in 8 (1.1%) patients. Patients were followed for a mean of almost 10 years (although the range was quite broad at 1.5–236.4 months). Of the 204 (27.6%) individuals in whom recurrences were noted, 73 (9.9%) experienced local relapses, 90 (12.2%) distant metastases, and 41 (5.5%) a combination of local and distant recurrences. Factors found to be significantly associated with recurrent nodal disease were young age at diagnosis, multifocal carcinomas, N1 status, and no neck lymph node dissection performed. Significant risk factors for lung metastases were female gender, young age at diagnosis, and presence of symptoms. Postoperative hypoparathyroidism was significantly associ-

ated with multifocal tumors, central compartment removal, and ipsilateral dissection. Overall 5- and 10-year survival rates were higher than 98%. The authors concluded that “total thyroidectomy followed by radioiodine therapy is an optimal treatment strategy that makes it possible to achieve a cure in a vast majority of pediatric patients with differentiated thyroid carcinomas.”

Annals of Surgery

Increasing Radioiodine Uptake in Thyroid Cancer Metastases

Liu et al. from the Leiden University Medical Center (The Netherlands) reported in the April issue of the *European Journal of Endocrinology* (2006;154:525–531) on a study in which the retinoid X receptor activator bexarotene was assessed for its potential to increase ^{131}I uptake in treatment for metastases of differentiated thyroid carcinoma (DTC). The study included 11 patients with metastases from DTC and documented insufficient ^{131}I uptake. Each patient received injections of recombinant human thyroid-stimulating hormone and was imaged with whole-body scintigraphy and SPECT 3 days after administration of 185 MBq ^{131}I . Each patient then received 6 weeks of treatment with 300 mg of bexarotene per day, and the imaging protocol was repeated. The authors found that bexarotene treatment induced ^{131}I uptake in metastases in 8 patients, but uptake was evident only on SPECT, with incomplete matching to metastases on CT. They concluded that bexarotene partially restores ^{131}I uptake in metastases of DTC, but that “the clinical relevance of this observation may be limited due to the differential responses of the different

metastases within each patient and the low intensity of ^{131}I uptake.”

European Journal of Endocrinology

Diagnosis

SPECT in Pediatric Back Pain

Takemitsu and an international group of researchers from Japan, Thailand, and the United States reported in the April 15 issue of *Spine* (2006;15:909–914) on a retrospective study of pediatric athletes with low back pain and unilateral tracer uptake at the pars interarticularis on SPECT but no defect on radiographs. The study included 22 children (average age, 12.3 ± 2.5 years) with these histories and with pain presumed to have resulted from athletic activities. The average duration of pain was 21 ± 23 weeks. Investigation of the clinical record indicated that 19 (86%) children had been found to have increased uptake at L5, 6 (27%) to have spina bifida occulta, and 8 (36%) to have scoliosis. Despite the fact that the majority of patients (18, 82%) had good outcomes, the authors cautioned that those with longer histories of symptoms were more likely to be at risk for persistent pain with athletic activity. They recommended that these patients and those with spina bifida occulta be followed carefully for increased risk of low back pain.

Spine

Selection of Sentinel Nodes for Biopsy

In an article e-published ahead of print in the April 18 edition of the *European Journal of Surgical Oncology*, Morota et al. from the Cancer Institute Hospital (Tokyo, Japan) reported on a study of radioactivity thresholds for sentinel node biopsy in breast cancer. The study included 1,179 procedures for primary breast cancer, in which the level of radioactivity and order of removal of each lymph node were compared with results from pathology. An average

of 1.9 radioactive nodes were biopsied in 686 of 1,177 breasts. Sixty-four of 142 breasts showed metastasis to the most radioactive node only, 39 showed metastasis to nodes other than the most radioactive node, and 39 showed metastasis to both the most radioactive node and other radioactive nodes. The authors concluded that, “it is necessary to harvest radioactive lymph nodes other than the most radioactive” and advised that efforts to remove every radioactive lymph node will minimize false-negative results.

