

## Molecular and Cellular Imaging in Oncology

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Although beginning within a specific organ, cancer is a systemic disease with a genetic basis and viewed as a failure of multiple chemical processes. 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. 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. PET or SPECT make it possible to measure the utilization of substrates that supply energy or nucleotides, and provides pharmacokinetic 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. Amino acid transport across tumor cell membrane has

been found to differentiate malignant from nonmalignant tumors.

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 a  $\alpha\beta_3$ -targeted MRI. Tumor hypoxia has also been detected and quantitated noninvasively by using misonidazol derivatives labeled with F-18 or Tc-99m. Unique and most important to PET or SPECT application that may be useful in predicting response and tailoring treatment is the ability to measure tumor drug uptake using radiolabeled chemotherapeutic agents. PET or SPECT offers many research opportunities to explore in the field of oncology, and allows a physiologic view of tumor biology, which no other method can provide. Tc-99m hydrazinonicotinamide (HYNIC) or ethylenecysteine (EC) coupled to annexin V has been used to quantify apoptic 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. 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. 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. 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 brain 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. Phosphocholine is a membrane precursor, and increased choline reflects increased membrane synthesis consistent with rapid cell turnover. 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. Critical issues regarding gene therapy will include localizing gene delivery, optimizing site-specific delivery, monitoring the uptake and expression of therapeutic genes. Imaging endogenous gene

expression is somewhat difficult because there is no obvious differentiating characteristics to exploit, but immunofluorescent labeling and confocal microscopy have advanced in vitro imaging of gene expression. 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. Imaging of HSK-TK expression is reliant on the use of F-18 ganciclovir, penciclovir and uracil (FMAU). MRI also demonstrated transfected cells to have markedly higher signal intensity after gene transfer than nontransfected cells. One goal of oncologic gene therapy is to selectively induce apoptosis which is a programmed cell death with cytoplasmic condensation and cellular DNA fragmentation. 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.