Imaging in Oncology

NEWER IMAGING MODALITIES

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This regular feature will enhance your knowledge of imaging technology in oncologic diagnosis, treatment, and evaluation.

Tissue-Specific and Physiologic Nuclear Medicine Modalities

The search for greater sensitivity for detecting small subclinical tumor deposits and improved specificity for distinguishing between malignant and benign masses has led to the development of techniques for linking radioactive labels to tumor-specific antibodies or tissue-specific biochemical agents.1,2 Major progress is occurring as well in the development of nonspecific physiologic nuclear medicine modalities, most prominent among them being positron emission tomography (PET) and the recently adapted cardiac imaging agents. The current status of these new approaches is discussed below.

Tumor-Specific Monoclonal Antibody Radioimmunoscintigraphy

The early use of polyclonal murine antitumor antibodies for tumor localization has been succeeded by monoclonal antibody-based agents, although these, too, are of murine origin thus far.3,4 The majority of agents under development are labeled with either a technetium 99m (99mTc) or indium 111 (111In) radiometal chelate.5 These are popular because of their ease of preparation, their suitability for standard camera imaging, and the compatibility of their half-lives to the in vivo clearance of the antibody proteins. Whole antibodies and large fragments require the longer half-life of 111In although this carries with it the disadvantage of high liver clearance, compromising imaging within and adjacent to the liver and, to a lesser extent, the gut. Smaller, more quickly cleared antibody Fab' fragments can be labeled advantageously with the shorter half-lived 99mTc. Technetium is predominantly cleared by the kidneys, and the combination of fast biologic clearance of the antibody fragment and fast renal clearance of the radiolabel should result in less extensive background activity.

Despite their theoretical appeal, the performance of these preparations can still be compromised by problems of poor tumor perfusion, low tumor cell-surface antigen representation, antigen heterogeneity, and nonspecific uptake.5,6 One approach to reducing the confounding effects of high background activity has been the use of background subtraction techniques, as in the use of 99mTc-labeled albumin in conjunction with 99mTc-labeled antibody fragments; however, it is not clear whether improved specificity is in fact achieved.7 A more recent elaboration on this approach has been the fusion of bone scan or computed tomography (CT) images with single-photon emission tomography (SPECT) images of the radioantibody scan.8 Only limited experience with these approaches is yet reported.9 An alternative approach attempts to apply the phenomenon of tumor antigen augmentation from exposure to cytokines such as interferon.10,11 Here, too, the limited published clinical experience is inadequate to predict whether this phenomenon will be the basis of improved imaging performance.12

A particularly intriguing approach, championed at the University of Milan, attempts to adapt the techniques of laboratory immunology to the clinical setting.13 In this method, the monoclonal antibody is prelabeled with biotin, a vitamin D analog, which has very strong affinity for avidin, a tetravalent protein. After injection, the antibody is allowed to clear until the optimal ratio of tissue-bound to circulating antibody has been reached. Cold avidin is then injected and the unbound fraction allowed to clear. At that point, 111In-labeled biotin is injected and avidly taken up by the tetravalent avidin bound to the biotin-labeled tissue-bound antibody. Imaging is performed after the swift clearance of the free biotin. The authors have proposed a number of adaptations of this innovative idea.14,15 Yet another related strategy calls for the raising of bispecific monoclonal antibodies with one binding site for the tumor and one for the radiolabel chelate.16

In contrast to the variety of radioimmunoscintigraphic strategies and preparations under investigation, only one agent has been approved for clinical use in the United States:11 In satumomab pendetide (CYT-103, OncoScint CR/OV Kit - Cytogen) is a conjugate of a chelator (DTPA) and a monoclonal murine antibody (MAB B72.3) specific for a tumor-associated glycoprotein (TAG-72) frequently expressed by colorectal and ovarian carcinomas. The TAG-72 antigen is by no means restricted to these malignancies, and antibody labeling regularly occurs in salivary glands, post-ovulatary endometrium, and benign ovarian tumors. OncoScint is approved for imaging of colon and ovarian cancer and has its role in the search for clinically occult recurrent disease suggested by rising tumor markers when no other imaging or physical examination technique can locate the expected disease.

