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EDITORIAL

Tissue Characterization in Nuclear Oncology: Its Time Has Come

In this issue of the *Journal*, Hirano et al. proposed methodology for producing ^{99m}Tc(V)-DMSA from a kit (*1*) presents a new role for nuclear medicine imaging in oncology: characterization of lung cancer. Various types of lung cancers were visualized with ^{99m}Tc(V)-DMSA (90%) in their study, but the semiquantitative target-to-background ratio was higher in squamous-cell carcinoma than in the adenocarcinoma or metastatic bone lesions. Moreover, benign lesions did not take up ^{99m}Tc(V)-DMSA.

Technetium-99m-(V)-DMSA is only one of several imaging agents that are undergoing clinical or experimental trials in producing images that can reflect the character of the tissues. Several other radiopharmaceuticals currently used or that are potentially useful in discriminating tumor masses and characterizing malignant tissues include: (1) radioelement pharmaceuticals such as ^{67}Ga and ^{201}Tl; (2) tumor characterizing organic compounds such as ^{99m}Tc-sestamibi for SPECT, ^{18}F-fluorodeoxyglucose (FDG) for PET; and (3) peptides and cutting edge radiopharmaceuticals such as receptor imaging peptides, single-chain binding proteins and biologically active peptides, as well as several experimental tumor imaging agents.

Received Oct. 24, 1994; accepted Oct. 24, 1994.
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Radioelement Pharmaceuticals

Gallium-67, ^{201}Tl SPECT and planar imaging emerged in the 1980s as major functional imaging tools in oncology. They are both radioisotopes of naturally occurring elements and are commercially available as ^{67}Ga-citrate and ^{201}Tl-chloride. Although ^{67}Ga imaging has been used for years as a tumor marker in nuclear imaging, recent efforts have begun to assess its potential role in tissue characterization to differentiate recurrent tumors from necrotic mass after radiotherapy or chemotherapy. Masses identified on a follow-up CT scan as lymphoma and other tumors have been successfully differentiated by ^{67}Ga (*2,3*). The high uptake of this nonspecific radiopharmaceutical indicates the viability of tumor malignancy. Gallium-67 is used to detect not only effectiveness of therapy in oncology, but also prognostication of outcome (*4,5*). The shift toward tissue characterization and higher specificity in nuclear oncology is highlighted by the increasing use of ^{201}Tl instead of ^{67}Ga in tumor characterization.

Thallium-201 imaging in the follow-up of post-therapy brain tumors has been found to be most helpful in discriminating residual postradiation necrotic tissue from recurrent or residual viable tumor (*6–8*). A major attraction of ^{201}Tl imaging over ^{67}Ga is the time needed to complete the study: 3–4 hr versus 48–72 hr needed for imaging with ^{67}Ga. Thallium-201 is also more specific than ^{67}Ga in a variety of brain, breast and mediastinal tumors (*7–10*). When used conjointly with ^{67}Ga, however, ^{201}Tl can identify Kaposi's sarcoma and differentiate it from lymphoma in HIV-positive patients (*9,10*). The retention index of ^{201}Tl, which compares the early target-to-background ratio with the delayed ratio (1 to 3 hr later), has been found to be highly accurate in identifying tumor viability after chemotherapy and radiotherapy (*11–13*). Suga et al. (*14*) used ^{201}Tl in experimental monitoring of radiotherapeutic effects of tumor proliferative potential after treatment. Other clinicians also have found thallium's retention index to be useful in characterizing histological types of tumors (*6,15*). Thallium-201 imaging also has been used in breast cancer (*16,17*) to separate benign from malignant lesions prior to biopsy in patients who had an equivocal or inconclusive mammogram [but has been found to have a slightly lower negative predictive value than sestamibi (96%

vs. 100%)]. Most researchers concur that ^{99m}Tc-sestamibi has a greater potential for tissue characterization in breast cancer than ^{201}Tl, but ^{201}Tl has superior specificity for tissue characterization in the axillary lymph nodes. As we come to understand the mechanisms of tumor localization of ^{201}Tl and ^{67}Ga on a molecular level, additional uses will emerge. Unfortunately, both radiopharmaceuticals have relatively high radiation exposures, making the use of ^{99m}Tc-labeled compounds, with their lower exposures, more attractive.

