*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 recently 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 both 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.*

**MOLECULAR IMAGING**

## Monitoring Stem Cell Migration and Metabolism

In an article e-published on June 22 ahead of print in *Contrast Media and Molecular Imaging*, Cicchetti et al. from the Centre Hospitalier Université Laval (Quebec City, Canada) reported on dual-modality in vivo monitoring of subventricular zone (SVZ) stem cell migration and metabolism in rats. Both MR and multitracer PET imaging were used to follow the migration and effects of SVZ cells labeled with superparamagnetic iron oxide particles. Normal adult rats were transplanted with the cells into either the right rostral migratory stream or striatum and followed for 3 months. Cells implanted in the striatum underwent only minimal migration by 3 weeks, whereas cells implanted into the rostral migratory stream migrated toward the olfactory bulb at only 1 week after transplantation. $^{18}$F-FDG PET indicated enhanced glucose utilization in the striatum of all transplanted animals. At 3 months, $^{11}$C-raclopride and $^{11}$C-WIN 35,428, 2ß-carbomethoxy-3ß-(4-fluorophenyl)tropane PET studies indicated elevated dopamine receptor accumulations in the striatal grafts. Additional PET imaging with $^{11}$C-PK11195 showed no significant inflammation associated with the implanted stem cells. Histologic analysis at 7 weeks after transplantation showed viable labeled cells, indicating a prolonged presence of undifferentiated neural stem cells as well as post-transplantation differentiation into neuronal and astrocytic phenotypes. The authors concluded that "combining MRI and PET enables monitoring of cell migration and metabolism noninvasively in vivo for extended periods of time."

*Contrast Media and Molecular Imaging*

## Long-Term Monitoring of Stem Cells

Guzman et al. from the Stanford University School of Medicine (CA) reported on June 12 in the *Proceedings of the National Academy of Sciences USA* (2007;104:10211–10216) on an investigation of the utility of MR imaging in long-term monitoring of transplanted human neural stems cells. The group showed that magnetic nanoparticle labeling did not affect survival, migration, differentiation, or action of human central nervous system stem cells transplanted into rodent brain. MR imaging monitored the cells after transplantation into neonatal, adult, and injured rodent brain and indicated that the cells survived long-term, migrated, and differentiated in site-specific patterns identical to those seen in nonlabeled cells. The authors also described MR characteristics of graft cell death and subsequent clearance and concluded that this work supports the use of MR in long-term monitoring of stem cell transplantation. They added that "knowledge of migration patterns and implementation of noninvasive stem cell tracking might help to improve the design of future clinical neural stem cell transplantation."

*Proceedings of the National Academy of Sciences USA*

## Molecular Markers in Esophageal Cancer Treatment

Banki et al. from the University of Southern California (Los Angeles) reported in the June issue of the *Archives of Surgery* (2007;142:533–539) on a study designed to identify a molecular marker for completeness of resection and recurrent disease in patients with esophageal cancer. The study included 44 healthy volunteers and 45 patients with esophageal cancer before surgery. Of these patients, 6 were unresectable, and 39 proceeded to complete resection. Plasma DNA levels were measured at baseline in all participants and in 20 patients after resection. At baseline, plasma DNA levels were higher than normal levels in 38 (84%) patients, and all 6 unresectable patients' levels were higher than normal. At initial follow-up, these levels remained higher than normal in only 2 (10%) of 20 patients assessed, and systemic disease was subsequently found in both these patients. In the remaining 18 (90%) patients assessed after surgery, plasma DNA levels dropped lower than or remained normal. At a median follow-up of 12 months (range, 3–20 months) no evidence of recurrent disease was found in 14 patients. In the remaining 4, plasma DNA levels rose on follow-up, and all developed systemic disease as detected by CT or PET. In all, 6 of the 20 patients developed systemic disease during follow-up, in 4 of whom

elevated plasma DNA levels were identified before imaging indicated the presence of disease. The authors concluded that because plasma DNA levels are significantly elevated in patients with esophageal cancer but after complete resection should return to normal, then "persistently elevated plasma DNA levels after resection or levels that rise on follow-up indicate residual or recurrent disease."