Because MAb-72 is an intact antibody, the 111In label, bound by the chelator, therefore provides the best match of radiolabel half-life to antibody clearance for resolution of lesional uptake from the substantial background activity. Nonspecific background uptake is so pronounced in the liver that US Food and Drug Administration (FDA) approval of the agent is for detection of “extranecrotic” spread of colorectal and ovarian tumors. Nonspecific uptake is also substantial in spleen and bone marrow as well as the gastrointestinal and genitourinary systems. Focal nonspecific uptake is seen in colostomies, aneurysms, adhesions, and areas of inflammation, particularly diseased joints.

OncoScint for Ovarian Carcinoma

The advantages and shortcomings of this agent are amply illustrated in the findings of the multicenter trial that led to its approval for imaging of presumptive occult
ovarian carcinoma.\textsuperscript{17} In this trial, 108 presurgical patients with known primary or recurrent ovarian carcinoma or with suspect disease prior to second-look surgery were examined. OncoScint studies were reviewed by the surgeon, along with CT examinations and all other pertinent studies, including CA125 blood values, preoperatively. Among the patient subsets of greatest interest were the 42 patients undergoing second-look surgery with all standard studies normal, including CT and serum CA125 levels. A total of 17 of these were found to have tumor at surgery; OncoScint detected only 6, yielding a negative predictive value of 28%. Consistently, the sensitivity of the test varied with tumor size, falling from approximately 80\% for masses larger than 2 cm to approximately 50\% for smaller masses and less than 10\% for microscopic disease. Clearly, a negative OncoScint study does not obviate an otherwise necessary second-look procedure.\textsuperscript{18}

Although the overall sensitivity and specificity for carcinomatosis were both higher (68\% and 71\%) with OncoScint than with CT (44\% and 45\%), it remains controversial whether even this advantage will prove so dramatic against state-of-the-art CT technology.\textsuperscript{19} There were false-positive findings at 19 sites in 17 patients, 10 of which were caused by adhesions or inflammatory loci, while 5 were due to benign ovarian tumors. A second primary carcinoma produced 1 false-positive, and 3 could not be attributed. It remains to be seen whether other antibody preparations or routes of administration -- e.g., intraperitoneal -- will provide better sensitivity or specificity.\textsuperscript{20}

\textbf{OncoScint for Colorectal Carcinoma}

The application of radioimmunoscintigraphy (RIS) in colorectal carcinoma is limited to the search for recurrent disease in patients in whom aggressive palliative or salvage treatment is contemplated. Its role, if any, in the staging of primary colorectal carcinoma awaits clinical studies that would demonstrate benefit to patients from treatment of occult disease detected by RIS alone (Figs 1A-B).

Although uncommon, isolated recurrences of colorectal carcinoma in liver, pelvis, abdomen, or lung are resectable for cure in up to 20\% of presentations, with a substantial minority of such patients experiencing long-term palliation or cure.\textsuperscript{21-24} Doerr and associates\textsuperscript{25} have reported on their use of \textsuperscript{111}In CYT-103 in 19 such patients. All had undergone conventional workup for suspected recurrence, including physical examination, CT studies, and carcinoembryonic antigen blood testing. On the basis of the preoperative evaluation, 4 were believed to have locoregional recurrence and 6 liver recurrence, while 9 patients had CEA elevation as the sole evidence of recurrent disease. Among these 9, MAb imaging correctly identified the site of recurrence in 6. All extrahepatic abdominal and pelvic recurrences found at surgery were located preoperatively by MAb RIS. The sensitivity of CT for these lesions was only 43\%. The authors report RIS to have influenced clinical management in 55\% of the patients.

