



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. Although the selections are divided into sections on therapy and diagnosis, the lines dividing such categories are increasingly blurred as nuclear medicine capabilities rapidly expand. Many diagnostic applications are now enlisted in direct support of and, often, in real-time conjunction with therapies. The expanding range of molecular studies—including this month's selections on stem cells—are examples of such dual-purpose benefits. 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 After Cytoreductive Surgery in Peritoneal Carcinomatosis

In an article e-published on November 23 ahead of print in the *Annals of Surgical Oncology*, Aarts et al. from Radboud University/Nijmegen Medical Centre (The Netherlands) reported on a small animal study designed to determine optimal timing of radioimmunotherapy (RIT) as an adjuvant treatment after cytoreductive surgery in peritoneal carcinomatosis resulting from colorectal cancer. Rats with experimentally induced peritoneal carcinomatosis underwent either exploratory laparotomy as a control procedure, cytoreductive surgery alone, or cytoreductive surgery plus RIT with  $^{177}\text{Lu}$ -labeled anti-CC531 antibody at different times after surgery. Median survival times in the control and

cytoreductive surgery-only groups were 29 and 39 days, respectively. Median survival times for rats after surgery plus adjuvant RIT was 77, 52, and 45 days when RIT was administered immediately after surgery, at 4 days, and at 14 days after surgery, respectively. This indicated that the efficacy of adjuvant RIT after cytoreductive surgery for the treatment of peritoneal carcinomatosis of colonic origin decreases “when the administration of radio-labeled monoclonal antibodies is postponed.” The authors concluded that these data suggest that “adjuvant RIT should be given as early as possible after surgery.”

*Annals of Surgical Oncology*

### Sandostatin Treatment in Progressive Thyroid Cancer

Kohlfuerst et al. from the PET/CT Center Klagenfurt (Austria) reported in the November issue of *Thyroid* (2006;16:1113–1119) on a study undertaken to determine whether treatment with a long-acting somatostatin receptor analog is effective in patients with  $^{131}\text{I}$ -negative but somatostatin receptor-positive metastases from differentiated and anaplastic thyroid cancer. The study included 12 patients who showed progressive disease confirmed by radiologic evaluation, increasing serum thyroglobulin (Tg), and negative diagnostic or post-therapeutic  $^{131}\text{I}$  whole-body scans. All patients underwent  $^{18}\text{F}$ -FDG PET/CT imaging,  $^{99\text{m}}\text{Tc}$ -depreotide whole-body SPECT imaging, and serum Tg assessment. Positive somatostatin-receptor expression was found on SPECT in 8 of the patients, who were subsequently treated with Sandostatin (Novartis Pharmaceuticals; Basel, Switzerland) once per month over a period of 6 months, with repeated imaging and Tg assessments. When tumor progression

was noted, doses were increased. All patients showed progressive disease during the study period, with only 3 patients able to undergo long-term (1–1.5 years) treatment. In all patients, serum Tg increased, as did the number of lesions and extent of tumor size on PET/CT and SPECT. The authors concluded that although receptor expression did not change during the treatment period, clear tumor progression indicated a failed attempt to achieve disease stabilization with this somatostatin analogue.

*Thyroid*

### Compassionate Use of rhTSH in Metastatic Thyroid Cancer

In the same issue of *Thyroid* (2006;16:1121–1130), Robbins et al. from the Memorial Sloan-Kettering Cancer Center (New York, NY) and members of the U.S. and Canadian Thyrogen Compassionate Use Program Investigator Group reported on recombinant human thyrotropin (rhTSH)-assisted  $^{131}\text{I}$  therapy for patients with metastatic thyroid cancer. The study included 115 patients who were either unable to elevate endogenous TSH during thyroxine withdrawal or in whom thyroxine withdrawal was contraindicated for medical reasons. The retrospective study assessed the ability of rhTSH to elevate serum TSH, to avoid complications of hypothyroidism, and to stimulate  $^{131}\text{I}$  uptake and serum thyroglobulin. After rhTSH administration, serum TSH levels rose to  $\geq 25$  mU/L in all 112 patients in whom levels were measured. Hypothyroid complications were seen in only 3 of 25 patients who had experienced them in the past, and in only 4 of 51 patients at high risk for such complications.  $^{131}\text{I}$  uptake was evident on whole-body scans in 105 of the 115 patients, and serum thyroglobulin

levels were lower than baseline in 73% of patients assessed at 1 year, with cancer-related symptoms improved in ~25%. Serious adverse effects were reported in 2 patients. The authors concluded that “rhTSH elevates serum TSH and facilitates radioiodine uptake in patients who cannot produce endogenous TSH or who cannot tolerate hypothyroidism.”

