ELSEVIER

Seminars in
NUCLEAR
MEDICINE

Hypoxia Positron Emission Tomography Imaging With ^{18}F-Fluoromisonidazole

Sze Ting Lee, MBBS, FRACP, and Andrew M. Scott, MBBS, MD, FRACP, DDU

The importance of hypoxia in disease pathogenesis and prognosis is gathering increasing clinical significance and having a greater impact on patient management and outcome. Previous efforts to evaluate hypoxia have included the invasive assessment of hypoxia with immunohistologic and histographic oxygen probes. The emergence of new radiotracers has allowed noninvasive assessment of hypoxia, with the most extensively investigated and validated positron emission tomography radiotracer of hypoxia to date being ^{18}F-fluoromisonodazole (^{18}F-FMISO). This review discusses the relevance and biology of hypoxia in cells and organ systems, and reviews the laboratory and clinical applications of ^{18}F-FMISO in oncology and noncancer disease states.
Semin Nucl Med 37:451-461

Fluoromisonidazole (FMISO) has a chemical structure of 1-(2′nitro-1′-imidazolyl)-3-fluoro-2-propranol (Fig. 1A). It is a derivative of the nitroimidazole group of compounds, which have been investigated as hypoxic cell sensitizers. Nonpharmacological doses of FMISO have been labeled with fluorine to image hypoxic tissues in vivo with positron emission tomography (PET) (Fig. 1B).

Biological Relevance of Hypoxia in Disease

Hypoxia has been shown to be present in many disease states, as evidenced by pO_2 histography probe measurements, immunohistochemistry, and scintigraphic imaging. The degree of hypoxia is highly relevant in functional recovery in ischemic events such as stroke and myocardial ischemia but, in particular, tumor hypoxia is an important determinant of treatment response, relapse-free survival, and overall prognosis, which is independent of the treatment modality used in cancer patients.[1,2]

Centre for PET, Austin Health, Heidelberg, Victoria, Australia.
Ludwig Institute for Cancer Research, Austin Hospital, Heidelberg, Victoria, Australia.
Department of Medicine, University of Melbourne, Austin Health, Heidelberg, Victoria, Australia.
Address reprint requests to Andrew M. Scott, MBBS, MD, FRACP, DDU, Director, Centre for PET & Ludwig Institute for Cancer Research, Melbourne Centre for Clinical Sciences, Austin Health, 145, Studley Road, Heidelberg, Victoria 3084, Australia. E-mail: andrew.scott@ludwig.edu.au

There is increasing evidence that hypoxia-mediated aggressive tumor behavior and resistance to therapy is mediated by the heterodimeric transcription factor, hypoxia inducible factor-1 (HIF-1), via molecular events that allow for the adaptation of tumor cells to hypoxia, such as unregulated glycolysis, angiogenesis, and p53 mutation.[3-8] HIF-1 activates transcription genes whose protein products act to either increase oxygen availability or to allow metabolic adaptation to a hypoxic environment.[9] HIF-1 protein is overexpressed in multiple types of cancer and in regional and distant metastases. Benign noninvasive tumors do not usually express HIF-1. HIF-1-positive cells have been noted to be prominent at tumor margins and surrounding areas of tumor neovascularization.[10] Furthermore, strong HIF-1 expression has been observed in glioblastoma multiforme and hemangioblastomas, which are the most malignant and highly vascularized tumors of the central nervous system, suggesting a correlation with tumor angiogenesis and disease progression. HIF-1 has been found to correlate with tumor grade in gliomas, which suggests that the expression of HIF-1 is upregulated in response to oncogene activation and/or tumor suppression gene activation during glioma progression.[11] There is also significant correlation between HIF-1 expression and both apoptosis and pro-apoptotic factors.

Both in vitro and in vivo studies have demonstrated that hypoxia can alter cell behavior, for example by promoting the expansion of cells with a low apoptotic index or increasing cell mutation rates.[2,12-14] In addition, hypoxia can also promote gene expression related to growth and survival of tumor cells, such as vascular endothelial growth factor (VEGF), glycolytic enzymes and signaling molecules.[15] Other factors that

0001-2998/07/$-see front matter
doi:10.1053/j.semnuclmed.2007.07.001

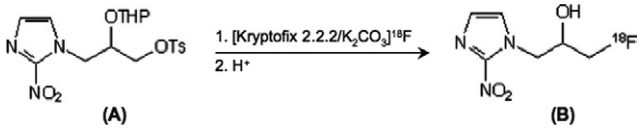

Figure 1 Chemical structure of FMISO (A) and radiolabeled with fluorine-18 (B).

are associated with the presence of hypoxia include genetic factors, the most significant one being the loss of function of the von Hippel-Lindau (vHL) tumor suppressor protein, for example, in renal cancer, which results in activation of the HIF pathway.[16] HIF-1 also controls the expression of a variety of genes that play a crucial role in the adaptation of tumor cells to a hypoxia environment, including the enhancement of erythropoiesis and glycolysis, inhibition of apoptosis, promotion of cell survival, inhibition of cell differentiation, and angiogenesis.[16] These adaptive changes in the genome and proteome of tumor cells result in a more-aggressive tumor cell phenotype.

Hypoxia develops in solid tumors through the inadequate supply of oxygen by the vascular supply to the growing tumor mass. Both low pO_2 and nutrient deficiency contribute to impaired tumor growth, such that tumor growth beyond 2 mm requires tumor neovascularization.[16] New tumor vessels, however, are functionally and structurally abnormal compared with normal tissue, which have a structured vasculature pattern.[17] Tumor blood vessels are leaky, tortuous, dilated, and saccular with a distorted architecture, and the endothelial cells themselves have an altered morphology, with distorted basement membrane and disordered supporting pericytes.[18,19] These features contribute to spatial and temporal heterogeneity in tumor blood flow, even within tumors of the same type.[20] In addition, pressure on the blood vessels generated by the tumor growth itself compresses intratumoural blood and lymphatic vessels, resulting in impaired blood flow as well as lymphatic flow.[21] The result of all these features in tumor vascularity lead to abnormal intratumoural microenvironment characterized by hypoxia, acidosis, and interstitial hypertension (elevated hydrostatic pressure outside the blood vessels), which contribute toward impairment of delivery of cancer therapies to these cells.[19]

Hypoxic cells have been shown to be many times more resistant to ionizing radiation compared with aerobic cells, resulting in treatment resistance.[22] Thresholds for hypoxia effects on cellular function have been reported as: impairment of immunotherapy effect at 30 to 35 mmHg; photodynamic therapy effect at 15 to 35 mmHg; cell death on exposure to radiation at 25 to 30 mmHg; binding of hypoxia immunohistochemical markers at 10 to 20 mmHg; proteome changes at 1 to 15 mmHg; and genome changes at 0.2 to 1 mmHg.[23] However, it should be recognized that the sensitivity of cells to radiation is dependent on the phase of the cell cycle, as cells in the G1 phase are more radiosensitive than cells in the S-phase. Hypoxia-induced radioresistance is multifactorial, with the presence of oxygen-mediating DNA damage through the formation of oxygen free radicals that occur after the interaction of radiation with intracellular water. There is also increasing evidence that hypoxia-mediated proteomic and genomic changes also may contribute to radioresistance by increasing the levels of heat shock proteins, which are induced in response to environmental stresses like heat, cold, and hypoxia.[24] There is continuing debate about the critical intratumoral pO_2, below which detrimental changes begin to occur that are common across all cell types.