The same group has compared the sensitivity of \textsuperscript{111}In CYT-103 and CT in a larger group of patients with preoperative primary and recurrent colorectal carcinoma and found monoclonal RIS to have a sensitivity and accuracy of approximately 70\% in both extrahepatic abdomen and pelvis.\textsuperscript{26,27} For extrahepatic abdominal disease, this was twice the sensitivity obtained by CT and reflected the capacity to detect peritoneal tumor sites as well as tumor within normal-sized lymph nodes (Figs 2A-B). Within the pelvis, the authors found monoclonal antibodies to be particularly effective for distinguishing between recurrent tumor and postoperative or postradiation scarring (Figs 3A-B and Figs 4A-C). Overall, this modality was alone responsible for detecting disease sites in 10\% of patients. Results such as these, as well as the advantage of whole-body imaging, have led some authorities to recommend \textsuperscript{111}In CYT-103 imaging as standard, following chest x-ray and abdominopelvic CT, for the evaluation of suspected recurrent colorectal carcinoma.\textsuperscript{28}
Enthusiasm for this modality should be tempered, however, by an appreciation of the still limited data on the clinical impact of its use.\textsuperscript{29} False-positive and false-negative studies are both seen in over 10% of patients.\textsuperscript{30} Although it has been demonstrated that the sensitivity of the test depends on the density of TAG-72 antigen expression of the particular tumor deposit, there is no current \textit{in vivo} method for measuring this variable.\textsuperscript{31} In addition, administration of the agent can induce human antimouse antibody (HAMA) production. The presence of HAMA reduces the sensitivity of repeat studies and may confound the reliability of unrelated serologic tests that use murine antibodies. In addition, they introduce the risk of allergic reactions. Abdel-Nabi and colleagues\textsuperscript{32} observed allergic reactions, including anaphylaxis, in 16\% of patients undergoing repeat studies. A role for \textsuperscript{111}In CYT-103 in the management of primary colorectal carcinoma is not yet defined.\textsuperscript{33} Winzelberg and associates\textsuperscript{34} studied 23 patients with primary colorectal carcinoma preoperatively with RIS in addition to standard workup. Planar imaging detected 16 and SPECT imaging 21 of the 23 primary lesions. At surgery, 5 patients were found to have regional adenopathy, of which 3 were detected preoperatively on SPECT images. Unfortunately, false-positive scans were reported for both planar and SPECT techniques.

**Tissue-Specific Biochemical Radioimaging**

**OctreoScan**

Somatostatin is a 14-amino-acid polypeptide synthesized in the hypothalamus. It suppresses metabolic activity by inhibiting the release of a great variety of amine and peptide neurotransmitter and hormones.\textsuperscript{35} These include, among others, anterior pituitary hormones, serotonin, and gastroenteropancreatic hormones such as insulin and glucagon.\textsuperscript{36} Its primary targets are cells of neural crest origin that synthesize hormonally active or neurotransmitter polypeptides. These were formerly dubbed amine precursor uptake and decarboxylation (APUD) cells. Mercifully, the designation has been changed to \textit{neuroendocrine} cells, reflecting their function and heavy distribution throughout the nervous and endocrine systems. In fact, cells with somatostatin receptors have been found in most body tissues.\textsuperscript{37} Of the five receptor types thus far identified, the type 2 receptor has been identified on many malignancies.\textsuperscript{38} This receptor appears linked to the ability of somatostatin to inhibit tumor growth and angiogenesis.\textsuperscript{39} A high incidence of somatostatin receptor positivity has been found in tumors of neuroendocrine origin, including not only such curiosities as insulinomas and tumors secreting vasoactive intestinal polypeptide (VIPomas) but also pheochromocytomas, medullary thyroid carcinomas, and small cell lung carcinomas.\textsuperscript{40}

