Published in final edited form as:

PET Clin. 2009 January 1; 4(1): 39–47. doi:10.1016/j.cpet.2009.05.009.

Positron Emission Tomography Imaging of Hypoxia

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Synopsis

Hypoxia imaging has applications in functional recovery in ischemic events such as stroke and myocardial ischemia, but especially in tumors in which hypoxia can be predictive of treatment response and overall prognosis. Recently there has been development of imaging agents utilizing positron emission tomography for non-invasive imaging of hypoxia. Many of these PET agents have come to the forefront of hypoxia imaging. Halogenated PET nitroimidazole imaging agents labeled with ¹⁸F ($t_{1/2} = 110$ m) and ¹²⁴I ($t_{1/2} = 110$ m) have been under investigation for the last 25 years, with radiometal agents (⁶⁴Cu-ATSM) being developed more recently. This review focuses on these positron emission tomography imaging agents for hypoxia.

Keywords

PET; hypoxia; ¹⁸F-MISO; ⁶⁴Cu-ATSM

Introduction

Hypoxia in tissue is characterized as a lack of oxygen required for cells to function normally. It is usually defined as the oxygen tension at which the metabolic demand in stoma, endothelial cells and tumor cells exceeds the supply¹. This imbalance between oxygen and delivery causes numerous downstream effects which has implications in various situations and disease states.

Hypoxia imaging has applications in functional recovery in ischemic events such as stroke and myocardial ischemia, but especially in tumors in which hypoxia can be predictive of treatment response and overall prognosis.

Hypoxia can occur in both heart and brain tissue following arterial occlusions and other events². The heart is a very aerobic organ, consuming some 8–15 ml O₂/min/100g tissue at rest and requires a constant supply of oxygen to maintain function and viability³. The heart

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can become exposed to ischemic conditions resulting from acute coronary events. Brief periods of ischemia (<20 minutes) are reversible if followed by reperfusion⁴. If the duration of oxygen deprivation becomes longer, sections of the heart may become necrotic and non-viable⁴. During a stroke, blood flow to the brain is interrupted, and if this condition persists, brain function becomes impaired, sometimes irreversibly⁵. The longer the duration of hypoxia, the larger and more diffuse the area of the brain is affected. The high energy requirements of the brain render this organ particularly vulnerable to hypoxia⁴.

Hypoxia usually develops in tumors through a disruption in the vascular blood supply to the growing tumor mass. Tumor vessels are typically structurally and functionally abnormal compared to normal tissue, with the vasculature being characterized by vigorous proliferation which leads to structurally immature, defective and ineffective vessels. This results in vessels that are tortuous and leaky which can contribute to heterogeneity in blood flow and thus varied levels of oxygenation in tumors^{6, 7}. Blood flow in these abnormal vessels can vary considerably, from 0.01 to 2.0 ml/g/min⁷, thus tumors can exhibit perfusion that is characteristic of a wide range of metabolic rates. In addition to the abnormal vasculature, fluid accumulating in the tumor matrix and the rapidly proliferating cancer cells themselves can cause high interstitial pressure which restricts and compresses the intratumor vessels causing collapse and reducing blood supply even further^{7, 8}. Hypoxia can also be caused by a deterioration of diffusion geometry within the tumor (again due to the abnormal blood vessels) or disease/therapy associated anemia which leads to a reduced oxygen transport by the blood⁹. Thus hypoxia can result from diffusion and effusion issues and is usually the result of a combination of these problems¹. There is evidence that tumors may consist of up to 50–60% hypoxic or anoxic tissue heterogeneously distributed within the tumor mass with tumor to tumor variability greater than intra-tumor variability⁹. Clinically relevant hypoxia is detected in 50% of all solid tumors irrespective of size, stage, nodal status or other histopathological features with local recurrences typically having a higher hypoxic fraction than that of primary tumors⁷.

Hypoxia is associated with restrained proliferation, differentiation, necrosis or apoptosis and can lead to the development of a more aggressive cancer phenotype⁹. Hypoxia-induced proteome or genome changes may trigger mechanisms which enable cells to escape this “hostile” environment and hence favor unrestricted growth and mobility⁷. Lack of nutrients to the cells (due to reduced blood supply) in combination with hypoxia may also lead to these cellular changes thus causing progression, local growth and metastasis⁷. This situation can manifest as a higher rate of recurrence and metastasis and in the long term, decreased survival.