It is the increasing importance of detection of hypoxia levels in predicting treatment response and as a prognostic marker that has resulted in the pursuit for objective evidence of hypoxia. The traditional "gold standard" for measuring oxygen tension in tissue has been with the pO_2 electrode,[25] but this method is invasive and restricted to easily accessible tumors. Noninvasive methods to detect hypoxia also have been developed, including functional imaging modalities such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and magnetic resonance imaging/magnetic resonance spectroscopy (MRI/MRS), and surrogate markers of hypoxia, for example carbonic anhydrase IX (CA-IX), hypoxia inducing factors and osteopontin.[2] However, to date, ^{18}F-FMISO remains the most extensively studied PET radiotracer of hypoxia in both animals and humans.[26]

In Vivo Properties of ^{18}F-FMISO

^{18}F-FMISO enters cells by passive diffusion, where it is reduced by nitroreductase enzymes to become trapped in cells with reduced tissue oxygen partial pressure. When oxygen is abundant in normally oxygenated cells, the parent compound is quickly regenerated by reoxidation and metabolites do not accumulate. However, in hypoxic cells, the low oxygen partial pressure prevents reoxidation of ^{18}F-FMISO metabolites, resulting in tracer accumulation in hypoxic cells, as illustrated in Figure 2. Because FMISO only accumulates in hypoxic cells with functional nitroreductase enzymes, FMISO only accumulates in viable cells but not dead necrotic cells.

Time–activity curves have shown that the activity of ^{18}F-FMISO in a typical normal muscle region of interest (ROI)

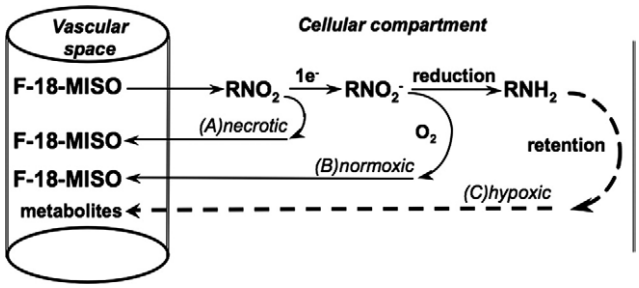

Figure 2 Mechanism of FMISO cell trapping. Fluoromisonidazole diffuses into cells, where it is reduced by enzymes. In necrotic cells (A), there is no reduction; therefore, no retention occurs. In normoxic cells (B), the FMISO is reoxidized and eventually diffuses out of the metabolic compartment. In hypoxic cells (C), further reduction of the FMISO results in cell retention.

achieves equality with plasma levels within 30 minutes, but selective retention of ^{18}F-FMISO is observed in hypoxic tissue by 1 hour after injection and persists until 2.5 hours.[27] The quantitation of ^{18}F-FMISO tumor/plasma ratio can be optimally performed at 2 hours after injection, when normal tissues have equilibrated with plasma, and hypoxic tissue continues to have selective retention of FMISO, resulting in favorable information about the hypoxic volume being assessed.[27] A complete histogram of in vivo FMISO tissue/plasma ratios constructed from animal studies has defined the normal FMISO/plasma ratio as <1.3 in 905 of cases. Therefore, a conservative selected "threshold" of ^{18}F-FMISO tumor/plasma ratio of ≥ 1.4 at 2 hours after injection will be an indicator of significant hypoxia.[27,28] This value was modified in a more recent study to 1.2 in patients with soft-tissue sarcoma.[29] Although these values are useful in allowing objective comparisons across different studies, they do not allow for individual variation in ^{18}F-FMISO uptake in different tissues; therefore, a comparison of ^{18}F-FMISO uptake in the tumor to that of normal parenchyma has been proposed to give a ratio for individual patients using themselves as controls.[30] This was performed in recent studies looking at the use of FMISO in renal cell carcinoma and nonsmall cell lung carcinoma.[30,31] In these studies, the investigators applied a ROI around the area of maximal ^{18}F-FMISO uptake. For each slice, a ROI was applied over the contralateral organ of interest and the mean voxel activity in the ROI was calculated. The SUV_{max} was defined as the highest 10% of voxel values within the operator-defined ROI.[30]

Dosimetry and Biodistribution of ^{18}F-FMISO

The biological half-life of misonidazole (MISO) is 50 minutes and has an octanol/water partition coefficient of 0.41,[32,33] resulting in equilibration with total body water in normoxic, nonmalignant tissues.[34] FMISO uptake also has been observed in the brain, which although small in quantity, indicates that FMISO is freely diffusible across the blood–brain barrier.

^{18}F-FMISO is metabolized by the liver and excreted by the kidney and bladder.[35] Bowel uptake may be prominent, presumably secondary to intraluminal anaerobic bacteria.[27] Biodistribution data in preclinical rat model have shown that the highest concentration of activity is in the urine, with uptake also evident in the intestine, liver, and kidney. The lowest activity is noted in the blood, spleen, heart, lung, muscle, bone, and brain.[36] Similar data have been shown in human subjects. The normal tissue distribution of ^{18}F-FMISO is demonstrated in Figure 3.

The effective dose equivalent for ^{18}F-FMISO PET scan is 0.013 mSv/MBq in men and 0.014 mSv/MBq in women, with a standard dose of 3.7 MBq/kg (0.1 mCi/kg).[37] The individual organ effective dose in women is not different from men. Assuming bladder voiding at 2- or 4-hour intervals, the critical organ receiving the highest dose is the urinary bladder wall (0.021 mGy/MBq for 2-hour voiding intervals or 0.029 mGy/MBq for 4-hour voiding intervals). The organ doses for ^{18}F-FMISO are comparable with other commonly performed nuclear medicine tests and indicate that potential radiation risk associated with ^{18}F-FMISO PET studies are within the generally accepted limits. The dosimetry calculations and typical radiation absorbed dose to individual organs have been reported previously.[37]

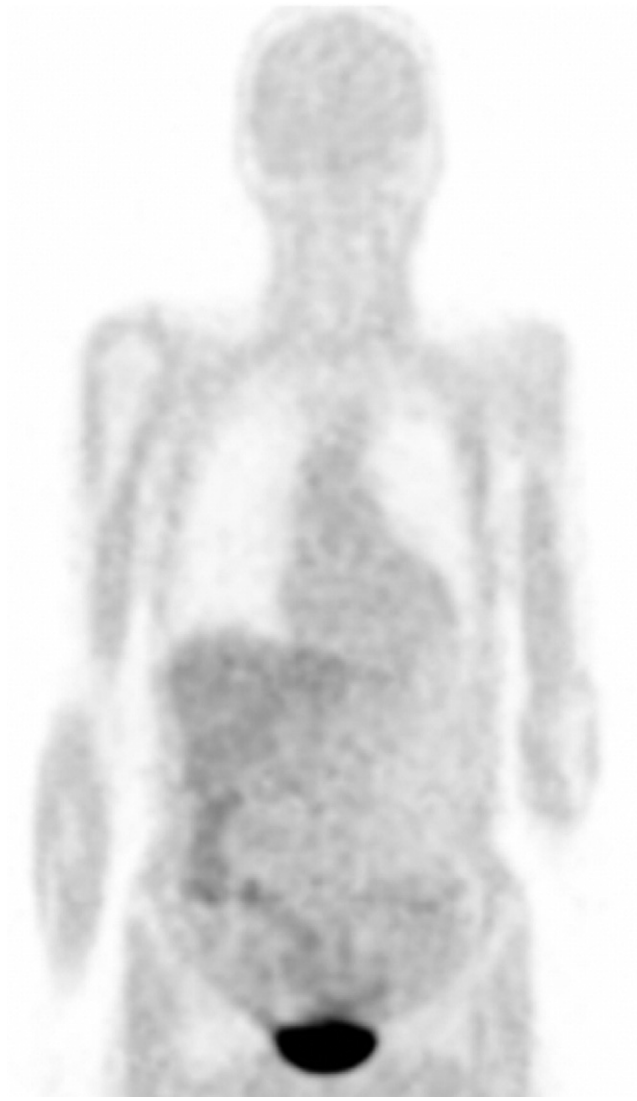

Figure 3 Normal biodistribution of ^{18}F-FMISO 2 hours after injection. Mild background activity is noted in the brain, liver, and bowel. Excreted activity is noted via the renal system, in the urinary bladder.