Understandably, somatostatin and its analogs have been investigated for both therapeutic and diagnostic applications. Since the natural product has a biologic half-life of only approximately 2 minutes, more practical analogs have been developed with longer half-lives. Two octapeptide analogs, octreotide and lanreotide, have had substantial clinical use; the former, with a half-life of 90 to 120 minutes, is approved in the United States for control of diarrhea from VIP secreting tumors and carcinoids as well as growth hormone control in patients with acromegaly.\textsuperscript{41,42} The labeled \textsuperscript{111}In-DTPA pentetretide (OctreoScan, Mallinckrodt Medical, St Louis, Mo) preparation of octreotide is available for imaging. Excretion of OctreoScan is primarily by the renal route with only 2\% excreted via the liver. This allows for good upper abdominal visualization since appreciable gut activity is not seen for nearly 24 hours (Fig 5). The spleen and kidneys show intense background activity, precluding useful imaging. Faint, homogeneous activity is seen as a rule in the liver and thyroid. The gallbladder and bladder understandably will also be identifiable.\textsuperscript{43} Optimal tumor/background ratios are obtained at 24 to 48 hours, coinciding with endocytosis of the receptor-ligand complexes into intracellular lysosomes, while the radiopharmaceutical not incorporated into tissue has largely been cleared.\textsuperscript{44}
One particularly intriguing aspect of OctreoScan is the potential for manipulating or anticipating the imaging performance of the scan by the use of octreotide. Dorr and associates\textsuperscript{45} were able to reduce liver, kidney, and spleen background activity by prior administration of unlabeled octreotide. This improved the conspicuity of liver metastases. Woltering and colleagues\textsuperscript{46} have described administration of a test dose of 100 µg of unlabeled octreotide with checking of circulating peptide levels before and after. They found that greater than 50% suppression identified a group of patients whose tumors would virtually always show uptake with OctreoScan. Tumors in patients whose peptide levels did not suppress were unlikely to be visualized.

Considerable clinical experience with OctreoScan imaging of gastroenteropancreatic neuroendocrine tumors is beginning to accumulate. In the European multicenter study, OctreoScan uniquely identified tumor sites in 28% of patients thoroughly examined by all other modalities.\textsuperscript{47} Positive studies were obtained in 87% of patients with carcinoids and 73% of patients with gastrinomas but in only 46% of patients with insulinomas. Comparable results have been obtained in the United States by Woltering and colleagues,\textsuperscript{46} who recommend OctreoScan as the first imaging modality to be obtained in patients diagnosed as having neuroendocrine tumors. King and associates,\textsuperscript{48} reporting on a smaller retrospective review employing SPECT in all patients with negative planar scans, found OctreoScan to be less sensitive than CT but complementary and advocated its use in patients with disseminated pathology or negative or equivocal CT scans (Figs 6A-B). Our approach at the University of South Florida is to perform OctreoScan imaging after a thorough noninvasive evaluation and prior to angiography or surgical intervention. By this means, SPECT studies can be tailored to areas of concern identified on CT, MRI, or clinical evaluation.

Although not a situation for which OctreoScan is ordinarily considered, the management of small-cell lung cancer can occasionally be aided by its use. Octreo-Scan has been shown to have very high sensitivity for identifying the primary site of small-cell lung cancer (Figs 7A-B). Its sensitivity for metastatic disease is less certain. Most provocative has been the identification of residual disease in a number of patients thought to be in complete remission.\textsuperscript{49} This affinity for small-cell lung cancer is not surprising in view of the neuroendocrine origin of the malignancy. Presumably Merkel cell tumors will prove similarly amenable to scanning for occult disease, with, however, less potential practical application.
In a similar vein, OctreoScan holds promise of identifying areas of viable tumor in Hodgkin’s disease. Bong and associates,\textsuperscript{50} demonstrated a 91% sensitivity for OctreoScan, including a number of sites not seen by CT. The sensitivity of OctreoScan for non-Hodgkin’s lymphoma is much lower, especially for indolent lymphomas and in particular for intrabdominal disease. Specificity of the scan can be compromised by uptake in normal gut and mucosa-associated lymphoid tissue; in fact, the scan is sensitive in general for nonmalignant conditions involving activated lymphocytes, including, for example, rheumatoid arthritis, sarcoid and tuberculosis.

