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## **MOLECULAR IMAGING OF BRAIN TUMORS**

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### **ABSTRACT**

*Clinical and experimental use of positron emission tomography (PET) is expanding and allows quantitative assessment of brain tumor's pathophysiology and biochemistry. PET therefore provides different biochemical and molecular information about primary brain tumors when compared to histological methods or neuroradiological studies. Common clinical indications for PET contain primary brain tumor diagnosis and identification of the metabolically most active brain tumor reactions (differentiation of viable tumor tissue from necrosis), prediction of treatment response by measurement of tumor perfusion, or ischemia. The interesting key question remains not only whether the magnitude of biochemical alterations demonstrated by PET reveals prognostic value with respect to survival, but also whether it identifies early disease and differentiates benign from malignant lesions. Moreover, an early identification of treatment success or failure by PET could significantly influence patient management by providing more objective decision criteria for evaluation of specific therapeutic strategies. Specially, as PET represents a novel technology for molecular imaging assays of metabolism and signal transduction to gene expression, reporter gene assays are used to trace the location and temporal level of expression of therapeutic and endogenous genes. PET probes and drugs are being developed together as molecular probes to image the function of targets without disturbing them and in mass amounts to modify the target's function as a drug. Molecular imaging by PET helps to close the gap between in vitro to in vivo integrative biology of disease.*

### **Key words:**

*Molecular Imaging, Brain, Tumor.*

### **Definition of Molecular Imaging**

The term molecular imaging can be broadly defined as the in vivo characterization and measurement of biologic processes at the cellular and molecular level (Schaller, 2004). In contradistinction to "classical" diagnostic imaging, it sets forth to probe the molecular abnormalities that are the basis of disease rather than to image the end effects of these molecular alterations. While the underlying biology represents a new arena for many radiologists, concomitant efforts such as development of novel agents, signal amplification strategies, and imaging technologies clearly dovetail with prior research efforts of our specialty. Radiologists will play a leading role in directing developments of this embryonic but burgeoning field. This article presents some recent developments in molecular sciences and medicine and shows how imaging can be used, at least experimentally, to assess specific molecular targets. In the future, specific imaging of such targets will allow earlier detection and characterization of disease, earlier and direct molecular assessment of treatment effects, and a more fundamental understanding of the disease process.

### **Molecular Imaging in Research**

As the research on cellular changes has shed invaluable light on the pathophysiology and biochemistry of brain tumors, clinical and experimental use of molecular imaging methods is expanding and allows quantitative assessment (Schaller 2005). The term molecular imaging is defined as the in vivo characterization and measurement of biologic processes at the cellular and molecular level. Molecular imaging sets forth to probe the molecular abnormalities that are

the basis of disease rather than to visualize the end effects of these molecular alterations and, therefore, provides different additional biochemical or molecular information about primary brain tumors compared to histological methods "classical" neuroradiological diagnostic studies. Common clinical indications for molecular imaging contain primary brain tumor diagnosis and identification of the metabolically most active brain tumor reactions (differentiation of viable tumor tissue from necrosis), prediction of treatment response by measurement of tumor perfusion, or ischemia. The interesting key question remains not only whether the magnitude of biochemical alterations demonstrated by molecular imaging reveals prognostic value with respect to survival, but also whether it identifies early disease and differentiates benign from malignant lesions. Moreover, an early identification of treatment success or failure by molecular imaging could significantly influence patient management by providing more objective decision criteria for evaluation of specific therapeutic strategies. Specially, as molecular imaging represents a novel technology for visualizing metabolism and signal transduction to gene expression, reporter gene assays are used to trace the location and temporal level of expression of therapeutic and endogenous genes. Molecular imaging probes and drugs are being developed to image the function of targets without disturbing them and in mass amounts to modify the target's function as a drug. Molecular imaging helps to close the gap between in vitro and in vivo integrative biology of disease.

### **Molecular Imaging of Brain Tumors**

Gliomas are the most common types of brain tumors. Although sophisticated regimens of conventional therapies are being carried out to treat patients with gliomas, the disease invariably leads to death over months or years (Jacobs 2003). Before new and potentially more effective treatment

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strategies, such as gene- and cell-based therapies, can be effectively implemented in the clinical application, certain prerequisites have to be established. First of all, the exact localization, extent, and metabolic activity of the glioma must be determined to identify the biologically active target tissue for a biological treatment regimen; this is usually performed by imaging the expression of up-regulated endogenous genes coding for glucose or amino acid transporters and cellular hexokinase and thymidine kinase genes, respectively. Second, neuronal function and functional changes within the surrounding brain tissue have to be assessed in order to save this tissue from therapy-induced damage. Third, pathognomonic genetic changes leading to disease have to be explored on the molecular level to serve as specific targets for patient-tailored therapies. Last, a concerted noninvasive analysis of both endogenous and exogenous gene expression in animal models as well as the clinical setting is desirable to effectively translate new treatment strategies from experimental into clinical application. All of these issues can be addressed by multi-modal radionuclide and magnetic resonance imaging techniques and fall into the exciting and fast growing field of molecular and functional imaging. Noninvasive imaging of endogenous gene expression by means of positron emission tomography (PET) may reveal insight into the molecular basis of pathogenesis and metabolic activity of the glioma and the extent of treatment response. When exogenous genes are introduced to serve for a therapeutic function, PET imaging may reveal the assessment of the "location," "magnitude," and "duration" of therapeutic gene expression and its relation to the therapeutic effect. Detailed reviews on molecular imaging have been published from the perspective of radionuclide imaging (Gambhir et al., 2000; Tjuvajev et al., 2002) as well as magnetic resonance and optical imaging (Weissleder, 2002). The present review focuses on molecular imaging of gliomas with special reference on the status and perspectives of imaging of endogenous and exogenously introduced gene expression in order to develop improved diagnostics and more effective treatment strategies of gliomas and, in that, to eventually improve the grim prognosis of this devastating disease.

### Conclusion

The amount of information to be gained from applying the increasing number of radionuclides in a variety of pathological situations is potentially very great. Biochemical or molecular imaging with radionuclides of processes that occur at a cellular level provides information that complements findings obtained by anatomical imaging aimed at depicting structural, vascular, and histological changes. For brain tumor diagnosis, radiolabeled amino acids demonstrate adequate sensitivity and specificity. For tumor grading, the role of the current data is still controversial because conflicting reports exist. In addition, thresholds frequently are defined retrospectively – a methodologically suboptimal choice – and the true clinical impact is therefore unclear. Reasonable evidence exists that radiolabeled amino acids have supplemental value in the evaluation of treatment and the detection of recurrence of brain tumors. PET represents a unique methodology for examining the biochemical features of brain tumors and can therefore function as a translational bridge between in vitro biological discovery and clinical medicine.

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