Production of ^{18}F-FMISO

^{18}F-FMISO is typically synthesized from a commercially available precursor using methods previously described[38] and purified by preparative high-pressure liquid chromatography. The purity of the final product is usually between 95% and 99%, the specific activity between 1 and 3 Ci/mol, and pH between 5 and 8. After ^{18}F-FMISO is prepared, quality control includes radiochemical and chemical purity testing before administration.

Table 1 Summary of Clinical Studies Validating ^{18}F-FMISO PET as a Noninvasive Marker of Hypoxia in Oncology

Tumor Type	No. of Patients	Patient Cohort	Clinical Study	Results	Conclusion(s)	Reference
Brain tumor	3	High-grade brain tumor	Rubidium-82 and ^{18}F-FMISO PET with blood sampling.	Rubidium imaging showed BBB defect at tumor site with initial FMISO uptake > normal cortex. Normal cortical activity decreased after 40 minutes.	Feasibility study of using FMISO PET to detect hypoxia in gliomas.	71
	11	Residual or recurrent brain tumor	^{18}F-FMISO PET scan with arterial blood sampling and quantification of FMISO kinetics. Comparative ^{15}O-H_2O perfusion and MRI scan.	Increased FMISO uptake and volume in glioblastomas, with higher uptake rate compared to normal brain. Higher uptake rate in meningiomas, but lower distribution volume. Early positive correlation between FMISO uptake and perfusion, but late FMISO uptake was independent of perfusion.	Late FMISO PET provides a spatial description of hypoxia independent of BBB disruption and tumor perfusion.	72
	17	Primary brain tumor	Presurgical (biopsy or resection) ^{18}F-FDG and ^{18}F-FMISO PET and MRI scans. Comparative biomarkers of hypoxia & angiogenesis.	Significant correlation between FDG and FMISO uptake with Ki-67 and VEGFR-1 expression.	FMISO PET is a noninvasive assessment of hypoxia.	73
Head and neck tumor	16	Advanced disease	Intraoperative pO_2 measurement, ^{18}F-FMISO and ^{18}F-FDG-PET scans.	Good correlation between pO_2 and FMISO tumor-to-muscle uptake. No correlation between pO_2 and FDG uptake.	FMISO uptake is a feasible non-invasive measure of tissue pO_2.	66, 67
Soft-tissue tumors	13	Suspected soft-tissue sarcoma	Intraoperative pO_2 measurements and presurgical ^{18}F-FMISO PET scan.	FMISO positive in 6/7 malignant tumors and 3/6 benign tumors. No correlation between FMISO uptake and pO_2 measurements.	FMISO is not feasible for detection of tumor hypoxia in variety of soft tissue tumors.	56
	19	Soft-tissue sarcoma	Analysis of VEGF expression, pre-treatment ^{18}F-FDG and ^{18}F-FMISO PET scans.	FMISO positive in 14/19 - pretherapy hypoxia volume is independent of tumor volume. Poor correlation between tumor grade, hypoxia volume and FDG uptake.	FMISO can identify hypoxia with no significant correlation with FDG uptake.	29
Renal tumours	17	Presumed renal cell carcinoma (RCC)	Pre-surgical ^{18}F-FMISO and ^{18}F-FDG-PET. Intraoperative pO_2 measurement. Analysis of angiogenesis.	Mild FMISO uptake not statistically significant, median pO_2 9.6 mmHg. MVD greater in RCC compared to normal kidney.	Mild FMISO uptake may reflect renal tumor oxygenation of >9.5 mmHg.	30
Nonsmall cell lung cancer (NSCLC)	21	NSCLC	Presurgical ^{18}F-FDG and ^{18}F-FMISO PET scans. Comparative biomarkers of hypoxia.	Low FMISO uptake with no correlation with FDG uptake and tumor markers of hypoxia & angiogenesis.	Low hypoxic cell fraction in NSCLC with no correlation with glucose metabolism or tumor markers of hypoxia.	31

BBB, blood–brain barrier; MRI, magnetic resonance imaging; VEGFR-1, vascular endothelial growth factor receptor-1; VEGF, vascular endothelial growth factor; MVD, microvascular density.

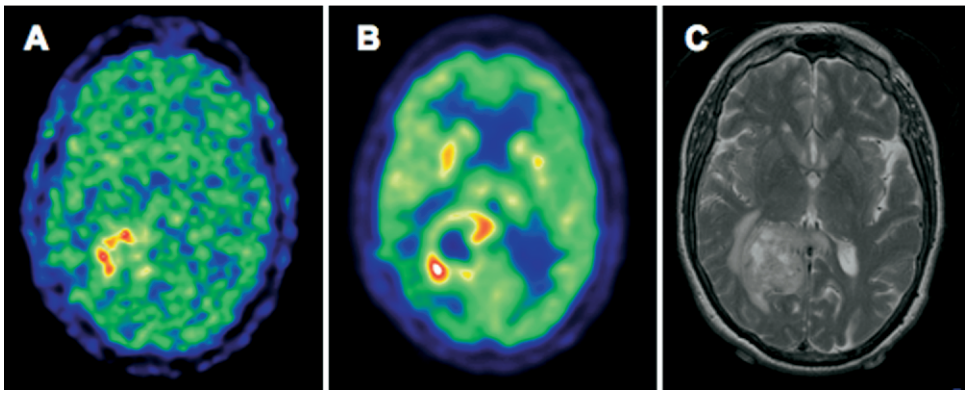

Figure 4 Hypoxia imaging in high-grade glioma. Postsurgical assessment of residual tumor, showing (A) hypoxic areas in the lateral surgical margin of the tumor on ^{18}F-FMISO PET; (B) postoperative metabolic changes on ^{18}F-FDG PET; and (C) the preoperative MRI showing tumor in the right posterior parieto-occipital lobe.

Direct Measurement of Hypoxia and Correlation With ^{18}F-FMISO

Direct pO_2 measurements in tumor have been performed using the Eppendorf pO_2 hypoxymeter, which measures oxygen tension using a polarographic oxygen microelectrode. This method uses a very fine 300-μm cathode needle, which is inserted into the tumor and a current generated by ionization of oxygen is measured to provide an estimate of oxygen concentration at the site of insertion.[39] Multiple readings are taken and recorded by a computer, which have been found to correlate well with radiobiological hypoxia, and is able to predict response and metastatic potential of tumors.[3,40,41] This method has been validated and is considered the gold standard of hypoxia measurement by the American Cancer Institute and is suitable for routine measurements of tissue oxygenation in situ.[25,42]

Tumor hypoxia has been confirmed by direct measurements with this oxygen sensing electrode in breast cancer,[43-45] uterine cervix cancer,[6,46-53] renal cell carcinoma,[30] melanoma,[54] soft-tissue sarcoma,[55-57] and in head and neck cancers.[40,58-64] In most of these tumors, the median pO_2 has been measured at $<$10 mmHg.[2] The most widely studied tumors with the needle polarography has been in head and neck cancers and uterine cervix cancers. These tumors have been reported to have a median pO_2 of 4.5 mmHg and 12.5 mmHg, respectively. The patients with hypoxic tumors also had worse prognosis, with worse locoregional control and shorter disease free survival.[4,64,65]