European Journal of Surgical Oncology

PET and Axillary Lymph Node Assessment

Gil-Rendo et al. from the Clinica Universitaria of Navarra (Pamplona, Spain) reported in an article e-published ahead of print on April 18 in the *British Journal of Surgery* on the value of ^{18}F -FDG PET in detecting axillary lymph node involvement in breast cancer. The study included 275 women with breast cancer. All underwent ^{18}F -FDG PET imaging. Axillary lymph node dissection was performed in a subgroup of 150 women, regardless of imaging results. In the second group of 125 women, sentinel lymph node biopsy was performed only in those women in whom pathologic axillary uptake was not demonstrated on PET. In the entire group of 275 patients, the sensitivity and specificity of ^{18}F -FDG PET for detecting axillary involvement were 84.5% and 98.5%, respectively (2 false-positives and 22 false-negatives). PET showed pathologic uptake in 21 women, indicating involvement of the internal mammary lymph node chain. Whole-body PET also identified second synchronous tumors in 5 asymptomatic patients and hematogenous metastases in 2 patients. The authors concluded that the high positive predictive value of PET suggests that tracer uptake in the axilla could be an indication for full axillary lymph node detection without previous sentinel lymph node biopsy.

British Journal of Surgery

Value of Lymphadenectomy in Melanoma

In an article e-published ahead of print on April 12 in the *Annals of Surgical Oncology*, Wong et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) reported on a multi-institutional outcomes study of patients with melanoma who were found to have positive sentinel nodes but did not undergo complete lymphadenectomy. The study included data on 134 patients (median age, 59 years) from 16 institutions who did not undergo complete lymph node dissection (CLND) after positive sentinel lymph node procedures. The primary melanoma was located on the extremities, trunk, and head or neck in 45%, 43%, and 12% of patients, respectively. Median follow-up was 20 months, and median time to recurrence was 11 months. Nodal recurrence was a component of the first site of recurrence in 20 patients (15%), and nodal recurrence-free survival was not statistically different from that seen in a comparative group of patients who underwent CLND. Nor was disease-specific survival for positive-SLN patients who did not undergo CLND (80% at 36 months) significantly different from the group that underwent CLND. The authors concluded that this study emphasizes the “the importance of ongoing prospective randomized trials in determining the therapeutic value of CLND after positive sentinel lymph node biopsy in melanoma patients.”

Annals of Surgical Oncology

PET as Predictor in Esophageal Cancer Treatment

Levine et al. from Wake Forest University (Winston-Salem, NC) reported in the April issue of *Annals of Surgery* (2006;243:472–478) on a study designed to assess the value of ^{18}F -FDG PET in predicting response among patients undergoing concomitant chemoradiation for locally advanced esophageal cancer. Although

approximately 25% of such patients undergo a pathologic complete response to the treatment, most proceed to scheduled resection because other diagnostic methods (CT, endoscopy, ultrasound) are unable to verify response. At the time of publication, the ongoing study had included 64 patients with T3–T4N0M0 or T1–T4N1M0 esophageal cancer who underwent PET imaging before and 4–6 weeks after chemoradiation (cisplatin, 5-fluorouracil, and 50.4 Gy radiation). All patients underwent esophagectomy, and response was determined from pathology results. As expected, a pathologic complete response was found in 27% of patients, with pathologic residual microscopic disease in 14.5%, partial response in 19%, and stable or progressive disease in 39.5%. A pretreatment standardized uptake value (SUV) ≥ 15 was associated with an observed 77.8% significant response (both complete response and residual microscopic disease) compared with only 24.2% significant response for patients with a pretreatment SUV < 15 . Significant response was observed in 71.4% of patients with a posttreatment decrease in SUV ≥ 10 compared with 33.3% when the SUV decreased < 10 . The authors concluded that pre- and posttreatment ^{18}F -FDG PET assessment can be “useful for predicting significant response to chemoradiation in esophageal cancer” and that “these data should be considered in evaluation of patients for esophagectomy after chemoradiation.”