*Archives of Surgery*

## Suicide Gene Therapy and Radiation in Pancreatic Cancer

In an article e-published on June 5 ahead of print in *Molecular Therapy*, Freytag et al. from the Henry Ford Health System (Detroit, MI) reported on the efficacy and toxicity of a combination of replication-competent, adenovirus-mediated suicide gene therapy and radiation in a preclinical model of pancreatic cancer. As part of canine studies in preparation for a phase 1 clinical trial, the group monitored activity using $^{18}$F-fluoro-3-hydroxymethylbutylguanine PET. Two lines of human pancreatic adenocarcinoma cells were found to be sensitive to the oncolytic effects of a replication-competent adenovirus and to the cytotoxic effects of the yeast cytosine deaminase and herpes simplex virus thymidine kinase genes in vitro. The authors found that injection of the replication-competent adenovirus in canine pancreas at doses analogous to those that would be used in humans resulted in mild pancreatitis but no peritonitis or hepatotoxicity. PET imaging indicated activity in the pancreas but not in collateral tissues. Combining adenovirus-mediated suicide gene therapy with radiation significantly increased tumor control beyond that achieved with either approach alone. The authors concluded that adenovirus-mediated suicide gene therapy has the "potential to augment the effectiveness of pancreatic radiotherapy without resulting in excessive toxicity" and that these results provide scientific data to support phase 1 trials of this combined approach.

*Molecular Therapy*

## Microbubble US, PET, and MR in Tumor Perfusion

Niermann et al. from Vanderbilt University Medical Center (Nashville, TN) reported in the June issue of the *Journal of Ultrasound in Medicine* (2007;26:749–756) on a study correlating microbubble contrast-enhanced sonography with dynamic contrast-enhanced MR imaging and $^{18}$F-FDG PET in the characterization of perfusion in murine tumors before and after a variety of treatments. The study included 17 lung carcinoma–implanted mice assigned to radiation therapy alone, antiangiogenic chemotherapy alone, combined chemoradiation, or as controls. On day 0, microbubble-enhanced ultrasound and contrast-enhanced MR images were acquired in each tumor. On day 5 of treatment, ultrasound and MR imaging were repeated, along with dynamic $^{18}$F-FDG PET imaging. The authors found that on day 5 sonography showed intratumoral perfusion, blood volume, and blood velocity to be highest in the untreated control group and successively lower in the radiation therapy, antiangiogenic chemotherapy, and combined chemoradiotherapy (which resulted in the largest reduction) groups. Sonography also indicated steady decreases in tumor perfusion, blood volume, and microvascular velocity over the 5-day course of chemoradiotherapy and respectively increasing values over this period for untreated tumors. Although dynamic contrast-enhanced MR showed small average decreases in tumor perfusion for the variously treated tumors, these results were not statistically significant. Dynamic PET at 5 days confirmed delayed uptake of tracer in tumors undergoing chemoradiotherapy. The authors concluded that these correlations with MR and PET imaging suggest that "microbubble contrast-enhanced sonography has considerable potential in the clinical assessment of tumor neovascularization and in the assessment of the response to treatment."

*Journal of Ultrasound in Medicine*

## Single Cell Detection with MR

In an article e-published on May 31 ahead of print in *Contrast Media and Molecular Imaging*, Shapiro et al. from Yale University School of Medicine (New Haven, CT) reported on a novel iron oxide labeling technique that facilitates single-cell detection by MR imaging. The researchers labeled rat peripheral T cells in vitro in whole blood with strepatividin-coated, micron-sized iron oxide particles (MPIOs), with resulting iron concentrations as high as 80 picograms of iron per cell—30 times the labeling efficacy reported with ultrasmall particles of iron oxide. A biotinylated anti-CD5 antibody specific for peripheral T cells was used to mediate the labeling. Electron microscope analysis indicated that labeled MPIOs remained for the most part extracellular with some intracellular uptake. The authors concluded that these results indicated that "the use of MPIOs for achieving high iron concentrations for cellular MRI is potentially an effective new modality for noninvasive imaging of lymphocytes" in animal studies, with the possibility of imaging single lymphocytes.