Multiple studies correlating direct oxygen measurements with ^{18}F-FMISO uptake have been performed.[30,66,67] In a recent study correlating ^{18}F-FMISO uptake with direct pO_2 histographic measurements in renal cell carcinoma, the degree of ^{18}F-FMISO uptake correlated with low tissue oxygen tension. In this study, it was shown that ^{18}F-FMISO uptake requires a hypoxic level of $<$10 mmHg.[30] In metastatic head and neck cancer, the retention of ^{18}F-FMISO is significantly greater in hypoxic tumors than in normoxic tumors, with a strong correlation between the ^{18}F-FMISO uptake and pO_2 readings of $<$5 mmHg.[67] Two studies comparing ^{18}F-FMISO with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and pO_2 measurements in biopsy proven head and neck carcinoma found a good correlation between pO_2 measurements and FMISO tumor/muscle uptake ratio, but there was no correlation between pO_2 measurement and FDG uptake.[66,67]

In soft-tissue sarcoma, ^{18}F-FMISO uptake has been demonstrated and correlated with VEGF expression, although there was no correlation between tumor grade, hypoxic volume, and FDG uptake.[29] In a further study of 13 patients with soft-tissue tumors (7 confirmed malignant tumors and 6 benign tumors), no correlation between ^{18}F-FMISO uptake and pO_2 measurements was found.[56] An important consideration in the analysis of the results of these studies is that direct measurement of hypoxia with the hypoxymeter does not provide an overall picture of the hypoxic, necrotic and aerobic regions within a particular tumor, all of which can be assessed with ^{18}F-FMISO PET scan.

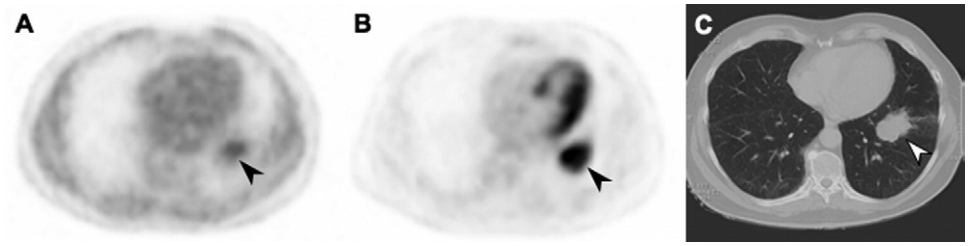

Figure 5 (A) ^{18}F-FMISO uptake in nonsmall cell lung carcinoma (arrow). (B) Uptake of ^{18}F-FDG in the left lung tumor (black arrow). (C) Corresponding CT slice showing the left lung tumor (white arrow).

Table 2 Summary of Clinical Studies Using ^{18}F-FMISO PET as a Prognostic Indicator in Oncology

Tumor Type	No. of Patients	Patient Cohort	Clinical Study	Results	Conclusion(s)	Reference
Head and neck cancer (HNC)	15	Advanced disease (T3/4 ± N2/3)	Phase I chemoradiation and tirapazamine (hypoxia-sensitizer) had serial ^{18}F-FDG & ^{18}F-FMISO PET scans.	13/15 FMISO positive in primary and/or nodal disease. Marked decreased uptake at 4 weeks; with 5-year survival 50% and 5-year free from locoregional failure 68%.	Hypoxia on FMISO PET can predict adverse prognosis. Early resolution of FMISO uptake is associated with good locoregional control.	76
	45	Advanced disease (Stage 3 or 4)	Phase I chemoradiation ± tirapazamine had pre- and post-treatment ^{18}F-FMISO PET scan.	32/45 FMISO positive in primary and/or nodal disease. Risk of locoregional failure higher in hypoxic tumors. Patients on Tirapazamine had lower risk of locoregional failure.	Hypoxia on FMISO PET imaging in patients not receiving Tirapazamine is associated with higher risk of locoregional failure.	78
	73	All disease stages	Pretreatment ^{18}F-FMISO and ^{18}F-FDG-PET scans.	58/73 FMISO positive in primary and/or nodal disease. Tumor/background ratio, hypoxia volume and nodal stage was associated with patient survival.	Pretherapy FMISO uptake has potential as an independent prognostic measure.	74
	12	Advanced disease (Stage 3)	Pre-radiotherapy ^{18}F-FMISO and ^{18}F-FDG PET scans.	No significant correlation between FDG SUV_{max} and treatment outcome, but correlation with FMISO uptake was statistically significant. No correlation between FDG and FMISO uptake.	FMISO PET is a prognostic indicator of treatment response.	75
HNC & NSCLC	HNC 26; NSCLC 14)	Advanced disease	Preradiotherapy ^{18}F-FMISO PET scan–time activity curve.	High FMISO tumor/muscle ratio and tumor/mediastinal ratio correlated with higher risk of relapse.	Treatment outcome can be predicted on the basis of kinetic behavior of FMISO in tumor.	65
NSCLC	7	NSCLC	Preradiotherapy and serial ^{18}F-FMISO PET scans.	No correlation between tumor size and fractional hypoxic volume.	Unpredictable changes in oxygenation during radiotherapy.	80
	8	NSCLC	Pre and postchemotherapy and postchemoradiotherapy ^{18}F-FMISO and ^{18}F-FDG-PET scans.	Decreased FMISO and FDG uptake post-treatment had favorable outcome, but no correlation between high initial FMISO uptake & treatment outcome/response.	Decrease in FMISO and FDG uptake may predict treatment response and overall survival.	79

SUV_{max}, maximum standardized uptake value.

Table 3 Summary of Clinical Studies That Evaluate Nononcological Applications of ^{18}F-FMISO PET

Disease Type	No. of Patients	Clinical Study	Results	Conclusion(s)	Reference
Ischemic stroke	15	Early (within 48 hours) and late (6 patients) ^{18}F-FMISO PET scan & CT imaging.	Peripheral FMISO uptake in 9 patients on early studies. No FMISO uptake on late studies.	FMISO PET can detect hypoxic, probably penumbral tissue, which does not persist to subacute phase of disease.	81
	24	^{18}F-FMISO PET scan within 48 hours of stroke onset and CT imaging.	Peripheral FMISO uptake in 15/24 patients, with uptake decreasing over time. Significant correlation between hypoxic volume and clinical outcome.	Hypoxic tissue representing amount of infarct tissue amenable to effective treatment.	82
	66	^{18}F-FMISO PET scan within 12 and 24 hours of stroke onset and CT/MRI imaging.	FMISO uptake in 33/66 patients. Spontaneous survival of hypoxic tissue is associated with better neurological outcome.	Hypoxic tissue which progressed to infarction may represent target for early intervention.	83
Haemorrhagic stroke	6	^{18}F-FMISO PET scan between 24 and 43 hours of intracranial haemorrhage.	No FMISO uptake in any patient.	Earlier imaging (before 24 hours) may identify areas amenable to earlier treatment.	86

CT, computed tomography; MRI, magnetic resonance imaging.