Annals of Surgery

Protocols for PET/CT Treatment Volumes

Riegel et al. from St. Vincent's Comprehensive Cancer Center (New York, NY) reported ahead of print on April 18 in the *International Journal of Radiation Oncology, Biology, Physics* on the need for gross tumor volume (GTV) delineation protocols for PET/CT use in treatment planning in head and neck cancers. The study included 16 patients with head and neck

cancers. Two neuroradiologists and 2 radiation oncologists were asked to contour GTVs first with the information provided by CT alone and then with PET/CT data. The authors found near-significant variation across physicians' CT volumes and significant variation across PET/CT volumes. They noted that whereas 1 radiation oncologist's PET/CT volumes were significantly larger than his CT volumes, the other radiation oncologist's CT volumes were larger than his PET/CT volumes. Although no significant interdisciplinary variation was found, the significant differences in GTVs across these observers led the authors to conclude that the need for a delineation protocol had been confirmed.

International Journal of Radiation Oncology, Biology, Physics

PET/CT in Anal Carcinoma

In another article e-published ahead of print in the April 18 issue of the *International Journal of Radiation Oncology, Biology, Physics*, Cotter et al. from the Washington University School of Medicine (St. Louis, MO) reported on a study comparing the relative efficacies of CT and PET/CT in staging of carcinoma of the anal canal, with special attention to abilities in identifying spread to inguinal lymph nodes. The study included 41 patients with biopsy-proven anal carcinoma who underwent a complete staging procedure, including physical examination, CT, and ^{18}F -FDG PET. PET/CT detected 91% of nonexcised primary tumors (compared with 59% for CT) and identified abnormal uptake in the pelvic nodes of 5 patients with normal pelvic CT scans. PET/CT detected abnormal nodes in 20% of groins that were normal on CT and in 23% that were unremarkable on physical examination. PET/CT also showed abnormal uptake in 17% of groins negative on both CT and physical examination. The authors concluded that PET/CT “detects the primary tumor more often than CT” and “detects substantially more abnormal inguinal lymph nodes than are identified by

standard clinical staging with CT and physical examination.”

International Journal of Radiation Oncology, Biology, Physics

PET for Outcomes Evaluation in Malignant Lymphoma

In an article published in the April issue of *Haematologica* (2006;91:522–529), Zijlstra et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported on a study designed to systematically review the literature on the diagnostic performance of ^{18}F -FDG PET in evaluation of first-line therapy of Hodgkin's disease and non-Hodgkin's lymphoma (NHL). The authors searched major European and U.S. publication databases for relevant studies up to January 2004. After reviewers assessed the methodologic quality of studies reporting adequate statistical results and follow-up periods, 15 studies with a total of 705 patients met the inclusion criteria. The authors noted that most studies were deficient in that they did not indicate whether the gold standard or reference test was interpreted with or without knowledge of PET findings. Pooled sensitivity and specificity for detection of residual disease in Hodgkin's disease were 84% and 90%, respectively, and for NHL were 72% and 100%, respectively. The authors concluded that although PET showed reasonable sensitivity and high specificity for evaluation of first-line therapy in Hodgkin's and NHL, “standardization of procedures is required before implementation in clinical practice.”

Haematologica

PET for Initial Diagnosis in NSCLC

Herder et al. from the VU University Medical Center (Amsterdam, The Netherlands) reported in the April issue of the *Journal of Clinical Oncology* (2006;12:1800–1806) on a cooperative study investigating the utility of PET for initial diagnostic management

(Continued on page 41N)

(Continued from page 36N)

in patients with non-small-cell lung cancer (NSCLC). The study included 465 patients enrolled at 22 hospitals. Patients referred for imaging with a provisional diagnosis of NSCLC were randomly assigned to a traditional work-up according to international guidelines (233 patients) or to ^{18}F -FDG PET imaging with either histologic/cytologic verification or follow-up (232 patients). Patients in the second group whose images indicated noncentral tumors with no mediastinal or distant metastases proceeded directly to thoracotomy. The authors found that the number of procedures to finalize staging was equal in the 2 groups, although the early PET approach significantly reduced the number of mediastinoscopies. Agreement between initial diagnoses and final staging was good in both groups, and costs did not differ significantly. The authors concluded that initial diagnostic use of ^{18}F -FDG PET in patients with suspected lung cancer “does not reduce the overall number of diagnostic tests, but maintains quality of TNM staging with the use of less invasive surgery.”

