

## The Significance of Novel PET/CT Biomarkers for Radiation Therapy

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Whole body imaging with PET/CT utilizing [18F] Fluorodeoxyglucose or [18F]FDG has become a standard of care in staging, restaging, evaluation of treatment response, and radiation treatment planning. Because many malignancies exhibit mutations that result in increased metabolism, glucose often serves as an excellent surrogate marker for detection of cancer. The very same glucose transporter proteins (GLUT receptors) that facilitate the intracellular transport of glucose are often overexpressed in cancer cells and result in intracellular transport of the glucose analogue [18F] FDG. While the sensitivity, specificity, and accuracy of [18F]FDG have been well established there are situations in which normal metabolism and biodistribution of glucose, cancer biochemistry, and altered biodistribution necessitates biomarkers that detect malignancy via a different mechanism.

Because of challenges sometimes associated with [18F]FDG imaging biomarkers that target specific receptors, radiolabeled amino acids/amino acid analogues, cellular proliferation, and hypoxia/angiogenesis are utilized whenever advantageous. It is often important to determine the receptor status of a given cancer cell prior to initiation of therapy. This can be accomplished utilizing in-vitro tissue stains or in-vivo utilizing a biomarker which exhibits a high affinity for the receptor in question. It has been shown that imaging with [18F]Fluoroestradiol is a useful means for determining if a given breast cancer cell is estrogen receptor positive thereby resulting in the administration of hormone based systemic therapy.

PET/CT biomarkers that are essentially radiolabeled amino acids or analogues have shown advantages in tissue where normal glucose metabolism, such as the brain, makes [18F]FDG imaging difficult. In situations where inflammation results in upregulation of glucose metabolism in macrophages or is induced by post radiation treatment changes [18F]Tyrosine, a marker for upregulation of amino acid synthesis, often helps differentiate recurrent tumor from normal tissues (3). Some cancers do not display markedly increased glucose metabolism thus do not exhibit increased concentrations of [18F]FDG when compared to normal tissues. Neuroendocrine tumors which may be imaged with [18F]DOPA (1) and prostate carcinoma which can be detected with [18F]ACBC both demonstrate the usefulness of radiolabeled amino acid pathway imaging.

[18F]Fluorothymidine or [18F]FLT allows for quantification of thymine kinase activity. Upregulation of cellular division results in increased demand for thymine and its analog radiolabeled thymidine. A comparison of pre and post therapy imaging exams which shows a marked decrease of [18F]FLT accumulation within a tumor carries a positive prognostic value for the effectiveness of the therapy (4).

The conversion of a tumor from aerobic metabolism to anaerobic metabolism is an important consideration when administering external beam radiotherapy. As the presence of oxygen or the lack thereof determines the amount of cancer cell damaging free radicals that can be produced, a hypoxic tumor may require more fractions of radiation to effectively treat. Imaging agents such as [18F]FMISO (7) and [18F]FAZA (8) have been shown useful in evaluation of tumor hypoxia.

While [18F]FDG will likely remain the PET/CT imaging agent of choice for initial staging of most cancers other biomarkers will gain importance as the modality continues to mature. Issues such as poor glucose metabolism and inflammation can be overcome by imaging other upregulated pathways such as amino acid/protein synthesis and cellular proliferation. Furthermore new biomarkers will yield important information which will result in personalization of treatment regimens such as cell receptor status and tumor hypoxia.

**References**

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