Cancer Imaging (2005) **5,** 128–130
DOI: 10.1102/1470-7330.2005.0103

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EDITORIAL

Where are we with imaging oxygenation in human tumours?

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Date accepted for publication 27 June 2005

Abstract

Tumour hypoxia represents a significant challenge to the curability of human tumours leading to treatment resistance and enhanced tumour regression. Tumour hypoxia can be detected by non-invasive techniques but the inter-relationship between these techniques needs to be better defined. [^{18}F]Fluoromisonidazole (^{18}F-MISO) and Cu-labelled diacetyl-bis(N(4)-methylthiosemicarbazone (Cu-ATSM) PET, and blood oxygen level-dependent (BOLD) MRI are 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; these techniques are the primary focus of this editorial.

Keywords: *Hypoxia; angiogenesis; radiotherapy; BOLD-MRI; Cu-ATSM PET; ^{18}F-MISO PET.*

The fact that tumour hypoxia increases resistance to radiotherapy has been known for over 70 years. Forty-five years ago, Tomlinson and Gray showed that hypoxia exists in human tumours and that necrosis occurs about 100 μm from the nearest blood vessel which is also the diffusion distance of soluble oxygen. Decades of research in radiation therapy have focused on attempts to circumvent hypoxia mediated radio-resistance with moderate success. Over the last decade, it has become known that hypoxia changes the pattern of gene expression that alters the malignant potential of tumours leading to more aggressive survival traits, as a result of which cancer cells become difficult to treat by radiation and chemotherapy[1].

The presence of oxygen has long been recognised as a sensitiser mediating the cytotoxic effects of ionising radiation. Typically, well-oxygenated cells are three times more sensitive to radiation than the same cells when they are hypoxic. The oxygen enhancement ratio (OER) typically ranges between values of 2.5 and 3.0; OER is the relative sensitivity of oxic cells/anoxic cells to the lethal effects of low linear-energy-transfer (LET) radiation.

The presence of hypoxia within human tumours before starting treatment has been observed in squamous cell carcinomas, gliomas, adenocarcinomas (breast and pancreas) and in sarcomas. In cervix cancer, for example, the oxygenation status is independent of size, stage, histopathological type, grade of malignancy. Eppendorf pO_2 histography has shown heterogeneity within and between the same tumour types and that hypoxia contributes to poor prognosis; $pO_2 < 10$ mmHg results in poor local tumour control, disease-free survival and overall survival in squamous carcinomas of the head and neck and of cervix cancers. However, for some tumours, there are other features besides hypoxia that are more powerful in predicting outcome (e.g. nodal involvement in breast cancer).

There are three principle types of tumour hypoxia: (1) perfusion-related (acute) hypoxia resulting from

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1470-7330/05/000128 + 03

inadequate blood flow in tumours resulting from recognised structural and functional abnormalities of tumour neovasculature; such acute hypoxia is often transient, caused by temporary occlusions and transient rises in interstitial pressure, and affects all cells right up to the vessel wall; (2) diffusion-related (chronic) hypoxia caused by increased oxygen diffusion distances due to tumour expansion affects cells greater than 70–100 μm from the nearest blood vessel; (3) anaemic hypoxia which may be tumour-associated or treatment-related.

As hypoxia is an important biological characteristic and there is no good or easy way to predict its presence, it has been suggested that imaging may be a good way of selecting cancer patients who would benefit from treatments that overcome, circumvent or take advantage of the presence of hypoxia. Key requirements of any method that evaluates tumour hypoxia include non-invasive assessments that allow serial changes during treatment to be monitored and evaluation of heterogeneity between and within tumours. 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. From an imaging perspective, an ideal test would: (1) distinguish normoxia/hypoxia/anoxia; (2) distinguish between perfusion-related (acute) and diffusion-related (chronic) hypoxia if possible; (3) reflect cellular in preference to vascular pO_2; (4) be applicable to any tumour site with complete loco-regional evaluation; (5) be simple to perform, non-toxic and allow repeatable measurements; and (6) be sensitive at pO_2 relevant to tumour therapy.

