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Quantification of Tumor Hypoxia with Positron Emission Tomography in Preclinical Models and Patients

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Tumor hypoxia correlates with treatment failure. Several methods are available to define the hypoxic fraction of a tumor, but results are variable across techniques. Non-invasive methods, e.g., positron emission tomography (PET) with ^{18}F-fluoromisonidazole (^{18}F-FMISO), can quantify the spatial distribution of tumor hypoxia. However, this technique is not currently being used to quantify tumor hypoxia in the clinic to improve patient treatments.

To elucidate this, this work had 2 main aims: 1) To investigate the quantification methods for tumor hypoxia in a preclinical model by using dynamic ^{18}F-FMISO PET to measure hypoxic fractions (HF) and tracer kinetic modeling to improve quantification while making comparisons with tumor-to-blood ratios and tumor oxygen status as defined by Eppendorf pO_2 measurements; 2) To investigate tumor hypoxia in patients with non-small cell lung cancer (NSCLC) undergoing stereotactic body radiotherapy (SBRT) by using ^{18}F-FMISO PET imaging to quantify the tumor HF, to elucidate the potential roles of reoxygenation and tumor vascular response at high doses, and to identify an optimal time point for imaging with prognostic value.

Quantification of the tumor hypoxic fraction

Male BALB/c mice (n=6) with murine mammary tumor xenografts were selected for imaging and pO_2 measurements. Anaesthetized mice were injected with ^{18}F-FMISO and imaged using 120-min dynamic PET and Computed Tomography (CT). Data from dynamic ^{18}F-FMISO scans were fit to a 2-compartment (2TC) irreversible 3-rate constant model (K_1, k_2, k_3) and a Patlak model (K_i). Different thresholds were applied to derived K_i and k_3 values to calculate the HF for each tumor. HFs derived using tracer kinetic models and conventional tumor-to-blood (TBR) ratios were compared to pO_2 values measured by Eppendorf electrode.

All six mice showed mean tumor pO_2 values that ranged between 1-9 mmHg and were within expected ranges. Additionally, an expected inverse relationship was observed between mean pO_2 and mean ^{18}F-FMISO values. However, median hypoxic fraction (HF) calculated using pO_2 <10 mmHg, was 85%, a variation of up to 4.4 when compared to median HF calculated by TBR and kinetic parameter thresholds. Moreover, a variation of up to a factor of 3 was observed between median HFs calculated by TBR versus kinetic modeling parameters.

This study showed that the use of different PET imaging metrics (TBR and kinetic modeling parameters) and thresholds can substantially alter the quantification of the tumor hypoxic fraction. Future experiments are needed to help us move away from the use of arbitrary thresholds, or refine pO_2 measurement techniques to better quantify hypoxic fractions. More accurate hypoxia quantification techniques have the potential to impact patient treatment decisions and aid the development of alternative tumor hypoxia measurement methods.

Effect of high doses on the tumor hypoxic fraction

Patients with NSCLC tumors >1 cm and eligible for SBRT were prospectively enrolled in an IRB-approved study. CT and dynamic PET images (0-120 min, 150-180 min, and 210-240 min post-injection of radiotracer) were acquired using a Siemens Biograph mCT PET/CT scanner.^{18}F-FMISO PET imaging was performed on 6 patients at 3 different time points around a single SBRT dose of 18 Gy. Comparisons of HFs were made using a tumor-to-blood ratio (TBR) > 1.2.

For patients #2 through #6, HFs were calculated on ^{18}F-FMISO 3DPET (uncorrected for respiratory motion) and 4DPET (corrected for respiratory motion) images. We found that uncorrected 3DPET may mask the effect of SBRT on HF, perhaps due to motion blurring. From the 4DPET data, baseline (prior to SBRT) HFs ranged from 0% to 37% (mean: 15.5%). HFs on day 2 (24-48 hours after SBRT) and day 4 (72-96 hours after SBRT) ranged from 0% to 56% (mean: 28.2%) and from 0% to 75% (mean: 28.0%), respectively. A temporal variation in mean HF is seen using 4DPET images across all patients with baseline HF >0%. Mean HF appears to increase post-SBRT and decrease 72-96 hours later.

For SBRT NSCLC patients, ^{18}F-FMISO PET can measure temporal changes in tumor hypoxia. This novel pilot study highlights the potential benefit of this non-invasive imaging. Results indicate (1) heterogeneity between baseline levels of hypoxia between patients (as expected) & (2) potential for large variations in tumor hypoxic fractions post-SBRT. ^{18}F-FMISO PET demonstrated that the hypoxic fraction may increase as a result of high dose SBRT in NSCLC patients with baseline hypoxia. This finding implies that perhaps SBRT NSCLC patients should be stratified based on ^{18}F-FMISO PET. The hypoxic group could receive an alternate fractionation schedule e.g. one fraction per week for three weeks to allow for tumor reoxygenation or be administered a hypoxic cell radiosensitizer to combat hypoxia-induced radioresistance. The non-hypoxic group could be prescribed a lower dose to reduce normal tissue complications. Future studies are needed to test this hypothesis in a larger number of patients and the development of tracer kinetic analysis of respiratory-corrected data to enable treatment individualization.

In conclusion, ^{18}F-FMISO PET imaging is a powerful tool for visualizing tumor hypoxia and could be used to improve the outcomes of NSCLC patients treated with SBRT. However, technological advances and alternative quantification metrics are required before ^{18}F-FMISO PET can become widely accepted as the ‘gold standard’ for tumor hypoxia quantification.