*Thyroid*

## Diagnosis

### Gamma Probe Detection of NSCLC Micrometastases

Nwogu et al. from the Roswell Park Cancer Institute/State University of New York at Buffalo reported in the November issue of the *Annals of Thoracic Surgery* (2006;82:1815–1820) on a study designed to determine the value of radioguided detection of lymph node micrometastases in non-small cell lung cancer. The study included 10 patients with resectable lung cancers who underwent preoperative <sup>18</sup>F-FDG PET imaging and mediastinoscopy. Within 4 hours of scheduled surgery, patients were injected with <sup>18</sup>F-FDG. During surgery, a handheld gamma detector assessed increased tracer uptake in thoracic lymph nodes. Lymph nodes with increased uptake but negative findings on conventional hematoxylin and eosin staining underwent further serial sectioning and immunohistochemistry. The handheld probe detected all lesions with <sup>18</sup>F-FDG uptake on presurgical PET imaging and in 3 patients detected nodes with micrometastases that would have been missed by conventional pathology analysis. Additional micrometastases were detected by the probe in a fourth patient in areas near to those detected by conventional methods. The authors concluded that “It is feasible to detect occult metastases in lymph nodes by using an FDG-sensitive intraoperative gamma probe, resulting in upstaging of patients” and called for expansion of this work in a larger study group to evaluate the sensitivity,

specificity, and clinical utility of such a device.

*Annals of Thoracic Surgery*

### ASCO Breast Cancer Follow-Up Guidelines

The Expert Panel of the American Society of Clinical Oncology (ASCO) recently released an update to the 1999 ASCO guideline on breast cancer follow-up and management in the adjuvant setting, publishing the results in the November 1 issue of the *Journal of Clinical Oncology* (2006;24:5091–5097). The updated recommendations came as the result of the panel’s review of the literature through March 2006. Among their conclusions and recommendations were: (1) regular history, physical examination, and mammography by experienced physicians are the cornerstones of appropriate breast cancer follow-up; (2) examinations should be performed every 3–6 months for the first 3 years of follow-up, every 6–12 months for years 4 and 5, and annually thereafter; (3) for women who have undergone breast-conserving surgery, mammography should be performed 1 year after the initial mammogram and at least 6 months after completion of radiation therapy, followed by yearly mammograms; and (4) patients at high risk for familial breast cancer syndromes should be referred for genetic counseling. The panel did not recommend other forms of imaging for routine follow-up, including PET, CT, MR imaging, bone scans, chest radiographs, or liver ultrasound. Complete blood counts and chemistry panels as well as routine assessment of tumor markers were not recommended.

*Journal of Clinical Oncology*

### PET and Early Response in Breast Cancer Treatment

In an article e-published on November 6 ahead of print in the *Journal of Clinical Oncology*, Rousseau and researchers from a consortium of French medical centers reported on a study as-

sessing the efficacy of sequential <sup>18</sup>F-FDG PET in evaluating early response to neoadjuvant chemotherapy in patients with stage II and III breast cancer. The study included 64 patients who underwent PET imaging at baseline and after the first, second, third, and sixth courses of chemotherapy. Ultrasound and mammography were also performed at these stages to assess tumor size, and surgery was performed after the final chemotherapy. Pathologic analyses showed gross residual disease in 28 patients and minimal residual disease in 36 patients. Standard uptake values (SUVs) on PET did not vary significantly over the course of treatment in nonresponders but decreased markedly to background levels in 94% (34 of 36) of responders. Using 60% of SUV at baseline as a cutoff value, the sensitivity, specificity, and negative predictive values of PET were 61%, 96%, and 68% after 1 course of chemotherapy; 89%, 95%, and 85% after 2 courses; and 88%, 73%, and 83% after 3 courses, respectively. The authors concluded that “pathologic response to neoadjuvant chemotherapy in stage II and III breast cancer can be predicted accurately by FDG PET after 2 courses of chemotherapy.”