Tumor Characterizing Organic Compounds

When used with planar or SPECT imaging ^{99m}Tc(V)-DMSA or sestamibi has unique tumor-localizing properties due to a special interaction with viable cell membrane and metabolically active mitochondria of cells. Hirano et al. (*1*) have shown that ^{99m}Tc(V)-DMSA is taken up by tumors other than lung tumors. In addition to high sensitivity for the primary lesions, ^{99m}Tc(V)-DMSA also is localized in metastatic lesions of the soft tissues and the bones (*18,19*). The next step, however, is to study the true potential of this agent in discriminating various tumors. Although ^{99m}Tc(V)-DMSA has been successful in characterizing lung tumors and in discriminating malignant tumors from infection, it has limitations in differentiating the types and degrees of malignancy in other tumors (*20*).

Technetium-99m-sestamibi is the agent of choice in functional imaging. Its use in detecting parathyroid adenomas is a well established technique which is free of the hazards of subtraction imaging. Nonspecific localization of sestamibi by several tumors is, in fact, highly specific for malignancy (*21,22*). Breast imaging (mammoscintigraphy) with ^{99m}Tc-sestamibi can reduce the number of unnecessary breast biopsies due to inconclusive mammographic examinations. Typically, only one of three to five patients referred for a biopsy after mammography actually have breast cancer. At many centers, clinicians rely more and more on ^{99m}Tc-sestimibi scan results. At my institution, ^{99m}Tc-sestamibi imaging is used in cases of questionable soft-tissue uptake of ^{99m}Tc-MDP in the breast during routine bone scanning. None of these indications have full clinical acceptance. The high negative predictive value of ^{99m}Tc-sestamibi imaging, however, makes it an attractive clinical tool in the management of breast cancer (*23*). The limited sensitivity for tumor involved axillary nodes, however, is of concern. Data from an ongoing multicenter clinical trial (DuPont Merck, Inc., North Billirica, MA) on breast cancer and ^{99m}Tc-sestamibi should provide some answers. Moreover, its use in malignancy identification of other tumors (*24*) awaits further clarification.

FDG

Fluorine-18-FDG imaging has been used successfully in a variety of cancers (*25,26*). Uptake of this agent depicts glucose metabolism in the tumor being imaged. High uptake of ^{18}F-FDG generally represents viability of the malignant tumor versus necrotic tissue. Gupta reported an accuracy rate of 92% for FDG in differentiating benign from malignant solitary pulmonary nodules and lymph nodes (*27*). Total body ^{18}F-FDG PET imaging and its cost-effectiveness in staging cancer is being studied. Because of the socioeconomic problems associated with PET, the only promising tumor-seeking compound is ^{18}F-FDG. The synergism between PET capabilities in tissue characterization and the glucose transport gene as well as other genetic subjects are discussed by Wagner (*23*) and Britton (*28*).

Peptides and Other Agents

Peptide imaging agents are the most likely candidates to satisfy the search for more specificity in nuclear medicine. There are several varieties of radiopharmaceuticals within the category of generic peptides. Some of them are offshoots of the scientific achievements from monoclonal antibody (Mabs) manufacturing in the late 1980s and early 1990s. The clinical role of imaging with Mabs may be questionable or limited to the search of occult malignancy. Nevertheless, the introduction of Mabs to clinical oncology has served to highlight the need for simpler and smaller molecules to identify various tumors and has stimulated the development of peptides for nuclear imaging (*29*). Researchers have recognized the pivotal role amino acids play as building blocks for a vast array of molecular signaling, signal transduction, and recognition/transformation units. Amino acids can act as biological transmitters themselves or participate in the formation of several classes of peptides currently used for nuclear imaging.

