BOLD MRI and PET Imaging of Tumor Oxygenation

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The presence of oxygen has long been recognised as a sensitizer mediating the cytotoxic effects of ionizing radiation. Conversely, the rapid growth of tumors results in nutrient demand and supply imbalances ultimately yielding cancer phenotypes characterized by the presence of hypoxia. Cancer cell hypoxia leads to the development of reactive homeostatic responses that have more aggressive survival traits, as a result of which cancer cells become difficult to treat by radiation and chemotherapy. Decades of research in radiation therapy have focused on attempts to circumvent hypoxia mediated radio-resistance with moderate success. It has been suggested repeatedly that imaging may be a good way of selecting cancer patients who would benefit from treatment with hypoxia modifiers or bioreductive drugs.

There are a number of ways in which tissue oxygenation status can be assessed *in vivo* (both invasive and non-invasive) or *in vitro* using material from surgical biopsy. The challenge for hypoxia imaging is to make images showing low levels of tissue pO_2. Currently available MRI and PET methods were compared at a NIH/NCI sponsored workshop in April 2004 and it was noted that only a few techniques have potential for *in vivo* assessment in humans particularly for repeated, sequential measurements. ^{18}F-MISO and Cu-ATSM PET, and BOLD-MRI were the lead contenders for human application based on their non-invasive nature, ease of use and robustness, measurement of hypoxia status, validity, ability to demonstrate heterogeneity and general availability. It is these techniques that will be the primary focus of this review where the scientific basis, validation, and clinical applicability will be discussed.

^{18}F-MISO is the prototype hypoxia imaging agent whose uptake is homogeneous in most normal tissues, that is not limited by perfusion. Oxygen tension is the major determinant of its retention above normal background in tissues. Hypoxia can be imaged with ^{18}F-MSIO PET in a procedure that is well-tolerated by the patients. Useful and well-validated images can be achieved 75 to 150 min after injection with a modest dose of radiation. No arterial sampling or metabolite analysis is required and synthesis is achieved through relatively simple modifications of Fluoro-deoxyglucose synthesis boxes. ^{18}F-MISO PET is able to monitor the changing hypoxia status of tumours during radiotherapy.

Cu-ATSM holds exceptional promise as an agent for delineating the extent of hypoxia within tumors. The mechanism of retention of the reagent in hypoxic tissues is incompletely understood but is noted to be marked at low oxygen tensions. Numerous pre-clinical and clinical studies have evaluated and validated its use for imaging of hypoxia. In human studies of lung and cervix cancers, encouraging evidence is emerging that ^{64}Cu-ATSM can act as a prognostic indicator for response to therapy. A number of radioactive copper isotopes with half lives up to 12.7 hours are available, enabling wide geographic distribution.

The primary source of contrast in BOLD MR images is endogenous, paramagnetic deoxyhaemoglobin which increases the MR transverse relaxation rate (R_2*) of water in blood and surrounding tissues. BOLD-MRI contrast is dependent on tissue perfusion, levels of oxygenation as well as on static tissue components. R_2* of tissues can be quantified but does not measure pO_2 directly. Synthetic R_2* images are free of the contribution of blood flow but changes in R_2* can be used to monitor changing tissue oxygenation status and vascular functioning in response to vasomodulation. The primary advantage of BOLD-MRI techniques is that there is no need to administer exogenous radioactive contrast material and images at high temporal and with high spatial resolution can be obtained and repeated as needed. Major limitations of BOLD-MRI include the fact that they do not measure tissue pO_2 directly, the images obtained have low contrast to noise ratio and clinical studies with carbogen vasomodulation are technically challenging.