Journal of Clinical Oncology

PET After Cervical Cancer Therapy

In an article e-published on March 27 ahead of print in *Gynecologic Oncology*, Chung et al. from the National Cancer Center (Goyang, Republic of Korea) reported on the use of ^{18}F -FDG PET in monitoring recurrence in women after treatment for cervical cancer. The retrospective study included 120 women who had undergone whole-body PET imaging after achieving complete response to therapy for cervical cancer. Associated records indicated that 76 patients would have recurrent disease, 20 of whom were asymptomatic at the time of imaging. PET detected 73 (96.1%) of these patients and correctly identified 38 (84.4%) of 45 patients with no recurrence. The specificity and accuracy of PET in assessment of recurrence were 84.4% and 91.7%,

respectively. PET significantly and positively changed management approaches in 24 patients. The authors concluded that PET is a “sensitive posttherapy surveillance modality for detection of recurrent cervical cancer even in asymptomatic patients and aids in deciding treatment plans and, eventually, may have favorable impact on prognosis and survival.”

Gynecologic Oncology

Dopamine Release Differs in Men and Women

In an article e-published ahead of print on April 7 in *Biological Psychiatry*, Munro et al. from the Johns Hopkins University School of Medicine reported on the results of a study using ^{11}C -raclopride PET to explore sex differences in striatal dopamine release in healthy adults. The study was widely covered in the popular and scientific press. The authors compared baseline striatal dopamine binding potential and dopamine release in men and women after either an amphetamine or placebo challenge. No differences were identified in baseline binding potential, but, after amphetamine challenge, men had significantly greater dopamine release than women in the ventral striatum and in 3 of 4 additional striatal regions. Men also rated the positive effects of amphetamines higher than did women. The researchers suggested that the robust dopamine release in men might account for increased vulnerability to stimulant use addictions and methamphetamine toxicity. They concluded that “future studies should control for sex and may have implications for the interpretation of sex differences in other illnesses involving the striatum.”

Biological Psychiatry

PET Correlation with Reported Memory Loss

In another article that was carried widely in the press (with accompanying admonitions to diagnosticians to listen more carefully to patients' self-reports of memory loss), Ercoli et al. from the University of California,

Los Angeles, reported in the April issue of the *Archives of General Psychiatry* (2006;63:442–448) on a study comparing perceived loss of memory ability with cerebral metabolic decline in individuals at genetic risk for Alzheimer's disease. The study included 30 cognitively intact adults (age range, 50–82 years) with age-associated memory complaints. Fourteen of these individuals were carriers of the apolipoprotein E-IV (APOE4) allele associated with risk for Alzheimer's disease. Each participant underwent standardized neuropsychological testing and a self-appraisal of memory functioning measuring frequency of forgetting, seriousness of forgetting, retrospective functioning, and mnemonics use. Each individual also underwent ^{18}F -FDG PET imaging at baseline and after 2 years. At initial evaluation, APOE4 carriers and non-carriers did not differ significantly on objective memory measures or on memory functioning questionnaire scores. However, the factor score for frequency of forgetting correlated significantly with global cerebral metabolic decline after 2 years in all subjects, regardless of genetic risk. The factor score for mnemonics use also correlated significantly with metabolic decline in the temporal regions in APOE4 carriers alone. These results indicated that memory complaints among middle-aged and older individuals may point to underlying and otherwise nonsymptomatic cerebral metabolic changes. Moreover, compensatory strategies, such as mnemonics use by APOE4 carriers, may reflect underlying metabolic changes in specific brain regions associated with prodromal Alzheimer's disease. The authors concluded that, “self-reported mnemonics use may be helpful in identifying persons for clinical monitoring.”