Application of ^{18}F-FMISO in Oncology

The principle use of ^{18}F-FMISO has been in oncology patients. The presence of hypoxic tissue has been increasingly recognized to confer resistance to chemotherapy and radiotherapy, both in vitro and in vivo, and accelerates tumor progression.[68,69] In vivo animal model studies have shown that intracellular retention of FMISO is dependent on oxygen concentration,[36] confirming in vitro studies which have shown that the rate of FMISO binding is up to 28 times greater under hypoxic conditions compared with normoxic conditions.[70]

There have been many reported human studies using ^{18}F-FMISO as a noninvasive technique for detection of hypoxia, with direct comparison with oxygen measurements and surrogate markers of hypoxia in various malignancies (Table 1). The first clinical FMISO feasibility study in high-grade glioma involved 3 patients, where initial FMISO uptake was found to be greater than normal cerebral cortex (Fig. 4).[71] Subsequent studies have shown a significant correlation between ^{18}F-FMISO uptake with Ki-67 and VEGFR-1 expression in gliomas, and ^{18}F-FMISO uptake and distribution volume was higher in glioblastomas compared with normal brain and meningiomas.[72,73] Another study that included the evaluation of tumor perfusion with ^{15}O-H_2O PET scan found that early FMISO uptake correlated with perfusion, but late FMISO uptake was independent of perfusion.[72]

In a more recent study performed in renal cell carcinoma patients, only mild FMISO uptake was observed. However, angiogenesis as measured by microvessel density was greater in renal cell carcinoma sections compared with normal renal tissue.[30] In nonsmall cell lung carcinoma (NSCLC), FMISO uptake has been found to be low, with no correlation with FDG uptake (Fig. 5). In this study, surrogate tissue markers of hypoxia, such as microvessel density and GLUT1, showed no significant correlation with FMISO uptake, although there was a weak correlation with Ki-67 proliferative marker.[31]

^{18}F-FMISO has also been studied to predict treatment response and evaluate prognosis (Table 2). The most widely studied tumor for these purposes with ^{18}F-FMISO is head and neck carcinoma. In a study of 73 patients with head and neck carcinoma studied with ^{18}F-FMISO PET, pretreatment ^{18}F-FMISO uptake was found to be an independent prognostic factor.[74] Another study of 12 patients with head and neck carcinoma who had ^{18}F-FMISO PET scan performed preradiotherapy reported that FMISO uptake was a prognostic indicator of treatment response to radiotherapy.[75] Further phase I studies exploring chemoradiation in head and neck cancer patients with the use of a hypoxia sensitizer (tirapazamine) concluded that FMISO can predict prognosis, with early resolution of FMISO uptake being associated with better locoregional control, and patients on tirapazamine had a lower risk of locoregional failure.[76-78] The use of ^{18}F-FMISO PET also supported the experimental observation that tirapazamine specifically acts on hypoxic cells.[78]

In patients with malignant glioma, preoperative ^{18}F-FMISO scans have been shown to be an accurate noninvasive marker of hypoxia, with FMISO uptake seen in all high grade gliomas, and was prognostic for treatment outcomes.[73] In

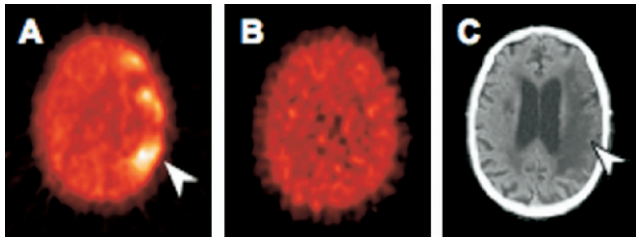

Figure 6 (A) Uptake of ^{18}F-FMISO in ischemic penumbral tissue in the left cerebral hemisphere (arrow) 22 hours postonset of symptoms. (B) No hypoxia evident on ^{18}F-FMISO PET 10 days after stroke. (C) Area of acute stroke evident on CT scan (arrow) 10 days afrer onset of stroke symptoms.

^{18}F-FMISO scans performed preradiotherapy in a group of 14 patients with NSCLC, a high tumor/muscle uptake ratio and tumor/mediastinal ratio was associated with a higher risk of relapse.[65] However, another study of 8 patients with NSCLC treated with a combination of chemotherapy and/or radiotherapy who had serial ^{18}F-FDG and ^{18}F-FMISO PET scans found that a decrease in FDG and FMISO uptake after treatment was associated with a favorable outcome, and a high initial FMISO uptake was a poor prognostic indicator and not associated with treatment response.[79] In a study of 7 patients with NSCLC, no correlation between tumor size and fractional hypoxic volume, defined by ^{18}F-FMISO PET was observed.[80]

Application of ^{18}F-FMISO in Nononcological Indications

The use of ^{18}F-FMISO in the nononcological setting has primarily been in evaluation of cerebral hypoxia, with a few studies reported in myocardial hypoxia. Clinical studies of ^{18}F-FMISO in the evaluation of cerebral hypoxia are summarized in Table 3. In one study in patients with acute ischemic stroke, ^{18}F-FMISO was shown to represent the ischemic penumbra, which is ischemic but viable cerebral tissue (Fig. 6).[81] Another study showed that hypoxic tissue, as demonstrated by ^{18}F-FMISO, was present up to 42 hours after an ischemic stroke, despite the expansion of the infarcted core at the expense of the penumbral tissue with time. There was also a correlation between a number or hypoxic tissue volume indices and clinical outcome.[82,83] The spatial extent of the ischemic penumbra has also been characterized using ^{18}F-FMISO PET scans performed within 48 hours of stroke onset, with a positive correlation between the ^{18}F-FMISO penumbral tissue uptake and time from stroke onset in the external zones of the infarct, but not in the central zones.[84] Statistical parametric mapping, which uses pooled variance and contralateral hemisphere normalization in individual subjects, has also been shown to be a useful method for assessing ^{18}F-FMISO uptake in acute ischemic stroke.[85] In intracerebral hemorrhage, ^{18}F-FMISO has not been shown to have any significant uptake in tissue adjacent to the infarcted tissue.[86]

Apart from investigation of hypoxic tissue in cerebral disease, previous preclinical studies more than a decade ago have assessed the use of ^{18}F-FMISO in evaluating myocardial hypoxia. Animal studies have shown the oxygenation dependent retention of ^{18}F-FMISO in ischemic myocardium in vivo in dogs,[87,88] as well as in an isolated ^{18}F-FMISO kinetic study of myocardial perfusion in rabbits.[44] However, there has been little development of these studies into humans since then.

In the setting of sepsis, a preclinical study using ^{18}F-FMISO in rats showed that sepsis did not invariably result in systemic, multi-organ cellular hypoxia as detected by ^{18}F-FMISO, and that cellular hypoxia was not the major pathophysiological abnormality in sepsis.[89] There has been one reported study of the use of ^{18}F-FMISO to detect anaerobic infections in humans, where ^{18}F-MISO PET was found to be sensitive for detection of anaerobic odontogenic infection in patients with head and neck tumors before radiation therapy.[90]

Other PET Radiotracers of Hypoxia Imaging

Other than ^{18}F-FMISO, other compounds that have been synthesized for imaging of hypoxia are listed in Table 4. The development of second-generation nitromidazoles has been reported for use in hypoxia imaging. A preclinical study comparing ^{18}F-FMISO with ^{18}F-fluoroazomycin arabinofuranoside (^{18}F-FAZA) in rat carcinosarcoma tumor, both in vitro and in vivo in rats, demonstrated that both compounds had similar accumulation in sites of hypoxia on early PET imaging, but ^{18}F-FAZA was eliminated faster from the blood, viscera and muscle tissue, via the renal system.[91] However, a more recent study in murine mammary carcinoma, squamous cell carcinoma and pancreatic acinar cell carcinoma found a lower tumor/blood ratio with ^{18}F-FAZA compared with ^{18}F-FMISO.[92]

In another preclinical study comparing ^{18}F-FMISO and ^{18}F- fluoroerythronitroimidazole (^{18}F-FETNIM) in mammary carcinoma mice models, it was demonstrated that the uptake of both agents correlated with the oxygenation status in tumors, with no significant difference in the intratumoral up-

Table 4 Other PET Radiotracers for Hypoxia Imaging

Radiotracer	Abbreviation	References
^{18}F-Fluoroazomycin arabinofuranoside	^{18}F-FAZA	91, 92, 94
^{64}Cu-diacetyl-bis(N4-methylthiosemicarbazone)	^{64}Cu-ATSM	95-100
^{18}F-Fluoroerythronitroimidazole	^{18}F-FETNIM	93, 101-104
1-(2-nitroimidazol-1[H]-yl)-N-(3-[^{18}F]fluoropropyl)acetamide)	^{18}F-EF1	105, 106
^{18}F[2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide]	^{18}F-EF5	107, 108

take between the 2 radiotracers. However, there was slightly greater uptake in normal tissues for ^{18}F-FMISO compared with ^{18}F-FETNIM in mouse models.[93]

To date, ^{18}F-FMISO remains the most extensively investigated radiotracer of hypoxia and is the only radiotracer that has been validated by multiple studies comparing uptake thresholds to direct pO_2 measurement with the Eppendorf pO_2 hypoximeter.[30,66]

Conclusion

The importance of hypoxia is crucial in the understanding of disease biology, which has direct relevance to improving treatments for patients. ^{18}F-FMISO is the most widely studied and validated PET radiotracer for noninvasive assessment of hypoxia, which is gaining increasing importance for its potential to predict response to treatment and provide prognosis in a wide range of pathological processes.