*Contrast Media and Molecular Imaging*

## SPECT/CT and Bioluminescence in Breast Cancer Metastasis

Cowey et al. from the University of Alabama at Birmingham reported on May 31 ahead of print in *Clinical and Experimental Metastasis* on an evaluation of bioluminescent imaging and microSPECT/CT for detecting bone metastasis in mice. The study included young (5-weeks old) mice that received an intracardiac injection of human breast cancer cells transduced with luciferase or a saline injection (controls). Seven mice underwent CT exposure once each week for 5 weeks,

and 6 did not. All mice underwent weekly bioluminescent imaging and select mice undewent $^{99m}$Tc-MDP microSPECT after 5 weeks. Results from pathology and histology were used to assess the effect of CT radiation on bone metastasis and for comparison with imaging results. Although bioluminescent imaging found no significant difference in metastases between irradiated mice and nonirradiated mice, histomorphometry of the knee joints revealed a significant increase in tumor area in the leg bones of mice that received CT exposure compared with those that did not. MicroSPECT imaging did not detect these lesions. Over all bioluminescent imaging of the leg and spine in animals studied showed excellent sensitivity (100%), good specificity (80%–90%), good accuracy (90%–96%), and positive and negative predictive values of 81%–93% and 100%, respectively. The authors concluded that although multimodality imaging techniques can be quite useful for monitoring bone metastasis in animal studies, "microCT X-rays should be used judiciously in order to limit irradiation that may stimulate increased metastasis to specific regions of the skeleton."

*Clinical and Experimental Metastasis*

**THERAPY**

## rhTSH-Stimulated $^{131}$I Therapy in Large Goiters

Bonnema et al. from the Odense University Hospital (Denmark) reported on June 12 ahead of print in the *Journal of Clinical Endocrinology and Metabolism* on a double-blinded randomized trial of the effect of $^{131}$I therapy amplification by recombinant human thyrotropin (rhTSH) prestimulation in individuals with very large goiters. The study included 29 patients (22 women, 7 men; ages, 37–87 years), each of whom had a large multinodular goiter (median, 160 mL, range, 99–440 mL) and who were randomized to receive a placebo or 0.3 mg rhTSH 24 hours before $^{131}$I therapy. Goiter volume was monitored by follow-up MR imaging. At 1 year posttherapy, the median goiter volume was reduced from 170 to 121 mL in the placebo group and from 151 mL to 72 mL in the rhTSH-pretreated group, corresponding to respective reductions of 34.1% ± 3.2% and 53.3% ± 3.3%. Although goiter reduction correlated positively with retained $^{131}$I thyroid dose in the placebo group, no such relationship was noted in the rhTSH group. The rhTSH group reported more adverse effects (pain) than the placebo group. At 12 months, goiter-related complaints were reduced (but not significantly different) in both groups. One patient in the placebo group and 3 patients in the rhTSH group developed hypothyroidism. The authors concluded that rhTSH-stimulated $^{131}$I therapy "improves the reduction of very large goiters by more than 50% compared with $^{131}$I therapy alone, but at the expense of more adverse effects following therapy." They added that the data in this double-blind test suggest that "rhTSH stimulation may work through mechanisms that go beyond the increase in thyroid $^{131}$I uptake."

