Molecular Imaging in Oncology

E. Edmund Kim, M.D.
Prof. of Radiology & Medicine

The University of Texas M.D. Anderson Cancer Center and
The University of Texas Medical School, Houston

Although beginning within a specific organ, cancer is a systemic disease with a genetic basis and is often associated with varied clinical and biochemical manifestations. No single test can alert the oncologist to detect the presence of a tumor, assess its extent, estimate its prognosis, and monitor its response to therapy. The histologic diagnosis of cancer can easily be made by fine needle aspiration or core biopsy under the guidance of high resolution ultrasonography, CT or MRI. The effective management of cancer patients involves the integration of clinical, laboratory and imaging data with the selection of effective treatment and the monitoring of therapeutic response and toxicity.

In the past 30 years there has been an enormous increase in the range of imaging techniques available to diagnose, stage and follow-up cancers. A well-designed imaging strategy is an implicit component of the approach to evaluating cancer patients. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are molecular imaging techniques that use radiolabeled molecules to image molecular interactions of biological processes in vivo. As a probe of in vivo chemistry, they provide ways to view a cancer not as a capricious invasion of the body but as a failure of normal control processes. PET or SPECT make it possible to measure the utilization of substrates that supply energy or nucleotides, and provides pharmakokinetic data concerning radiolabeled therapeutic agents. Because of the high glycolytic rate of many malignancies, PET or SPECT with the use deoxy-glucose (DG), has demonstrated the potential to detect malignant tissue and to quantify changes in tumor glycolysis during and after treatment. Diseases are biologic processes, and the differentiation of viable from nonviable tissue is fundamentally a metabolic question. Accumulation of thymidine into tumors is increased in the presence of increased DNA synthesis. Amino acid transport across tumor cell membrane has been found to differentiate malignant

from nonmalignant tumors. It has been found that C-11 methionine improves delineation of cerebral gliomas and shows greater sensitivity when compared with F-18 FDG. Radioloabeled tamoxifen or estradiol uptake makes it possible to determine the treatment of certain breast cancer patients on the basis of the number of functioning estrogen receptors. Angiogenesis is a requirement for malignant tumor growth and metastasis. It has been evaluated noninvasively by nuclear imaging using endostatin and vascular endothelial growth factor (VEGF) or by v3-targeted MRI. Tumor hypoxia has also been detected and quantitated noninvasively by using misonidazol derivatives labeled with F

Traditionally, T1 and T2-weighted images with or without fat suppression or contrast agent have formed the primary foundation for oncological study using MRI technique with high-resolution anatomical information. However, advanced MRI techniques provide a way to assess tissue function and physiology. Magnetization transfer (MT) magnetic resonance imaging (MRI) makes it possible to analyze the effects of protons with restricted motion in the vicinity of macromolecules on the total MR signal intensity from free protons. A recent report suggested that the MT ratio can be measured by comparing the signal intensity of the lesion on multisection fast spin echo (FSE) images with that on single-section FSE images. In that study, the MT ratio of endometrial cancer was significantly higher than that of endometrial hyperplasia or normal endometrium.

Diffusion-weighted MRI is now becoming more widely available and maps the motion of water protons. It exploits the random motion of the molecules, which causes a phase dispersion of the spins with a resultant loss of signals. On diffusion-weighted images, necrotic tumor showed low signal intensity, indicating rapid diffusion of water molecules as a result of loss of membrane integrity, while viable tumor demonstrated high signal intensity.

Proton MR spectroscopic (MRS) data indicates that decreases in NAA concentration is more directly related to the percent total volume occupied by the tumor plus associated pathology. Because of the anaerobic glycolytic process of tumor metabolism, it is reasonable to assume that many tumors should produce increased levels of lactate. Generally, primary brain tumors show increased choline levels. Phosphocholine is a membrane precursor, and increased choline reflects increased membrane synthesis consistent with rapid cell turnover. Glycerophosphocholine also can be generated during membrane breakdown. Phosphorus MR spectroscopy demonstrates information of bioenergies and membrane metabolites, reflecting cell viability and proliferation.

Gene therapy broadly defines various manipulations of genetic information and includes the introduction of marker genes into cells, the replacement of defective genes by site-specific recombination, the insertion of

exogenous genes for enzyme or protein production, and oligonucleotide antisense therapy. It is being increasingly applied in a wide variety of clinical settings, particularly neoplastic disease and primary deficiency disease. Critical issues regarding gene therapy will include localizing gene delivery, optimizing site-specific delivery, monitoring the uptake and expression of therapeutic genes. Transfected mouse fibroblasts and human embryonal renal cells containing tyrosinase messenger RNA showed a higher In-111 binding capacity than nontransfected cells, a difference readily detectable with scintigraphy. MRI also demonstrated transfected cells to have markedly higher signal intensity after gene transfer than nontransfected cells. There have been efforts by integrating multiple diagnostic and interventional imaging strategies to deliver genes of interest to specific target tissues and to monitor the efficacy of therapy. One goal of oncologic gene therapy is to selectively induce apoptosis which is a programmed cell death with cytoplasmic condensation and cellular DNA fragmentation. Tc-99m hydrazinonicotinamide (HYNIC) or ethylenecysteine (EC) coupled to annexin V has been used to quantify apoptotic cells in culture and in cell suspension. MRS has been used to examine the sequence of events coinciding with cell damage as early as 2-4 days into ganciclovir (GCV) treatment of herpes simplex thymidine kinase (HSV-tk)-transfected cells.

There are many biological processes that cannot be easily or directly monitored by CT, MRI or nuclear imaging because key molecules in these processes are not distinguishable from each other. Optical coherence tomography (OCT) uses infrared light and forms of subsurface boundaries from signals reflected at the boundaries. Induced fluorescence devices use light from lasers or incandescent sources to stimulate tissues. Cancerous tissues may fluoresce differently than normal tissues. In vivo microscopy also uses ultraviolet light for illuminating organs that depict microvasculature at the cellular level.

In summary, PET, SPECT, MT or diffusion-MRI, MRS and optical imaging can demonstrate metabolic/hemodynamic changes or metabolites to noninvasively differentiate tumors from non-tumor lesions, to characterize types or grades of tumors, and to monitor tumor regression, recurrence or response to therapy.