Acknowledgments

The authors thank Dr Henri Tochon-Danguy and Professor Geoff Donnan for contributions to Figures 2 and 6, respectively; Dr John Sachinidis and Gordan Chan for their experience and comments on the sections on the production of ^{18}F-FMISO and Figure 1; and the staff of the Centre for PET, Austin Hospital.

References

1. Tatum JL, Kelloff GJ, Gillies RJ, et al: Hypoxia: Importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy. Int J Radiat Biol 82:699-757, 2006
2. Foo SS, Abbott DF, Lawrentschuk N, et al: Functional imaging of intratumoral hypoxia. Mol Imaging Biol 6:291-305, 2004
3. Brizel DM, Scully SP, Harrelson JM, et al: Tumor oxygenation predicts for the likelihood of distant metastases in human soft tissue sarcoma. Cancer Res 56:941-943, 1996
4. Hockel M, Schlenger K, Aral B, et al: Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. Cancer Res 56:4509-4515, 1996
5. Hockel M, Schlenger K, Hockel S, et al: Tumor hypoxia in pelvic recurrences of cervical cancer. Int J Cancer 79:365-369, 1998
6. Sundfor K, Lyng H, Rofstad EK: Tumour hypoxia and vascular density as predictors of metastasis in squamous cell carcinoma of the uterine cervix. Br J Cancer 78:822-827, 1998
7. Walenta S, Wetterling M, Lehrke M, et al: High lactate levels predict likelihood of metastases, tumor recurrence, and restricted patient survival in human cervical cancers. Cancer Res 60:916-921, 2000
8. Powis G, Kirkpatrick L: Hypoxia inducible factor-1alpha as a cancer drug target. Mol Cancer Ther 3:647-654, 2004
9. Kerbel RS: New targets, drugs, and approaches for the treatment of cancer: An overview. Cancer Metastasis Rev 17:145-147, 1998
10. Zhong H, De Marzo AM, Laughner E, et al: Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. Cancer Res 59:5830-5835, 1999
11. Zagzag D, Friedlander DR, Margolis B, et al: Molecular events implicated in brain tumor angiogenesis and invasion. Pediatr Neurosurg 33:49-55, 2000
12. Hockel M, Schlenger K, Hockel S, et al: Hypoxic cervical cancers with low apoptotic index are highly aggressive. Cancer Res 59:4525-4528, 1999
13. Dachs GU, Tozer GM: Hypoxia modulated gene expression: angiogenesis, metastasis and therapeutic exploitation. Eur J Cancer 36: 1649-1660, 2000
14. Reynolds TY, Rockwell S, Glazer PM: Genetic instability induced by the tumor microenvironment. Cancer Res 56:5754-5757, 1996
15. Blancher C, Harris AL: The molecular basis of the hypoxia response pathway: Tumour hypoxia as a therapy target. Cancer Metastasis Rev 17:187-194, 1998
16. Padhani AR, Krohn KA, Lewis JS, et al: Imaging oxygenation of human tumours. Eur Radiol 17:861-872, 2007
17. Menon C, Fraker DL: Tumor oxygenation status as a prognostic marker. Cancer Lett 221:225-235, 2005
18. Jain RK: Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. Nat Med 7:987-989, 2001
19. Jain RK: Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 307:58-62, 2005
20. Wouters BG, Weppler SA, Koritzinsky M, et al: Hypoxia as a target for combined modality treatments. Eur J Cancer 38:240-257, 2002
21. Padera TP, Stoll BR, Tooredman JB, et al: Pathology: cancer cells compress intratumour vessels. Nature 427:695, 2004
22. Hall EJ: Radiobiology for the Radiologist (ed 3). Philadelphia, Lippincott, 1988
23. Hockel M, Vaupel P: Tumor hypoxia: Definitions and current clinical, biologic, and molecular aspects. J Natl Cancer Inst 93:266-276, 2001
24. Ciocca DR, Calderwood SK: Heat shock proteins in cancer: Diagnostic, prognostic, predictive, and treatment implications. Cell Stress Chaperones 10:86-103, 2005
25. Stone HB, Brown JM, Phillips TL, et al: Oxygen in human tumors: Correlations between methods of measurement and response to therapy. Summary of a workshop held November 19-20, 1992, at the National Cancer Institute, Bethesda, Maryland. Radiat Res 136:422-434, 1993
26. Hicks RJ, Dorow D, Roselt P: PET tracer development–a tale of mice and men. Cancer Imaging 6:S102-S106, 2006
27. Koh WJ, Rasey JS, Evans ML, et al: Imaging of hypoxia in human tumors with [F-18]fluoromisonidazole. Int J Radiat Oncol Biol Phys 22:199-212, 1992
28. Rasey JS, Koh WJ, Evans ML, et al: Quantifying regional hypoxia in human tumors with positron emission tomography of [18F]fluoromisonidazole: A pretherapy study of 37 patients. Int J Radiat Oncol Biol Phys 36:417-428, 1996
29. Rajendran JG, Wilson DC, Conrad EU, et al: [(18)F]FMISO and [(18)F]FDG PET imaging in soft tissue sarcomas: Correlation of hypoxia, metabolism and VEGF expression. Eur J Nucl Med Mol Imaging 30:695-704, 2003
30. Lawrentschuk N, Poon AM, Foo SS, et al: Assessing regional hypoxia in human renal tumours using 18F-fluoromisonidazole positron emission tomography. BJU Int 96:540-546, 2005
31. Cherk MH, Foo SS, Poon AM, et al: Lack of correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in non-small cell lung cancer assessed by 18F-fluoromisonidazole and 18F-FDG PET. J Nucl Med 47:1921-1926, 2006
32. Brown JM, Workman P: Partition coefficient as a guide to the development of radiosensitizers which are less toxic than misonidazole. Radiat Res 82:171-190, 1980
33. Grunbaum Z, Freauff SJ, Krohn KA, et al: Synthesis and characterization of congeners of misonidazole for imaging hypoxia. J Nucl Med 28:68-75, 1987
34. Fukuda K, Taniguchi H, Koh T, et al: Relationships between oxygen and glucose metabolism in human liver tumours: Positron emission tomography using (15)O and (18)F-deoxyglucose. Nucl Med Commun 25:577-583, 2004
35. Flockhart IR, Large P, Troup D, et al: Pharmacokinetic and metabolic studies of the hypoxic cell radiosensitizer misonidazole. Xenobiotica 8:97-105, 1978
36. Tochon-Danguy HJ, Sachinidis JI, Chan F, et al: Imaging and quantitation of the hypoxic cell fraction of viable tumor in an animal model of intracerebral high grade glioma using [18F]fluoromisonidazole (FMISO). Nucl Med Biol 29:191-197, 2002