*Journal of Clinical Endocrinology and Metabolism*

## $^{90}$Y-Labeled mAb in Ovarian Cancer

In a study published in the June 15 issue of the *International Journal of Cancer* (2007;120:2710–2714), Oei et al. from the Radboud University Nijmegen Medical Centre (The Netherlands) reported on a study analyzing the sites and patterns of disease recurrence in patients with epithelial ovarian cancer to assess the influence of a single intraperitoneal administration of $^{90}$Y-labeled murine monoclonal antibody (mAb). The study included 447 patients in a phase III trial who were in complete clinical remission with FIGO stage Ic–IV ovarian cancer and who were randomized to standard treatment plus a single intraperitoneal administration of $^{90}$Y-labeled mAb (224 patients) or to standard treatment alone after negative second-look laparoscopy (223 patients). Patients were followed for a median of 3.5 years. Relapse/recurrence was noted in 104 of the $^{90}$Y-labeled mAb group and in 98 of the control arm, with significantly fewer intraperitoneal and more extraperitoneal relapses occurring in the radioimmunotherapy arm. The time to intraperitoneal recurrence was significantly longer and time to extraperitoneal recurrence was significantly shorter for the $^{90}$Y-labeled mAb group. These and other data led the authors to conclude that no survival benefit accrued to this intraperitoneal radioimmunotherapy as consolidation treatment for epithelial ovarian cancer and that improved control of intraperitoneal disease was offset by increased extraperitoneal recurrences.

*International Journal of Cancer*

## $^{213}$Bi RIT in Early-Stage Gastric Cancer

Beck et al. from the Technische Universität München (Germany) reported on June 11 ahead of print in *Cancer Science* on a study designed to optimize the efficacy and evaluate the long-term toxicity of $^{213}$Bi-labeled immunoconjugate radioimmunotherapy (RIT) in a mouse model of early and advanced-stage disseminated gastric cancer. Nude mice inoculated with gastric cancer cells were treated with different activities of $^{213}$Bi-labeled monoclonal antibody at days 1 or 8 after inoculation. Therapeutic efficacy and long-term toxicity were evaluated by monitoring for up to 300 days. Survival was found to be significantly prolonged in mice treated with $^{213}$Bi-immunoconjugates at day 1 after tumor cell inoculation, with early-stage disease eradicated in 87% of cases. Treatment at day 8 after tumor cell inoculation was less efficient. Toxicity was limited to renal effects at the highest activities used. The authors concluded that RIT with this α-emitter "is a promising concept for treatment of early peritoneal carcinomatosis."

*Cancer Science*

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## Low-Dose-Rate $^{227}$Th RIT

In an article e-published on May 29 ahead of print in *Blood*, Dahle et al. from the Norwegian Radium Hospital (Oslo) reported on studies of targeted cancer therapy with a novel low-dose-rate α-emitting radioimmunoconjugate. The authors labeled rituximab with $^{227}$Th, a combination that effectively killed lymphoma cells in vitro. A single injection of the radioimmunoconjugate induced complete tumor regression in up to 60% of mice bearing macroscopic human B-cell lymphoma xenografts, with no toxicities noted. This treatment was significantly more effective than similar treatment with $^{227}$Th-trastuzumab (as a control) and $^{90}$Y-tiuxetan ibritumomab (as a β-emitting standard comparison). The authors concluded that $^{227}$Th-based constructs "may provide a novel approach for targeted therapy against a wide variety of cancers" and may help to overcome the challenges that have previously been associated with α-emitting antibody conjugate therapies.

