CLINICAL IMAGING OF HYPOXIA WITH POSITRON EMISSION TOMOGRAPHY

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Purpose: Hypoxia has prognostic significance in patients with certain malignancies, and is a critical factor in determining the response of solid tumors to chemotherapy and radiation therapy. Furthermore, reoxygenation following hyperthermia correlates with improved treatment outcome, making hypoxia a highly relevant parameter for monitoring hyperthermia therapy. Imaging techniques using positron emission tomography (PET) can provide non-invasive and semi-quantitative measurement of tumor hypoxia in patients. Several PET radiotracers have been developed which selectively accumulate in hypoxic tissues. However, additional considerations are necessary for a radiotracer to be practical for clinical use. These include factors such as commercial production and availability, and radiation dose to the patient. We present preliminary clinical data on two different PET tracers that show promise for clinical evaluation of hypoxia.

Methods and Results: ^{62}Cu-diacetyl-bis(N^4-methylthiosemicarbazone) (^{62}Cu-ATSM) is a small molecule which readily diffuses into cells, where it is selectively bioreduced and trapped within viable cells under hypoxic conditions. ^{62}Cu-pyruvaldehyde bis(N^4-methylthiosemicarbazone) (^{62}Cu-PTSM) is similar to ^{62}Cu-ATSM, but without the selectivity for hypoxic cells, and has been used as a surrogate marker for perfusion. ^{62}Cu is a short-lived positron emitting radionuclide ($t_{1/2}$=9.7 min). A ^{62}Zn/^{62}Cu generator has been developed to produce ^{62}Cu from the parent ^{62}Zn ($t_{1/2}$=9.3 hr), which can be delivered to the PET imaging facility on the day of imaging . This generator, along with a rapid radiosynthesis kit, enables ^{62}Cu-ATSM and ^{62}Cu-PTSM to be produced conveniently on-site. The short half-life of ^{62}Cu allows both ^{62}Cu-ATSM and ^{62}Cu-PTSM imaging to be performed serially in a single session.

Discussion: ^{18}F-labeled PET radiotracers have great promise for clinical applications. ^{18}F provides superior spatial resolution due to low initial positron energy. In addition, the 2-hour half-life allows ^{18}F radiotracers to be produced commercially and facilitates widespread distribution to PET centers. Practical methods for the radiosynthesis of ^{18}F-EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-[2,2,3,3,3-pentafluoropropyl] acetamide) have been developed. EF5 been shown to be an accurate surrogate marker for tissue hypoxia both in animal and human studies, and ^{18}F-EF5 has the potential to become an important PET tracer for imaging hypoxia.

Conclusions: ^{18}F-EF5 and generator-produced ^{62}Cu-ATSM and ^{62}Cu-PTSM have potential as PET imaging tracers which could be routinely used in clinical PET studies. EF5 may have greater specificity for hypoxia, but the short-lived ^{62}Cu compounds allow relative measurement of two parameters (hypoxia and blood flow) in a single imaging session. The full clinical utility of these tracers for evaluating hypoxia requires further investigation. Preliminary clinical examples of each tracer are shown.

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