OctreoScan has very high sensitivity for meninigiomas, but data are conflicting for its sensitivity in primary central nervous system (CNS) malignancies. As yet, it is not clear if in any clinical setting this would be relevant.\textsuperscript{51,52} So too, data for breast cancer are beginning to be developed. Van Eijck and colleagues\textsuperscript{53} have studied OctreoScan imaging in a small group of patients with early-stage breast cancer. Three-quarters of them showed uptake in the primary, with 85% of ductal and 56% of lobular carcinomas imaged. Additionally, a small number of patients were shown to have axillary nodal disease despite a benign clinical exam, and a few were noted to have metastatic disease not otherwise detected. Here again, it is not clear whether or how the scan might be incorporated into clinical practice.

Radioimmunoguided Surgery

Radioimmunoguided surgery (RIGS), an area of particular interest and potential, involves the use of intraoperative hand-held radiation detectors to guide the surgeon to areas of disease not visible to the radiologist on external scanning or, for that matter, to the surgeon on standard intraoperative examination. Both theoretical considerations and experimental in vivo results predict that, providing the probe can be brought close to the tumor deposit (preferably within a centimeter), sensitivity with a hand-held gamma probe should be superior to that for an external camera across a wide range of radiopharmaceuticals, administered doses, tumor uptake, and camera design.\textsuperscript{54} Experience with this approach is accumulating with immune, specific biochemical, and nonspecific physiologic radiopharmaceuticals.\textsuperscript{55}

Experience with radiolabeled B72.3 MAb and hand-held gamma probe intraoperative detection is described in a series of reports from Ohio State University.\textsuperscript{56,57} The hand-held probe system detected 82% of metastatic colorectal sites, including a number that were not evident to the surgeon, and altered surgical management in 26% of patients. In a more recent multicenter extension of this effort, RIGS localization was shown to have a sensitivity of 77% and a positive predictive value of 78%; it identified 30 apparent tumor sites among 26 patients.\textsuperscript{58} Consistent preliminary results with ovarian carcinoma have also been reported.\textsuperscript{59}

Badalament and associates\textsuperscript{60} reported on a pre-phase 1 study of 10 patients undergoing radioimmunoguided radical prostatectomy and lymphadenectomy. A B72.3 MAb tagged with iodine 125 (\textsuperscript{125}I) was injected prior to surgery. Intraoperatively, the ratio of gamma counts in tissues of concern to background counts was ascertained. Three patients had elevated nodal counts, and two of these had pathologically positive nodes. The technique successfully identified tumor in all involved prostatic lobes and predicted negative surgical beds in all patients with gland-confined disease. The authors suggest the technique as a means of confirming the safety of preserving one or both neurovascular bundles as well as an adjunct in laparoscopic lymph node sampling.

Attempts to utilize\textsuperscript{111}In-labeled OctreoScan for intraoperative localization have been thwarted by the relatively high energy of the\textsuperscript{111}In label, producing substantial confounding background activity within the operative field. Woltering and colleagues\textsuperscript{61} have reported encouraging results with intraoperative hand-held gamma-probe localization using investigational\textsuperscript{125}I-labeled octreotide and lanreotide in a small number of patients with carcinoids and gastrinomas. Their technique requires temporary common bile duct clamping to prevent the rapid biliary clearance of the iodine-labeled radiopharmaceuticals.\textsuperscript{62}

The most extensive potential use of RIGS, however, promises to be in the initial surgical staging of early-stage melanoma and, perhaps, breast cancer. This method, using \textsuperscript{99m}Tc antimony sulfur colloid, has shown great promise in mapping the lymphatic drainage of malignant melanomas and identifying the sentinel node of the relevant drainage basin, allowing nodal dissection procedure that are both more accurate and of lower risk.\textsuperscript{63,64} Recent published reports as well as our developing experience at the University of South Florida, H. Lee Moffitt Cancer Center, are highly encouraging for the eventual application of this technique to the axillary sampling necessary in early-stage breast cancer.\textsuperscript{65} Clearly, further validation of this technique is required before it can be recommended outside a research protocol.\textsuperscript{66}