*Blood*

**DIAGNOSIS**

## Laparoscopic SLN Mapping in Cervical Cancer

Kushner et al. from the University of Wisconsin School of Medicine and Public Health (Madison) reported on June 8 ahead of print in *Gynecologic Oncology* on a detailed time analysis of experience with a laparoscopic approach to sentinel lymph node (SLN) detection in cervical cancer. The study included 20 patients with stage IA2–IIA cervical cancer who were enrolled in a clinical trial and scheduled for primary radical surgery. Each underwent $^{99m}$Tc SPECT/CT lymphoscintigraphy, followed by blue dye injection immediately before surgery. After bilateral laparoscopic SLN inspection, all patients underwent complete laparoscopic pelvic lymphadenectomy. After pathology and histology, these patients then proceeded to laparoscopic-assisted radical vaginal hysterectomies ($n$ = 9), radical abdominal hysterectomies ($n$ = 7), laparoscopic-assisted radical vaginal trachelectomies ($n$ = 2), and laparoscopic lymphadenectomies alone ($n$ = 2; secondary to positive lymph nodes). The researchers found that 19% of the 64 SLNs were found in unexpected sites and that the negative predictive value of the combined technique was 100%. If blue dye alone had been used, not only would the rate of detection have been lower, but this rate would have suffered with elapsed time. Although the surgeons could visualize blue SLNs well for 30 minutes, this ability was entirely gone at 50 minutes. The authors concluded that this technique shows promise but cautioned that the "visualization of blue dye in SLNs is transient, and this negative time correlation may explain the previously reported inferior detection rates with this technique."

*Gynecologic Oncology*

## PET and Scintigraphy in Lymphoma: Pathologic Comparison

In an article e-published on June 20 ahead of print in *Cancer*, Tsukamoto et al. from the Gunma University Graduate School of Medicine (Japan) correlated the comparative efficacies of $^{18}$F-FDG PET and $^{67}$Ga scintigraphy in lymphoma with the World Health Organization (WHO) histologic subtypes of the disease. The study included 250 patients with lymphoma. All were staged with $^{18}$F-FDG PET and 191 were also assessed with $^{67}$Ga scintigraphy. CT and/or MR imaging were used to identify each disease site, and these anatomic results were compared with functional results from PET and scintigraphy. Pathology results were also compared on a site-by-site basis using the WHO classification system. A total of 913 disease sites were identified in 255 patients, with $^{18}$F-FDG PET identifying >97% of disease sites of Hodgkin's lymphoma and aggressive and highly aggressive non-Hodgkin's lymphoma. The detection rate of $^{18}$F-FDG PET was 91% for follicular lymphoma, 82% for extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, and ~50% for small lymphocytic lymphoma and splenic marginal zone lymphoma. Although $^{67}$Ga scintigraphy yielded similar results for most lymphomas, its sensitivity was quite low for mantle cell lymphoma and for the nasal type of natural killer/T-cell lymphoma (30%–38% for these 2 subtypes). The authors concluded by "strongly" recommending the use of $^{18}$F-FDG PET over $^{67}$Ga scintigraphy in patients with follicular lymphoma, mantle cell lymphoma, and nasal-type natural killer/T-cell lymphoma.

*Cancer*

## PET/CT and IMRT in Pharyngeal Carcinoma

Rothschild et al. from the University of Zurich (Switzerland) reported on June 9 ahead of print in *Radiation Oncology* on a study of the value added by hybrid $^{18}$F-FDG PET/CT in intensity-modulated radiotherapy (IMRT) for locally advanced pharyngeal carcinoma. The retrospective study included 45 patients with stage IVA pharyngeal carcinoma treated with chemoradiation and IMRT. Patients with PET/CT and IMRT were matched with patients without PET/CT but with 3D conformal radiotherapy. Overall survival times at 1 and 2 years for the patient group with PET/CT and IMRT were 97% and 91%, respectively. These figures were respectively 74% and 54% for the group without PET/CT but with 3D conformal radiotherapy. Event-free survival rates at 1 and 2 years for the PET/CT and IMRT group were 90% and 80%, respectively, compared with figures of 72% and 56% in the PET/CT and conformal radiotherapy group. The authors concluded that "implementation of modern technologies with PET/CT and IMRT in curative treatment with chemoradiation is likely to improve treatment outcome in pharyngeal carcinoma."