*Journal of Clinical Oncology*

### PET and Surgery for Colorectal Liver Metastases

Wiering et al. from Radboud University/Nijmegen Medical Center (The Netherlands) reported on November 5 ahead of print in the *Annals of Surgical Oncology* on a retrospective study designed to determine whether <sup>18</sup>F-FDG PET can improve patient selection for curative resection of colorectal liver metastases. In conventional approaches with CT, 60% of patients will develop recurrent disease within a few years after surgery. The study included data from 203 patients in 2 groups: 100 patients designated for hepatic surgery on the basis of CT chest and abdomen imaging only, and 103 patients selected for hepatic surgery by

these methods plus  $^{18}\text{F}$ -FDG PET. At laparotomy, disease was deemed too extensive or diffuse for additional treatment in 28% of the CT-only group and in 19.4% of the CT + PET group. For patients who progressed to resection, overall survival at 3 years was 57.1% in the CT-only group and 60.1% in the CT + PET group, with disease-free survival at 3 years at 23.0% and 31.4% for the respective groups. The authors concluded that although  $^{18}\text{F}$ -FDG PET may reduce the number of negative laparotomies in patients with colorectal liver metastases, the resulting effects on selection of patients for surgery does not seem sufficient to affect overall or disease-free survival after treatment.

*Annals of Surgical Oncology*

### PET/CT in Localized Prostate Cancer

In an article published in the November issue of the *Journal of Urology* (2006;175:2014–2018), Hacker et al. from the Elisabethinen Hospital (Linz, Austria) reported on a study comparing  $^{18}\text{F}$ -fluorocholine PET/CT and intraoperative laparoscopic radioisotope-guided sentinel pelvic lymph node dissection with conventional extended pelvic lymph node dissection in patients with clinically localized prostate cancer. The study included 20 men with clinically localized prostate cancer, prostate specific antigen levels  $>10$  ng/mL, a Gleason score sum  $\geq 7$ , and negative bone scans.  $^{18}\text{F}$ -fluorocholine PET/CT was performed before surgery, and sentinel pelvic lymph node dissection in each patient was followed by extended pelvic lymph node dissection, including the area of the obturator fossa, external iliac artery/vein, and internal iliac artery/vein up to the bifurcation of the common iliac artery. Laparoscopic radical prostatectomy was performed in each patient. The combined method detected lymph node metastases in 10 patients (50%), and 62% of these nodes were found outside the obturator fossa and would have been missed on standard lymph node dissection of the obturator fossa

only. The largest lymph node metastasis not seen on the PET/CT image was 8 mm, and PET/CT alone had both false-positive and false-negative findings. Extended pelvic lymph node dissection missed 1 lymph node metastasis (2 mm) and revealed a higher number of lymph node metastases for obturator fossa dissection only. The authors concluded that although  $^{18}\text{F}$ -fluorocholine PET/CT is not a useful approach in identifying occult lymph node metastases in clinically localized prostate cancer, sentinel-guided pelvic lymph node dissection allows the detection of even small lymph node metastases and that “The accuracy of sentinel pelvic lymph node dissection is comparable to that of extended pelvic lymph node dissection when the limitations of the method are taken into consideration.”

*Journal of Urology*

### Atropine and Heart Rate in MPS

In an article e-published on November 16 ahead of print in the *International Journal of Cardiovascular Imaging*, Sarullo et al. from the Buccheri La Ferla Fatebenefratelli Hospital (Palermo, Italy) reported on the safety and feasibility of atropine administration in patients with submaximal heart rates during myocardial perfusion SPECT (MPS) studies. The study included results from 3,150 patients (2,253 men and 897 women; mean age,  $55 \pm 6$  years) referred to an office-based nuclear cardiology lab for MPS. In the study group, 397 individuals were unable to continue with exercise before reaching the minimal heart rate, and each of these patients received 1 mg of atropine. Scintigraphic results for this group were compared with the second group of 2,753 patients who achieved target heart rates without atropine. In the atropine group, mean heart rates before and after injection were  $119.5 \pm 13.6$  and  $137.3 \pm 13.5$  beats per minute, respectively, with no adverse effects reported. The mean percentage of age-related heart rates achieved in this group was 83.5%

$\pm 8.1\%$ , with 76.1% of this group reaching more than 80% of their age-related heart rates. No significant differences were noted in the percentages of total positive perfusion studies in the 2 study groups. The authors concluded that, “Atropine added to exercise stress testing in patients who cannot achieve their 80% age-related heart rate is a safe, well-tolerated, and feasible method for MPS.”