37. Graham MM, Peterson LM, Link JM, et al: Fluorine-18-fluoromisonidazole radiation dosimetry in imaging studies. J Nucl Med 38: 1631-1636, 1997
38. Lim JL, Berridge MS: An efficient radiosynthesis of [18F]fluoromisonidazole. Appl Radiat Isot 44:1085-1091, 1993
39. Davda S, Bezabeh T: Advances in methods for assessing tumor hypoxia in vivo: Implications for treatment planning. Cancer Metastasis Rev 25:469-480, 2006
40. Gatenby RA, Kessler HB, Rosenblum JS, et al: Oxygen distribution in squamous cell carcinoma metastases and its relationship to outcome of radiation therapy. Int J Radiat Oncol Biol Phys 14:831-838, 1988
41. Rofstad EK, Sundfor K, Lyng H, et al: Hypoxia-induced treatment failure in advanced squamous cell carcinoma of the uterine cervix is primarily due to hypoxia-induced radiation resistance rather than hypoxia-induced metastasis. Br J Cancer 83:354-359, 2000
42. Kallinowski F, Zander R, Hoeckel M, et al: Tumor tissue oxygenation as evaluated by computerized-pO2-histography. Int J Radiat Oncol Biol Phys 19:953-961, 1990
43. Vaupel P, Schlenger K, Knoop C, et al: Oxygenation of human tumors: Evaluation of tissue oxygen distribution in breast cancers by computerized O2 tension measurements. Cancer Res 51:3316-3322, 1991
44. Shelton ME, Dence CS, Hwang DR, et al: Myocardial kinetics of fluorine-18 misonidazole: A marker of hypoxic myocardium. J Nucl Med 30:351-358, 1989
45. Cater DB, Silver IA: Quantitative measurements of oxygen tension in normal tissues and in the tumours of patients before and after radiotherapy. Acta Radiol 53:233-256, 1960
46. Fyles AW, Milosevic M, Wong R, et al: Oxygenation predicts radiation response and survival in patients with cervix cancer. Radiother Oncol 48:149-156, 1998
47. Kolstad P: Intercapillary distance, oxygen tension and local recurrence in cervix cancer. Scand J Clin Lab Invest Suppl 106:145-157, 1968
48. Knocke TH, Weitmann HD, Feldmann HJ, et al: Intratumoral pO2-measurements as predictive assay in the treatment of carcinoma of the uterine cervix. Radiother Oncol 53:99-104, 1999
49. Hockel M, Knoop C, Schlenger K, et al: Intratumoral pO2 histography as predictive assay in advanced cancer of the uterine cervix. Adv Exp Med Biol 345:445-450, 1994
50. Lyng H, Sundfor K, Rofstad EK: Oxygen tension in human tumours measured with polarographic needle electrodes and its relationship to vascular density, necrosis and hypoxia. Radiother Oncol 44:163-169, 1997
51. Doll CM, Milosevic M, Pintilie M, et al: Estimating hypoxic status in human tumors: A simulation using Eppendorf oxygen probe data in cervical cancer patients. Int J Radiat Oncol Biol Phys 55:1239-1246, 2003
52. Hockel M, Schlenger K, Mitze M, et al: Hypoxia and radiation response in human tumors. Semin Radiat Oncol 6:3-9, 1996
53. Nordsmark M, Loncaster J, Chou SC, et al: Invasive oxygen measurements and pimonidazole labeling in human cervix carcinoma. Int J Radiat Oncol Biol Phys 49:581-586, 2001
54. Lartigau E, Randrianarivelo H, Avril MF, et al: Intratumoral oxygen tension in metastatic melanoma. Melanoma Res 7:400-406, 1997
55. Nordsmark M, Hoyer M, Keller J, et al: The relationship between tumor oxygenation and cell proliferation in human soft tissue sarcomas. Int J Radiat Oncol Biol Phys 35:701-708, 1996
56. Bentzen L, Keiding S, Nordsmark M, et al: Tumour oxygenation assessed by 18F-fluoromisonidazole PET and polarographic needle electrodes in human soft tissue tumours. Radiother Oncol 67:339-344, 2003
57. Brizel DM, Rosner GL, Harrelson J, et al: Pretreatment oxygenation profiles of human soft tissue sarcomas. Int J Radiat Oncol Biol Phys 30:635-642, 1994
58. Brizel DM, Sibley GS, Prosnitz LR, et al: Tumor hypoxia adversely affects the prognosis of carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 38:285-289, 1997
59. Nordsmark M, Overgaard M, Overgaard J: Pretreatment oxygenation predicts radiation response in advanced squamous cell carcinoma of the head and neck. Radiother Oncol 41:31-39, 1996
60. Stadler P, Becker A, Feldmann HJ, et al: Influence of the hypoxic subvolume on the survival of patients with head and neck cancer. Int J Radiat Oncol Biol Phys 44:749-754, 1999
61. Eschwege F, Bourhis J, Girinski T, et al: Predictive assays of radiation response in patients with head and neck squamous cell carcinoma: A review of the Institute Gustave Roussy experience. Int J Radiat Oncol Biol Phys 39:849-853, 1997
62. Lartigau E, Le Ridant AM, Lambin P, et al: Oxygenation of head and neck tumors. Cancer 71:2319-2325, 1993
63. Becker A, Hansgen G, Bloching M, et al: Oxygenation of squamous cell carcinoma of the head and neck: comparison of primary tumors, neck node metastases, and normal tissue. Int J Radiat Oncol Biol Phys 42:35-41, 1998
64. Brizel DM, Dodge RK, Clough RW, et al: Oxygenation of head and neck cancer: changes during radiotherapy and impact on treatment outcome. Radiother Oncol 53:113-117, 1999
65. Eschmann SM, Paulsen F, Reimold M, et al: Prognostic impact of hypoxia imaging with 18F-misonidazole PET in non-small cell lung cancer and head and neck cancer before radiotherapy. J Nucl Med 46:253-260, 2005
66. Gagel B, Reinartz P, Dimartino E, et al: pO(2) Polarography versus positron emission tomography ([(18)F] fluoromisonidazole, [(18)F]-2-fluoro-2′-deoxyglucose). An appraisal of radiotherapeutically relevant hypoxia. Strahlenther Onkol 180:616-622, 2004
67. Zimny M, Gagel B, Dimartino E, et al: FDG—a marker of tumour hypoxia? A comparison with [(18)F]fluoromisonidazole and pO (2)-polarography in metastatic head and neck cancer. Eur J Nucl Med Mol Imaging 33:1426-1431, 2006
68. Brown JM, Giaccia AJ: The unique physiology of solid tumors: Opportunities (and problems) for cancer therapy. Cancer Res 58:1408-1416, 1998
69. Gatenby RA, Coia LR, Richter MP, et al: Oxygen tension in human tumors: In vivo mapping using CT-guided probes. Radiology 156: 211-214, 1985
70. Rasey JS, Nelson NJ, Chin L, et al: Characteristics of the binding of labeled fluoromisonidazole in cells in vitro. Radiat Res 122:301-308, 1990
71. Valk PE, Mathis CA, Prados MD, et al: Hypoxia in human gliomas: Demonstration by PET with fluorine-18-fluoromisonidazole. J Nucl Med 33:2133-2137, 1992
72. Bruehlmeier M, Roelcke U, Schubiger PA, et al: Assessment of hypoxia and perfusion in human brain tumors using PET with 18F-fluoromisonidazole and 15O-H2O. J Nucl Med 45:1851-1859, 2004
73. Cher LM, Murone C, Lawrentschuk N, et al: Correlation of hypoxic cell fraction and angiogenesis with glucose metabolic rate in gliomas using 18F-fluoromisonidazole, 18F-FDG PET, and immunohistochemical studies. J Nucl Med 47:410-418, 2006
74. Rajendran JG, Schwartz DL, O'Sullivan J, et al: Tumor hypoxia imaging with [F-18] fluoromisonidazole positron emission tomography in head and neck cancer. Clin Cancer Res 12:5435-5441, 2006
75. Thorwarth D, Eschmann SM, Holzner F, et al: Combined uptake of [18F]FDG and [18F]FMISO correlates with radiation therapy outcome in head-and-neck cancer patients. Radiother Oncol 80:151-156, 2006
76. Hicks RJ, Rischin D, Fisher R, et al: Utility of FMISO PET in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent. Eur J Nucl Med Mol Imaging 32:1384-1391, 2005
77. Rischin D, Peters L, Hicks R, et al: Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer. J Clin Oncol 19:535-542, 2001
78. Rischin D, Hicks RJ, Fisher R, et al: Prognostic significance of [18F]-misonidazole positron emission tomography-detected tumor hypoxia in patients with advanced head and neck cancer randomly assigned to chemoradiation with or without tirapazamine: A substudy of Trans-Tasman Radiation Oncology Group Study 98.02. J Clin Oncol 24: 2098-2104, 2006
79. Gagel B, Reinartz P, Demirel C, et al: [18F] fluoromisonidazole and [18F] fluorodeoxyglucose positron emission tomography in response