Archives of General Psychiatry

Serial PET in Relapsed Lymphoma

Schot et al. from the University Medical Center (Groningen, The Netherlands) reported in the April

issue of *Haematologica* (2006;91:490–495) on a study to determine the optimal time for pre-autologous stem cell transplantation PET imaging in patients with relapsed lymphoma. The study included 39 patients (28 with aggressive non-Hodgkin's lymphoma [NHL] and 11 with Hodgkin's disease) who were eligible for second-line chemotherapy and stem cell transplantation. Each patient underwent PET imaging at 2 or 3 time points: before treatment; after 2 cycles of induction chemotherapy; and, in individuals with an abnormal second PET, after a third cycle of chemotherapy, just before transplantation. Patients were followed for at least 6 months (median, 22 months) after therapy, and 54% relapsed after stem cell transplantation. Those patients who showed a complete response on PET after the second and third cycles of chemotherapy had 2-year progression-free

survival rates of 71% and 58%. Those who showed no response relapsed soon after transplantation. The authors concluded that 2 serial PET scans predict outcomes after autologous stem cell transplantation more precisely than the more standard single interim PET in patients with relapsed lymphoma.

Haematologica

Cervical Spinal Cord Stimulation

Clavo et al. from the Dr. Negrin University Hospital (Las Palmas, Spain) reported in the April issue of the *Journal of Neurosurgery* (2006; 104:537–541) on a study using ¹⁸F-FDG PET to evaluate changes in glucose metabolism in brain tumors before and during cervical spinal cord stimulation. The authors have previously reported in 3 articles (most

recently in *Ann Oncol.* 2004;15:802–807) on the effects of such stimulation on regional blood flow and oxygenation in head and neck tumors. The study included 11 patients with high-grade gliomas (6 recurrent), who underwent initial PET imaging to verify status, followed by cervical spinal cord stimulation. A second PET study was acquired during stimulation. Basal glucose metabolism was found to be higher in tumor than in peritumoral areas, with significant increases in glucose uptake during stimulation of 43% and 38%, respectively. The authors concluded that this study confirms a modification of locoregional blood flow and oxygenation by cervical spinal cord stimulation and suggest that these results “open up new approaches to modifying the effect of radiochemotherapy in the treatment of malignant brain tumors.”

Journal of Neurosurgery

(Continued from page 33N)

PET as Focus of Annual BMJ Spoof

The medical world waits with bated breath for the annual *British Medical Journal* (*BMJ*) contribution to straight-faced farce on April 1. This year, the fictitious but soberly reported offering focused on a neurologic application of PET in “a new and potentially life-threatening condition called motivational deficiency disorder (MoDeD).” Citing the groundbreaking work of Dr. Leth Argos, a neurologist at the University of Newcastle in Australia, the article described the primary symptoms of MoDeD as “overwhelming and de-

bilitating apathy, which in severe cases can lead to a potentially fatal complication: a lack of motivation to breathe.” PET was featured as the optimal diagnostic approach for the condition. The article noted that 1 study estimated that 1 in 5 Australians may have the condition, costing the economy \$1.7 billion per year in lost productivity. But, the article continued, help may be on the way in the form of Indolebant, a cannabinoid CB1 receptor to be marketed by Healthtec, an Australian biotechnology company concluding phase II trials of the MoDeD treatment. Argos was quoted as noting, “Indolebant is effective and well tolerated. One young man who could not leave his

sofa is now working as an investment adviser in Sydney.” *BMJ* carried the satire a step further with counter-comments from a clinical pharmacologist who accused his colleagues of “medicalizing” normal slacker tendencies. “Indolebant may bring some relief to those with a debilitating form of MoDeD,” he said, “But common laziness is not a disease. People have an absolute right to just sit there.”

Fans of the annual *BMJ* tradition are hard pressed to know which is more entertaining: the satire itself or the astonishing number of newspapers and other media outlets that pick up the story each year and unquestioningly run it as serious news.

British Journal of Medicine

Erratum

A typographical error on the second page of the article “SNMTS Announces 2006 Scholarship and Grant Recipients” in the April 2006 Newsline (*J Nucl Med.* 2006;47[4]:25N–26N) incorrectly associated the Mayo Clinic with Maryland (MD) rather than Minnesota (MN). A corrected version of the page has been placed in the online archives. Newsline regrets the error.