Hypoxia cells have been shown to have an increased resistance to radiotherapy. Radiotherapy is thought to rely mainly on the formation of free radicals which cause DNA damage, a mechanism which is enhanced by the presence of oxygen. Due to this oxygen enhancement effect, hypoxia can be a key factor in tumor development and therapy due to the increased radioresistance of hypoxic cells compared with normally oxygenated cells¹⁰. Early on, Gray *et al* determined the radiation dose required to achieve the same biologic effect is 2.8 to 3 times higher in the absence of oxygen than its presence¹¹. Hypoxia is one of the major factors which negatively affects radiotherapy outcome¹. Sustained hypoxia can also lead to alterations in the number of quiescent cells which leads to alterations in the response to radiation and chemotherapy⁷ as these therapies are primarily effective against rapidly proliferating cells¹².

In patients with cervical carcinoma, tumor hypoxia is an important prognostic factor that predicts for decreased overall and disease-free survival. Moreover, hypoxic tumors are less responsive to irradiation than are normoxic tumors. A higher frequency of metastatic disease has been reported in patients with hypoxic soft tissue sarcomas and cervical cancer^{13, 14}. Brizel *et al.*, have reported that a combination of radiotherapy and hyperthermia (to improve tumor

oxygenation) in 38 patients with nonmetastatic high grade soft tissue sarcoma resulted in improvement of tumor oxygenation measured by polarographic oxygen electrodes and had an impact on treatment outcome¹⁴. They reported that patients with <90% tumor necrosis in the resected specimen experienced longer disease free survival than those with $\geq 90\%$ necrosis. Höckel *et al* have studied 103 patients with advanced cervical cancer¹³. In cervical cancer, the oxygen status of the tumor was measured by invasive oxygen electrodes was noted to be the single most important prognostic factor. Patients with hypoxic cervical tumors had significantly worse disease-free survival and overall survival compared with nonhypoxic tumors. The poor outcomes in patients with hypoxic tumors was due to locoregional failure, irrespective of the mode of therapy (surgery or radiation) applied as primary treatment¹³.

Direct correlations have been made between imaging protocols and PO₂ measurements taken with an Eppendorf pO₂ hypoximeter which measures oxygen tensions using a polarographic oxygen microelectrode. This direct real-time measurement of oxygen tension in tissues provided the first concrete evidence that intratumoral oxygen tension was indicative of survival in human cancers¹³. This method of oxygen measurement has demonstrated the clinical relevance of tumor hypoxia, although this methodology is limited by its invasiveness and is feasible only for superficial or easily accessible tumors¹⁵ and can also yield variable results due to sampling errors. In addition, the pO₂ electrode only measures average oxygen tension and thus does not distinguish necrotic tissue from hypoxic but viable tissue which is a disadvantage for this technique¹³.

Noninvasive imaging protocols for the detection of hypoxia have been developed for Magnetic Resonance (MR). These techniques can be based on endogenous or exogenous contrast agents and can include Electron Paramagnetic Resonance (EPR)^{16, 17}, Magnetic Resonance Spectroscopy (MRS)¹⁸, and Blood oxygen-dependent level (BOLD) imaging^{19, 20}. EPR relies on the injections of free radical contrast agents which reflect the absolute oxygen tension present in the tissue¹⁷. Although hypoxia cannot be directly detected by MRS, physiological conditions (uptake of binding markers) associated with the lack of oxygenation can be detected, usually by ¹⁹F MRS. The patient is injected with perfluorocarbons to measure oxygen tension. This technique relies on the change in the relaxation rate of the ¹⁹F being enhanced in direct proportion to the O₂ concentration²¹, however these relaxation rates may depend on other physiological factors present in the tissue. Magnetic Resonance Imaging (MRI) can be used to detect paramagnetic deoxyhemoglobin distinctly from oxyhemoglobin and thus obtains a measure of blood oxygenation²⁰. This technique is known as Blood Oxygen Level Dependent (BOLD) imaging and has been used to indirectly measure oxygen levels in animal²⁰ and human²² tumors. A disadvantage of this technique is the inability to separate confounding effects related to blood flow heterogeneity¹² which is likely to be present in hypoxic tissue. Despite the development of these techniques, studies in humans with MR are limited¹².