Physiologic (Nonspecific) Imaging Techniques

Positron Emission Tomography

Positron emission tomography (PET) is a technology that utilizes the positron emitting radionuclides of carbon, nitrogen, oxygen, and fluorine to serve as tracers for following biochemical processes in vivo. Any molecule containing one of these elements can be tagged with a positron emitting radionuclide of that element, providing a radioactive tag that displays the metabolic fate of the tagged molecule, much like a transmitter strapped to a migrating animal to follow its path and fate in the wild. The positron, a positively charged electron, is released into tissue upon decay of the radionuclide. It travels from 2 to 7 mm before interacting with an electron in an “annihilation reaction” producing two 511 keV photons, which travel in opposite directions. Detectors arrayed around the imaged volume are paired at 180° angles so as to register the positions of the annihilation reactions. As a result, while PET can provide quantitative measures of metabolic processes using tracer kinetic models, it is limited in spatial resolution because of the variability in the length of the positron’s decay track.\textsuperscript{67} Consequently, some anatomic (as opposed to biochemical) imaging study must always be done in conjunction with a PET scan to provide a framework for its interpretation.

The largest PET experience has been accumulated with deoxyglucose tagged with radioactive fluorine 18 (\textsuperscript{18}FDG). This molecule was chosen to take advantage of the high glycolytic rate of many tumors.\textsuperscript{68} Although not thoroughly understood, the high glycolytic rate of tumors is due at least in part to alterations in glucose transport that have been shown to be linked to oncogene expression and to correspond in some instances to tumor growth rates.\textsuperscript{69,70} The \textsuperscript{18}FDG is rapidly phosphorylated to \textsuperscript{18}FDG-6-phosphate but -- lacking the hydroxyl group on C-2 -- cannot be metabolized further along the glycolytic pathway. \textsuperscript{18}FDG and \textsuperscript{18}FDG-6-P\textsubscript{O}\textsubscript{4} therefore accumulate preferentially within the tumor cells, and their concentration is measured by the PET scanner.

Background uptake is highest in areas of high glucose consumption: brain (especially gray matter), heart, lung, and inflammatory sites. The \textsuperscript{18}FDG PET technique, in fact, produces a map of metabolic activity within the imaged volume.\textsuperscript{71} It has proved highly accurate for distinguishing tumor recurrence from necrosis or scarring in treated glioma patients with indeterminate masses on CT or MRI.\textsuperscript{72} Quantitative measures have been shown to predict survival, tumor response to therapy, and tumor
The most challenging difficulty with FDG PET of the brain, however, is the relatively high background brain activity, particularly in gray matter. For this reason carbon 11 (\(^{11}\text{C}\)) methionine PET has been investigated and been shown to provide better delineation of tumor spread into gray matter and areas of edema. In small numbers of patients, Ogawa and associates\(^{83}\) and Mosskin and associates\(^{84}\) have found more reliable tumor mapping with \(^{11}\text{C}\) methionine PET than with CT or MRI, respectively. Unfortunately, uptake in low-grade tumors has proved variable and, consistent with this, prediction of tumor grade is not reliable.\(^{85}\)

Enhanced uptake in meningiomas and pituitary adenomas has been shown by \(^{11}\text{C}\) methionine PET, and it has been shown to mirror response to bromocriptine therapy in the latter.\(^{86,87}\)

Operations of PET applications outside the brain are beginning to accumulate (Fig 9).\(^{88,89}\) Goldberg and associates\(^{90}\) have described their experience in 38 patients with a variety of primary and metastatic liver lesions. They found the conspicuity of liver metastases to exceed that obtained with CT in the same patients and ascribe this to the relatively high levels of glucose-6-phosphatase in hepatocytes, allowing for dephosphorylation of FDG-6-phosphate and producing much lower background activity than in brain or heart.\(^{91}\) Well-differentiated primary liver tumors, however, and low-grade lymphoma did not show increased activity, and false-positive studies from nonmalignant inflammatory conditions were seen. More promising are early reports of successful differentiation between scar and recurrent tumor using FDG PET in posttreatment rectal and gynecologic carcinoma patients.\(^{92,93}\) In contrast, \(^{11}\text{C}\) methionine PET has shown poor specificity in the pretreatment staging of patients with gynecologic malignancy due to confounding background activity.\(^{94,95}\) Similarly, staging of chest malignancies with FDG PET has been hampered by high background activity in the mediastinum.\(^{96}\)