*Radiation Oncology*

## PET in Colorectal Cancer Diagnosis

In an article e-published on June 7 ahead of print in the *World Journal of Surgical Oncology*, Sarikaya et al. from the Ohio State University (Columbus) reported on the utility of $^{18}$F-FDG PET imaging in patients with clinically and/or radiologically suspicious colorectal cancer but whose carcinoembryonic antigen (CEA) results are normal. The study first reviewed the records of 308 patients with colorectal cancer in whom PET scans had been performed. Criteria for inclusion in this retrospective evaluation included normal CEAs and suspected tumor recurrence, yielding a study group of 39 individuals. PET imaging was positive in 26 (67%) and negative in 13 (33%) of these patients. Histopathology confirmed tumor recurrence in 27 of 39 (69%) and indicated that PET was true-positive in 22, false-positive in 4, true-negative in 8, and false-negative in 5 patients. PET accuracy was 76.9%, with negative and positive predictive values of 61.5% and 84.6%, respectively. False-positive findings were associated with chronic inflammation in the bowel. False-negative findings were associated with histopathologic confirmation of mucinous adenocarcinoma. The positive predictive value of PET for liver metastases was significantly higher (88.8%) than for local recurrence (73.3%). PET also indicated disease in 2 patients in whom CEA did not become positive until 2 months after imaging. The authors concluded that these results support the use of PET in the evaluation of individuals with suspected colorectal cancer recurrence, even in the absence of positive CEA findings.

*World Journal of Surgical Oncology*

## PET and Posttherapy Assessment in Head and Neck Cancer

Yao et al. from University of Iowa Health Care (Iowa City) reported in the June issue of the *American Journal of Clinical Oncology* (2007;30:264–270) on a study designed to determine whether $^{18}$F-FDG PET can predict the pathology status of residual cervical lymph nodes in patients undergoing definitive radiotherapy for head and neck squamous cell carcinoma. The study included patients with stage N2 or higher disease who underwent definitive radiotherapy. Those 23 patients in whom PET and CT imaging after definitive radiotherapy indicated persistent lymphadenopathy underwent either neck dissection or fine-needle aspiration of the lymph nodes under ultrasound guidance. PET findings were then correlated with pathology findings of residual cervical lymphadenopathy. All patients with negative posttherapy PET imaging as well as those with maximum standardized uptake values (SUVs) $<3.0$ were found to be free from residual viable tumor. The authors used the criterion of an SUV $<3.0$ for a negative PET study to derive sensitivity, specificity, and positive and negative predictive values of 100%, 84.2%, 62.5%, and 100%, respectively. They concluded that a negative posttherapy PET image is significantly predictive of negative residual lymph node pathology and that "a prospective clinical trial is warranted to determine if neck dissection can be withheld in these patients."

*American Journal of Clinical Oncology*

## PET as a Predictor in B-Cell Lymphoma

In an article published in the June issue of *Haematologica* (2007;92: 778–783), Dupuis et al. from the Paris XII University (Créteil, France) reported on the respective prognostic values of germinal center phenotype classification and early PET imaging in selecting optimal treatment strategies in patients with diffuse large B-cell lymphoma. The authors evaluated tumor expression characteristics in 81 patients with the disease who had also undergone early PET imaging. Tumors were classified as germinal center (38 patients, 51%) or nongerminal center (36 patients, 49%) -type phenotypes in 74 interpretable cases, and the results of both phenotyping and PET were correlated with outcomes and survival. Median follow-up was 33 months, with an estimated 3-year event-free survival average of 67%. The germinal center phenotype was not correlated with survival. However, 3-year event-free survival was 46% in the PET-positive group and 80% in the PET-negative group. The authors concluded that although the utility of germinal center phenotyping was not confirmed in this study, early PET findings were confirmed to be a "powerful predictor" of outcome and that "the impact of treatment decisions based on early PET results should be evaluated."

*Haematologica*