Recently there has been development of imaging agents utilizing positron emission tomography (PET) and single photon emission computed tomography (SPECT agents). Despite the wider availability of SPECT, many PET agents have come to the forefront of hypoxia imaging. Halogenated PET nitroimidazole imaging agents labeled with ¹⁸F ($t_{1/2} = 110$ m) and ¹²⁴I ($t_{1/2} = 110$ m) have been under investigation for the last 25 years, with radiometal agents (⁶⁴Cu-ATSM) being developed more recently. The structures of several of these agents are shown in Figure 1. With the use of these specific hypoxia tracers, PET can be used for assessment and quantification of tumor hypoxia in a non-invasive manner. This method has potential for determination of the intratumor distribution of regional tumor hypoxia and thus may be used to select patients for hypoxia therapies. This review focuses on these positron emission tomography imaging agents for hypoxia.

Radiolabeled 2-Nitroimidazoles as Markers for Hypoxia

Nitroimidazoles were first proposed as reducible hypoxia markers in 1979²³. These compounds enter cells by passive diffusion and undergo reduction forming a reactive intermediate species. In the presence of oxygen the molecule is reoxidized and the nitroimidazole diffuses back out of the cell, but under hypoxic conditions further reduction occurs, forming covalent bonds with intracellular macromolecules, thus trapping the compound inside the cell²⁴. This mechanism is shown in Figure 2. Since the rate of uptake is strictly dependent on the oxygen concentration in the cell, correlations can be made between tracer concentration and hypoxia conditions. There are several fluorinated and iodinated agents that have been developed based on the nitroimidazole basic structure.

[¹⁸F]fluoromisonidazole (FMISO)

¹⁸F-labeled misonidazole was proposed as a radioactive derivative of the nitroimidazoles in 1984^{25, 26}. Over the last decade [¹⁸F]FMISO has been studied as a PET agent for imaging hypoxia and to date, [¹⁸F]FMISO is currently the most widely used PET agent for mapping regional hypoxia and is generally considered to be the gold standard for PET hypoxia imaging. It has been shown to be retained in hypoxic cells both *in vivo* and *in vitro*.

In patients, time activity curves of this agent have shown that FMISO in normal tissue equilibrates with plasma levels within 30 minutes but is selectively retained in hypoxic tissue for up to 2.5 hours²⁷. Imaging protocols are typically 20–30 minutes and start from 75–150 minutes after injection of the radiotracer²⁸. A typical threshold of tumor to plasma ratio of 1.4 at 2 hours post injection can be considered to be indicative of hypoxia²⁷. This agent is metabolized by the liver and excreted through the kidneys and bladder. Organ doses for [¹⁸F]FMISO are comparable with other commonly performed nuclear medicine scans and indicate that the potential radiation risk associated with a [¹⁸F]FMISO scan is within generally accepted limits. The radiation exposure for an [¹⁸F]FMISO scan is equal to or lower than other radiopharmaceuticals²⁹.

It has been shown that significant [¹⁸F]FMISO uptake requires a hypoxic level of <10 mmHg²⁷. However, unlike the pO₂ measurements FMISO is only sensitive to the presence of hypoxia in viable cells²⁸ which may be advantageous for *in vivo* imaging in human subjects.

[¹⁸F]FMISO has been used in numerous oncology clinical studies including gliomas⁸, head and neck cancer³⁰, and non small cell lung cancer. In an early study involving patient with malignant glioma, a feasibility study demonstrated the use of FMISO to detect hypoxia in the brain *in vivo*³¹. [¹⁸F]FMISO uptake has also been observed in the brain indicating that it is freely diffusible across the blood brain barrier.

[¹⁸F]FMISO uptake has been correlated with low prognosis in both head and neck cancer and glioblastoma multiforme^{30, 32}. In patients with head and neck cancer a clear difference in [¹⁸F]FMISO uptake kinetics was observed in patients that responded to radiation therapy compared to non-responders³⁰. Although [¹⁸F]FMISO uptake varied widely between patients and considerably between different parts of tumors, patients that were non-responsive to radiation therapy generally displayed higher levels of [¹⁸F]FMISO accumulation. Non-responders also showed initially low perfusion of the tracers followed by accumulation indicating hypoxia, while responders showed high perfusion followed by rapid washout indicating well oxygenated, viable tumor tissue³⁰. In this study no pattern was observed in patients with non-small cell lung cancer indicating that the choice of hypoxia imaging agent should be dependent on tumor type. In glioblastoma multiforme patients, both the volume and intensity of hypoxia as determined by [¹⁸F]FMISO scans before radiotherapy was strongly correlated with shortened time to progression and survival³².