Operation of a PET program is cumbersome and costly; with few clear-cut indications for PET imaging as opposed to less costly alternatives, PET will probably remain for the time being an investigational tool occasionally resorted to for help in distinguishing necrotic brain from recurrent brain tumor. Knowledge of the relative clinical performance of different PET radiopharmaceuticals is very limited.\(^{97}\)

The results of future investigations of tumor energy or protein or nucleic acid metabolism

... aggressiveness in glioma patients.\(^{73-76}\) High uptake has also been seen in primary CNS lymphoma.\(^{77}\) In this regard, FDG PET has been suggested as an alternative to biopsy in patients with acquired immunodeficiency syndrome (AIDS) who are responding poorly to empiric therapy for presumed CNS toxoplasmosis.\(^{78}\) Conveniently, steroid administration does not appear to alter the results of FDG PET imaging.\(^{79}\)

It must be kept in mind that FDG PET is a nonspecific study (Fig 8).\(^{80}\) Postradiation inflammation, particularly in the first 6 months following treatment, may show substantial FDG uptake. This is less a problem than it may at first appear in that radiation necrosis is atypical within this time period. Potentially confounding uptake has also been described within brain abscesses and a range of inflammatory processes.\(^{81}\) In the evaluation of CNS metastatic disease, contrary to its performance with primary CNS neoplasms, FDG PET has shown highly variable patterns of uptake and a sensitivity clearly inferior to that of CT or MRI.\(^{82}\)

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Physiologic Radionuclide Imaging

The fortuitous discovery of primary lung cancers in patients undergoing cardiac perfusion studies has brought much attention to thallium 201 (\(^{201}\)T1) and more recently \(^{99m}\)Tc hexakis-2-methoxyisobutyl isonitrile (MIBI) as potential agents for the imaging of occult tumor and for distinguishing between viable tumor and necrotic tissue.\(^{99,100}\) Thallium 201 is a monovalent cationic radionuclide handled similarly to potassium, crossing the cell membrane via the Na\(^+\),K\(^+\)-ATPase pump.\(^{101}\) Unlike potassium, \(^{201}\)T1 has two binding sites on the enzyme system, which may explain its prolonged clearance from the cell. Uptake requires cell viability and has been shown to be greater in tumor cells than in normal connective tissue or inflammatory cells and minimal in areas of necrotic tissue.\(^{102}\) Steroid administration does not meaningfully alter uptake, at least in the brain.\(^{103}\) The typical background scan features high abdominal and pelvic activity with high activity also in the heart, and the thyroid and salivary glands.\(^{104}\) Correspondingly, the most promising oncologic applications of this radionuclide involve the brain and extremities, areas where background activity is relatively low.

Early reports of \(^{201}\)T1 imaging of primary brain tumors confirm the expectation that uptake corresponds to the histologic aggressiveness of the tumor. Reliable interpretations can be made using the contralateral homologous area of brain for comparison. Black and associates, using a simple ratio (thallium index) of average counts per pixel in corresponding regions, have, in fact, found this ratio to predict clinical outcome better than did the histologic grade of biopsy tissue; they surmise that the radionuclide study provides a global measure of metabolic activity and is not prone, as is biopsy, to sampling error.\(^{105}\) The mean thallium index of 14 low-grade gliomas was 1.27 ± 0.40, while the mean index of 11 high-grade gliomas was 2.40 ± 0.61 \((P<.0005)\). Carvalho and Schwartz and associates,\(^{106,107}\) using a ratio based on the activity in the contralateral scalp -- which they found initially to be less variable than that of contralateral brain -- have found excellent accuracy both for recognition of recurrence and for distinguishing recurrence from brain necrosis (Figs 10A-B). They report a dual-isotope method with \(^{99m}\)Tc-hexamethylpropilene amine oxime (HMPAO) to be helpful in patients with intermediate ratios. In our institutional experience, we have found contralateral homologous brain to be more reliable than contralateral scalp as a basis for interpreting \(^{201}\)T1 uptake. We have found \(^{99m}\)Tc HMPAO scanning to be fraught with difficulties in interpretation and do not use it in this setting.\(^{108}\)