*International Journal of Cardiovascular Imaging*

### SPECT and Bone Marrow Cell Transplantation in Acute MI

Meluzin et al. from the St. Anna Hospital (Brno, Czech Republic) reported in the November issue of the *American Heart Journal* (2006;152:e9–e15) on the use of SPECT to assess the impact of dose of transplanted autologous mononuclear bone marrow cells on myocardial function and perfusion in patients with acute myocardial infarction (MI). The study included 66 patients experiencing a first acute MI, who were divided equally into 3 groups that (1) received mononuclear bone marrow cells at a high cell dose; (2) received mononuclear bone marrow cells at a low cell dose; and (3) did not receive cell transplantation (controls). Patients were assessed at 3-month follow-up. Baseline peak systolic velocities of longitudinal contraction of the infarcted wall were 5.2 cm/s in controls, 4.5 cm/s in the low-dose group, and 4.3 cm/s in the high-dose group. At 3-month follow-up, these had increased by 0.0, 0.5, and 0.9 cm/s, respectively.  $^{99\text{m}}\text{Tc}$ -sestamibi SPECT indicated that baseline left ventricular ejection fractions of 42%, 42%, and 41% in control, low-dose, and high-dose groups increased by 2%, 3%, and by 5%, respectively, over the same time period. The authors concluded that “mononuclear bone marrow cell transplantation improves regional myocardial function of the infarcted wall in a dose-dependent manner.”

*American Heart Journal*

## PET/CT and Myocardial Molecular Interventions

Wagner et al. from the Technische Universitat Munchen (Germany) reported in the November 21 issue of the *Journal of the American College of Cardiology* (2006;48:2107–2115) on a study to assess the utility of PET/CT for in vivo characterization of an angiogenesis-directed molecular intervention in a swine model. PET/CT with multiple molecular-directed radiotracers was used in a model of regional adenoviral transfer of the VEGF(121) gene to myocardium in healthy pigs. Successful transgene expression was noninvasively confirmed 2 days later by a reporter probe targeting the co-expressed HSV1-sr39tk reporter gene. Ventricular function and morphology remained unchanged on CT, and increased regional perfusion was identified on PET in areas overexpressing VEGF, confirming in vivo effects on microvascular tone and permeability. The researchers found that regional angiogenesis-associated  $\alpha\beta3$  integrin expression was not enhanced and, therefore, not a likely contributor to the perfusion increase. In summarizing the advantages of the technique, they noted that the fusion of CT morphology and tracer-derived molecular signals allowed for “accurate regional localization of biologic signals.” The authors concluded that integrated PET/CT has the potential to elucidate “cardiovascular biologic mechanisms from gene expression to physiologic function and morphology” and that “VEGF overexpression in healthy myocardium increases myocardial perfusion without significant up-regulation of  $\alpha\beta3$  integrin adhesion molecules early after the intervention.”

*Journal of the American College of Cardiology*

## Imaging Implanted Stem Cells in Myocardium

In a review article also appearing in the November 21 issue of the *Journal of the American College of Cardiology* (2006;48:2094–2106), Zhou et al. from the University of Pennsylvania (Phil-

adelphia) discussed the current status of and potential for imaging stem cells implanted in infarcted myocardium. The authors described methods for cell visualization using several noninvasive modalities, including MR imaging, PET, SPECT, and bioluminescent imaging. One of the principle potential advantages of routine noninvasive imaging techniques is in the evaluation of survival, migration, and differentiation status of implanted stem cells in the same individual or experimental model over time. The authors compared the advantages and disadvantages of reporter-based cell visualization and direct cell labeling for short- and long-term cell tracking.

*Journal of the American College of Cardiology*

## Free Fatty Acid Depletion in Cardiomyopathic Heart Failure

In an article e-published on November 6 ahead of print in *Circulation*, Tuunanen et al. from the Turku PET Centre (Finland) reported on a study in which PET was used to assess the effect of acute free fatty acid withdrawal on cardiac function in patients with heart failure resulting from idiopathic dilated cardiomyopathy. The study included 18 such patients (ages,  $58.8 \pm 8.0$  years; ejection fraction  $33\% \pm 8.8\%$ ) and 8 healthy controls who underwent myocardial perfusion studies, metabolic imaging (PET imaging with  $[^{15}\text{O}]\text{H}_2\text{O}$ ,  $^{11}\text{C}$ -acetate, and  $^{11}\text{C}$ -palmitate), and echocardiography before and after acute reduction of serum free fatty acid concentrations by administration of acipimox, an inhibitor of lipolysis. Acipimox decreased myocardial free fatty acid uptake by  $>80\%$  in both groups. In healthy individuals, reduced cardiac work was accompanied by decreased oxidative metabolism; whereas in patients with idiopathic dilated cardiomyopathy, cardiac work fell while oxidative metabolism remained unchanged and efficiency fell. In failing hearts, however, free fatty acid depletion did not downregulate oxidative metabolism,

and myocardial efficiency deteriorated. The authors concluded that “failing hearts are unexpectedly more dependent than healthy hearts on free fatty acid availability” and suggested that “both glucose and fatty acid oxidation are required for optimal function of the failing heart.”