evaluation after chemo-/radiotherapy of non-small-cell lung cancer: A feasibility study. BMC Cancer 6:51, 2006
80. Koh WJ, Bergman KS, Rasey JS, et al: Evaluation of oxygenation status during fractionated radiotherapy in human nonsmall cell lung cancers using [F-18]fluoromisonidazole positron emission tomography. Int J Radiat Oncol Biol Phys 33:391-398, 1995
81. Read SJ, Hirano T, Abbott DF, et al: Identifying hypoxic tissue after acute ischemic stroke using PET and 18F-fluoromisonidazole. Neurology 51:1617-1621, 1998
82. Read SJ, Hirano T, Abbott DF, et al: The fate of hypoxic tissue on 18F-fluoromisonidazole positron emission tomography after ischemic stroke. Ann Neurol 48:228-235, 2000
83. Markus R, Reutens DC, Kazui S, et al: Hypoxic tissue in ischaemic stroke: Persistence and clinical consequences of spontaneous survival. Brain 127:1427-1436, 2004
84. Markus R, Donnan G, Kazui S, et al: Penumbral topography in human stroke: Methodology and validation of the 'Penumbragram'. Neuroimage 21:1252-1259, 2004
85. Markus R, Donnan GA, Kazui S, et al: Statistical parametric mapping of hypoxic tissue identified by [(18)F]fluoromisonidazole and positron emission tomography following acute ischemic stroke. Neuroimage 16:425-433, 2002
86. Hirano T, Read SJ, Abbott DF, et al: No evidence of hypoxic tissue on 18F-fluoromisonidazole PET after intracerebral hemorrhage. Neurology 53:2179-2182, 1999
87. Caldwell JH, Revenaugh JR, Martin GV, et al: Comparison of fluorine-18-fluorodeoxyglucose and tritiated fluoromisonidazole uptake during low-flow ischemia. J Nucl Med 36:1633-1638, 1995
88. Martin GV, Caldwell JH, Graham MM, et al: Noninvasive detection of hypoxic myocardium using fluorine-18-fluoromisonidazole and positron emission tomography. J Nucl Med 33:2202-2208, 1992
89. Hotchkiss RS, Rust RS, Dence CS, et al: Evaluation of the role of cellular hypoxia in sepsis by the hypoxic marker [18F]fluoromisonidazole. Am J Physiol 261:R965-972, 1991
90. Liu RS, Chu LS, Yen SH, et al: Detection of anaerobic odontogenic infections by fluorine-18 fluoromisonidazole. Eur J Nucl Med 23: 1384-1387, 1996
91. Sorger D, Patt M, Kumar P, et al: [18F]Fluoroazomycinarabinofuranoside (18FAZA) and [18F]Fluoromisonidazole (18FMISO): A comparative study of their selective uptake in hypoxic cells and PET imaging in experimental rat tumors. Nucl Med Biol 30:317-326, 2003
92. Piert M, Machulla HJ, Picchio M, et al: Hypoxia-specific tumor imaging with 18F-fluoroazomycin arabinoside. J Nucl Med 46:106-113, 2005
93. Gronroos T, Bentzen L, Marjamaki P, et al: Comparison of the biodistribution of two hypoxia markers [18F]FETNIM and [18F]FMISO in an experimental mammary carcinoma. Eur J Nucl Med Mol Imaging 31:513-520, 2004
94. Solomon B, Binns D, Roselt P, et al: Modulation of intratumoral hypoxia by the epidermal growth factor receptor inhibitor gefitinib detected using small animal PET imaging. Mol Cancer Ther 4:1417-1422, 2005
95. Fujibayashi Y, Taniuchi H, Yonekura Y, et al: Copper-62-ATSM: a new hypoxia imaging agent with high membrane permeability and low redox potential. J Nucl Med 38:1155-1160, 1997
96. O'Donoghue JA, Zanzonico P, Pugachev A, et al: Assessment of regional tumor hypoxia using 18F-fluoromisonidazole and 64Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) positron emission tomography: Comparative study featuring microPET imaging, Po2 probe measurement, autoradiography, and fluorescent microscopy in the R3327-AT and FaDu rat tumor models. Int J Radiat Oncol Biol Phys 61:1493-1502, 2005
97. Laforest R, Dehdashti F, Lewis JS, et al: Dosimetry of 60/61/62/64Cu-ATSM: A hypoxia imaging agent for PET. Eur J Nucl Med Mol Imaging 32:764-770, 2005
98. Lewis JS, McCarthy DW, McCarthy TJ, et al: Evaluation of 64Cu-ATSM in vitro and in vivo in a hypoxic tumor model. J Nucl Med 40:177-183, 1999
99. Obata A, Yoshimoto M, Kasamatsu S, et al: Intra-tumoral distribution of (64)Cu-ATSM: A comparison study with FDG. Nucl Med Biol 30: 529-534, 2003
100. Yuan H, Schroeder T, Bowsher JE, et al: Intertumoral differences in hypoxia selectivity of the PET imaging agent 64Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone). J Nucl Med 47:989-998, 2006
101. Gronroos T, Eskola O, Lehtio K, et al: Pharmacokinetics of [18F]FETNIM: A potential marker for PET. J Nucl Med 42:1397-1404, 2001
102. Lehtio K, Oikonen V, Gronroos T, et al: Imaging of blood flow and hypoxia in head and neck cancer: Initial evaluation with [(15)O]H(2)O and [(18)F]fluoroerythronitroimidazole PET. J Nucl Med 42:1643-1652, 2001
103. Lehtio K, Oikonen V, Nyman S, et al: Quantifying tumour hypoxia with fluorine-18 fluoroerythronitroimidazole ([18F]FETNIM) and PET using the tumour to plasma ratio. Eur J Nucl Med Mol Imaging 30:101-108, 2003
104. Tolvanen T, Lehtio K, Kulmala J, et al: 18F-Fluoroerythronitroimidazole radiation dosimetry in cancer studies. J Nucl Med 43:1674-1680, 2002
105. Evans SM, Kachur AV, Shiue CY, et al: Noninvasive detection of tumor hypoxia using the 2-nitroimidazole [18F]EF1. J Nucl Med 41:327-336, 2000
106. Kachur AV, Dolbier WR Jr., Evans SM, et al: Synthesis of new hypoxia markers EF1 and [18F]-EF1. Appl Radiat Isot 51:643-650, 1999
107. Dolbier WR Jr., Li AR, Koch CJ, et al: [18F]-EF5, a marker for PET detection of hypoxia: Synthesis of precursor and a new fluorination procedure. Appl Radiat Isot 54:73-80, 2001
108. Ziemer LS, Evans SM, Kachur AV, et al: Noninvasive imaging of tumor hypoxia in rats using the 2-nitroimidazole 18F-EF5. Eur J Nucl Med Mol Imaging 30:259-266, 2003