The most promising areas for the use of \(^{201}\)T1, aside from brain tumor management, are in the follow-up of treated patients with differentiated thyroid carcinomas and patients with bone and soft tissue sarcomas of the extremities. Ramanna and colleagues\(^{109}\) have evaluated \(^{201}\)T1, \(^{131}\)I, and thyroglobulin assays among 52 patients following thyroidectomy for differentiated thyroid carcinoma. They found \(^{201}\)T1 scanning to be particularly useful in patients with elevated thyroglobulin following postthyroidectomy ablation who failed to show uptake on \(^{131}\)I diagnostic scans. Sensitivity superior to \(^{131}\)I has also been shown for patients with the oncocytic (Hürthle cell) thyroid carcinoma variant (Figs 11A-D and Figs 12A-C).\(^{110}\) Rammana and coworkers\(^{111}\) have also investigated \(^{201}\)T1 imaging in the management of patients with bone and soft tissue sarcomas and found it to mirror treatment response in the majority of patients. They point out the particular advantage of \(^{201}\)T1 scanning over conventional \(^{99m}\)Tc-methylene diphosphonate (MDP) bone scans of eliminating confusion between residual tumor and healing bone. Others have been able to predict soft tissue sarcoma response to radiation therapy based on \(^{201}\)T1 uptake.\(^{112}\)
Limited experiences with $^{201}$Tl in differentiating recurrence from radiation necrosis in head and neck cancer and in the detection of systemic spread of AIDS-related Kaposi sarcoma -- as well as in breast and lung cancer staging -- will require further study.  

MIBI₂ - Methoxy Isobutyl Isonitrile

The complex lipophylic cation radionuclide $^{99m}$Tc MIBI is passively accumulated in mitochondria and bound there as long as the mitochondria continue to function.  

Cellular death releases MIBI from its mitochondrial binding sites.  

The intracellular accumulation of MIBI has recently been discovered to be inversely linked to the development of multiple drug resistance.  

Nonspecific increased uptake in tumor cells compared to fibroblasts is comparable to that seen for $^{201}$Tl, as is the pattern of normal scan background activity.  

Clinical information on scanning with $^{99m}$Tc MIBI in oncology remains very preliminary; however, it is logical that studies comparing this agent to $^{201}$Tl will be forthcoming for the gamut of applications for which the latter has been proposed.  

Some of the most promising data have been accumulated in the imaging of (benign) hyperparathyroidism, particularly in the evaluation of complicated and recurrent cases.  

Performance similar to that of $^{201}$Tl is anticipated for patients with thyroid carcinoma who require investigation for elevated thyroglobulin following surgery and $^{131}$I ablation, and in patients in whom metastatic disease is being searched for without thyroid hormone withdrawal.  

Another area of particular excitement has been the possible application of $^{99m}$Tc MIBI to the evaluation of early-stage breast carcinoma.  

It must be kept in mind, however, that even the apparently desirable 97% negative predictive value achieved in the most promising of these preliminary efforts will expose approximately every thirtieth woman with mammographically detected breast cancer to a false-negative diagnosis.  

In our opinion and experience, the more fruitful avenues of investigation will determine the performance of this technique in women who cannot be adequately examined by mammography or in cases of axillary adenocarcinoma adenopathy with no evident breast primary (Figs 13A-B).


93. Casey MJ, Gupta NC, Muths CK. Experience with positron emission tomography (PET) scans in patients with ovarian cancer. Gynecol Oncol. 1994;53:331-