*Circulation*

## PET and Carotid Plaque Inflammation

Tawakol et al. from the Massachusetts General Hospital and Harvard Medical School (Boston) reported in the November 7 issue of the *Journal of the American College of Cardiology* (2006;48:1818–1824) on a study designed to determine whether  $^{18}\text{F}$ -FDG PET could measure atherosclerotic carotid plaque inflammation in patients who subsequently underwent carotid endarterectomy. The study included 17 patients with severe carotid stenoses who underwent PET imaging, with carotid plaque tracer uptake determined as the ratio of plaque to blood activity (target-to-background ratio). All patients underwent carotid endarterectomy within 1 month, with histologic analyses performed on carotid specimens. The authors found a significant correlation between PET uptake in carotid plaques and macrophage staining from the corresponding histologic sections. When the mean  $^{18}\text{F}$ -FDG uptake was compared with mean inflammation for each patient, the correlation was even stronger. Tracer uptake did not correlate with plaque area, plaque thickness, or area of smooth muscle cell staining. The authors concluded that PET imaging can be used to assess the severity of inflammation in carotid plaques in patients and that if this increased activity can be documented in specific clinical events, “this noninvasive measure could be used to identify a subset of patients with carotid atherosclerosis in need of intensified medical therapy or carotid artery intervention to prevent stroke.”

*Journal of the American College of Cardiology*

## PET and Early Radiation-Induced Myocardial Damage

In the November 1 issue of the *International Journal of Radiation Oncology, Biology, Physics* (2006;66: 845–851), Jingu et al. from the Tohoku University School of Medicine (Sendai, Japan) reported on the utility of  $^{18}\text{F}$ -FDG PET in the early diagnosis of radiation-induced myocardial damage. The study included 64 patients who had been irradiated for thoracic esophageal cancer and who underwent  $^{18}\text{F}$ -FDG PET imaging at least 3 months after the completion of chemoradiotherapy. Thirteen of these patients showed high tracer uptake in the basal portion of the myocardium, and 8 of these patients underwent additional cardiac studies. Five of the 8 patients showed low  $^{123}\text{I}$ -BMIPP uptake and 4 showed low  $^{201}\text{Tl}$  uptake in the myocardium corresponding with high FDG uptake regions. MR studies in 2 patients showed delayed enhancement

in some areas that had shown high PET tracer uptake. The authors concluded that the not uncommon finding of focal increased uptake in the basal myocardium after radiotherapy for esophageal cancer “indicates the possibility of radiation-induced cardiac damage, and cardiac function and symptoms of such patients should be followed carefully.”

*International Journal of Radiation Oncology, Biology, Physics*

## Scintigraphy Before Lung Cancer Resection in Ventilatory Obstruction

Mineo et al. from the Policlinico Tor Verata University (Rome, Italy) reported in the November issue of the *Annals of Thoracic Surgery* (2006;82: 1828–1834) on a study conducted to evaluate the efficacy of preoperative lung perfusion scintigraphy performed by planar acquisition and SPECT in predicting postoperative pulmonary function in patients with resectable

lung cancer and obstructive ventilatory defect. The study included 39 patients who underwent pre- and postoperative pulmonary function tests. Cut-off values for postoperative forced expiratory volume in 1 second (FEV1) were 65% of the predicted value for pneumonectomy and 45% for lobectomy. Postoperative predicted FEV1 was estimated from both planar and SPECT lung perfusion scintigraphy images performed preoperatively. At surgery, 28 patients underwent lobectomy and 11 underwent pneumonectomy. Both planar imaging and SPECT proved more accurate in predicting postoperative FEV1 after lobectomy than after pneumonectomy. After additional analyses, the authors concluded that “both planar lung scintigraphy and SPECT can accurately predict postoperative FEV1 and can therefore be considered reliable tools in establishing operability of patients with lung cancer and ventilatory obstruction.”

*Annals of Thoracic Surgery*

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*Martin P. Sandler, MD*  
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