Molecular engineering has resulted in peptides that come in different forms and sizes. They may be single-chain antigen binding proteins such as Fv fragments which are 50% smaller than Fab, or they may be single-chain-binding proteins (sFvs) that are prepared by recombinant DNA technology. The target-to-background ratio, however, is better for sFvs because they clear much more rapidly from the circulation than Mab fragments. They have a high penetration into the tumor and better distribution within the tumor (*28,29*).

Hypervariable region peptide analogs, on the other hand, are even smaller than single-chain peptides. Technetium-labeled tripeptides are being used in nontumor applications (thrombi), but their oncologic use is being studied. More exciting are the natural biologically active peptides such as hormones, neurotransmitters and neuromodulators, as well as growth factors and cytokines. They generally have a higher affinity for specific tissues than antibody fragments and range in size from very small molecules made up of only three amino acid residues (i.e., bacterial chemotactic peptides) to larger molecules, such as interleukin-8 which has 79 amino acid residues (*29*). Much work has been done on chemotactic peptides, but their potential is greater in inflammatory/infection imaging than in tumor imaging (*30*) because they have an affinity for receptors on inflammatory polymorph nuclear cells and on mononuclear phagocytes. Syn-

thetic analogs are now available and have been labeled with both ^{111}In and ^{99m}Tc.

Another subtype of peptides with the greatest potential as clinically accepted imaging agents are receptor imaging peptide derivatives. The somatostatin analog octreotide is commercially available and is used for imaging neural crest tumors that have somatostatin receptors (*31–33*). On the other hand, some tumors have receptors specific for vasoactive intestinal peptide (VIP) localization. Indeed, VIP and its analogs have been labeled with ^{123}I for imaging VIP-positive and somatostatin-negative pancreatic tumors (*34*). Somatostatin generally sends an inhibitory message to its receptors, while VIP sends a facilitatory message. The relative clinical roles of these two receptor-oriented peptides in diagnosing neuroendocrine tumors are still to be fully realized. Other peptide imaging agents, such as corticotropin releasing factor, are under investigation (*35*).

Other potential radiopharmaceuticals for tissue characterization are already in experimental trials. Technetium-99m-glutathione identifies malignancy, but it also identifies areas of inflammation/infection. Technetium-99m-galactosyl neoglycoalbumen offers little competition to ^{99m}Tc-sestamibi in differentiating breast cancer (*28*). There are, however, novel peptides and amino acids [e.g., iodo-α-methyl tyrosine (IMT) for brain tumors and growth factors for tumor imaging (TGF-ßeta)]. Epidermal growth factors (EGF) also have been explored for glioma imaging (*29,36,37*). Other candidates include halogenated pyrimidines such as iododeoxyuridine, multidrug resistance peptides (e.g., colchicine) and anti-sense oligonucleotides, such as c-myc oncogene mRNA.

Peptide imaging agents are advantageous in that they have a high specific activity, they are labeled with short-lived radionuclides and they have specific biodistribution. They also have extremely small molecules which facilitate rapid localization, tumor penetration and blood clearance (*38*). Receptor binding agents have the additional advantages of localizing tumor or recurring tumors that are difficult to detect, for instance, gastrinoma and medullary carcinoma of the thyroid. Moreover, a positive scan may predict the therapeutic course. The potential to select the most effective therapy and to monitor treatment effectiveness is a beneficial result of peptide imaging.

Conclusion

In addition to tumor characterization, peptides and the other radiopharmaceuticals discussed above also have great potential in prognostication. The degree of receptor expression in tissue characterization imaging has been shown to be a prognostic indicator, such as somatostatin receptors in neuroblastomas. Developing prognostic indices has been a long-desired goal of nuclear functional imaging. Both ^{201}Tl and ^{67}Ga have been used in prognostication and in predicting response to therapy as well as evaluating the immediate response to chemotherapy and radiotherapy (*10*).

Nuclear medicine's role in oncology is accurate tissue characterization and a shift from sensitivity to increased specificity (*28*). Nuclear oncology can provide new images for disease and not just tests for old diagnoses (*23*). Thus, nuclear medicine may open up new communication with genetic studies of disease by exposing dissonant messages and characterizing disease as dissonance.

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