The critical pO_2 tensions below which cellular functions progressively cease or anticancer treatments are impaired are: effectiveness of immunotherapy (30–35 mmHg); photodynamic therapy (15–35 mmHg); cell death on exposure to radiation (25–30 mmHg); binding of hypoxia immunohistochemical markers (10–20 mmHg); proteome changes (1–15 mmHg) and genome changes (0.2–1 mmHg).

The challenge for hypoxia imaging is to make images showing low levels of tissue pO_2 demonstrating a phenomenon that occurs at a much smaller scale than can be achieved with human imaging techniques (1–5 mm resolution). Currently available magnetic resonance imaging (MRI) and positron emission tomography (PET) methods were compared at a National Institute of Health/National Cancer Institute of USA 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]Fluoromisonidazole (^{18}F-MISO) and Cu-labelled diacetyl-bis(N(4)-methylthiosemicarbazone (Cu-ATSM) PET, and blood oxygen level-dependent (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 are the primary focus of the rest of this editorial.

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, thus BOLD MRI is sensitive to pO_2 within and in tissues adjacent to perfused vessels. BOLD MRI contrast is also dependent on tissue perfusion, levels of oxygenation, as well as on static tissue components[2]. Intrinsic susceptibility (R_2^*) of tissues can be easily quantified but this measure 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 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.

^{18}F-MISO is the prototype hypoxia imaging agent whose uptake is homogeneous in most normal tissues, and whose delivery to tumours is not limited by perfusion due to its high partition coefficient[3]. The initial distribution is flow dependent with oxygen tension being the major determinant of its retention above normal background in tissues after 1–2 h (metabolites not fixed are rapidly cleared from plasma). ^{18}F-MISO accumulates by binding to intracellular macromolecules when $pO_2 < 10$ mmHg. Retention within tissues is dependent on nitroreductase activity (on reduction status of NO_2 group on the imidazole ring) and accumulation in hypoxic tissues over a range of blood flows has been noted including within the intestinal lumen within anaerobes! Hypoxia can be imaged with ^{18}F-MISO PET in a procedure that is well tolerated by the patients. Useful and well-validated images can be achieved 75–150 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. Unlike Eppendorf pO_2 histography, ^{18}F-MISO is only sensitive to the presence of hypoxia in viable cells (no sampling of necrosis). ^{18}F-MISO PET is able to monitor the changing hypoxia status of tumours during radiotherapy. Limitations of ^{18}F-MISO PET include intermediate signal-to-noise ratio of images and the need to obtain a venous blood sample to tumour/blood ratio (a T/B ratio of >1.2 is considered to represent the presence of hypoxia). The presence of normal liver uptake impairs complete assessment of liver lesions and there has been incomplete validation in terms of predicting patient outcomes.

Cu-ATSM holds exceptional promise as an agent for delineating the extent of hypoxia within tumours[4]. The

mechanism of retention of the reagent in hypoxic tissues is incompletely understood but is noted to be marked at low oxygen tensions and is appears to be related to the altered redox environment of hypoxic tumours (increased NADH levels). 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 h are available, enabling wide geographic distribution. Intriguingly, it has been suggested that the spatial distribution of Cu-ATSM on PET can be fused with computed tomography (CT) images to deliver higher doses of radiation via intensity modulated radiotherapy techniques (IMRT) to the most hypoxic regions of tumours by dose-painting techniques.

To summarise, tumour hypoxia is common and its effects represent a significant challenge to the curability of human tumours leading to treatment resistance and enhanced tumour progression. Tumour hypoxia can be detected by non-invasive and invasive techniques but the inter-relationship between these techniques needs to be better defined; human validation of imaging finding is sparse at best. Anti-hypoxia therapies exist in the clinic (but do not work very well or we do not know how to use them optimally) and more are on their way. Hypoxia imaging may allow better definition of a population that would benefit from novel anti-hypoxia directed therapies.

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