One study concluded that [^{18}F]FMISO was not suitable for detection of tumor hypoxia in a variety of soft tissue tumors with no correlation found between hypoxic tumors (as determined by O_2 electrode measurements) and those displaying enhanced [^{18}F]FMISO uptake³³. The authors of the publication with these negative [^{18}F]FMISO findings speculate that the low uptake of FMISO in the tumors could be due to large amounts of necrosis in the soft tissue tumors and/or tumor heterogeneity³³ but further studies are warranted to determine the validity of [^{18}F]FMISO in ascertaining the presence of hypoxia in soft tissue tumors.

Because of high lipophilicity, and slow kinetics of this tracer long imaging times are required and high contrast images are not typical with this agent (tumor to blood ratio >1.2). The slow washout of this tracer leading to a delay time of two hours required after injection to allow for clearance of the tracer from normal background tissues delays imaging and can result in poor statistics and images of limited quality³⁴.

[^{18}F]fluoroazomycin arabinoside (FAZA) and [^{124}I]iodoazomycin arabinoside (IAZA)

[^{18}F]fluoroazomycin arabinoside (FAZA) has been recently shown to have superior pharmacokinetics than [^{18}F]FMISO primarily due to faster clearance from normal tissues resulting in higher tumor to background ratios³⁵. This is due to increased lipophilicity of [^{18}F]FAZA as compared to [^{18}F]FMISO. [^{18}F]FAZA diffusion into cells is also faster, making it more readily available for reductive retention in hypoxia cells³⁶. Tumor uptake of [^{18}F]FMISO in mice bearing human squamous cell carcinoma xenografts was approximately two times higher than for [^{18}F]FAZA but tumor to blood ratios was significantly higher for [^{18}F]FAZA than [^{18}F]FMISO due to slower clearance of [^{18}F]FMISO. In human studies, imaging with [^{18}F]FAZA appears feasible in patients with head and neck cancer¹⁵. Image quality in these patients in a preliminary clinical study was determined to be adequate for clinical use. Tumor uptake was heterogeneous within individual tumors and between individuals suggesting large intertumor as well intratumor variability¹⁵. The authors from this study concluded that imaging at approximately two hours after radiotracer injection seemed to be a reasonable choice for [^{18}F]FAZA tumor imaging as early timepoints were largely dependent on perfusion of the radiotracer into the tumor. The arbitrarily hypoxia threshold chosen (tumor to muscle ratio of 1.5) in this study was slightly higher than that with [^{18}F]FMISO (between 1.2 and 1.4) again possibly indicating superior kinetics¹⁵. However, more studies are required to fully ascertain the benefits of imaging with [^{18}F]FAZA as opposed to [^{18}F]FMISO.

The iodinated analogue [^{124}I]IAZA has also been prepared but imaging at later time points which were not possible with the fluorinated versions resulted in no advantage. Significant thyroid uptake was also reported in this study indicating possible deiodination of the [^{124}I]IAZA³⁵.

[^{124}I] – iodoazomycin galactopyranoside (IAZG)

[^{124}I]IAZG was developed as a longer lived nitroimidazole PET radiotracer in order to obtain images at extended timepoints. Theoretically, in this manner images could be obtained after washout of the unbound tracer, thus yielding images with better contrast. [^{124}I]IAZG uptake was shown to be consistent with independent measures of hypoxia in rat liver tumors³⁷. In a comparison study between [^{18}F]FMISO and [^{124}I]IAZG in rats bearing liver and peritoneal metastasis, both tracers were shown to accumulate in hypoxic tumor tissue. The two tracers also demonstrated similar tumor to background ratios although the optimal imaging time differed (3 hours for [^{18}F]FMISO and 6 hours for [^{124}I]IAZG)³⁸. However, the [^{18}F]FMISO agent yielded higher quality scans as the absolute concentration of the tracer was higher in the tumor and thus higher counting statistics were obtained. The difference in kinetic behavior between these two molecules may be attributed to the difference in lipophilicity of these two tracers. The authors suggest that deiodination of the [^{124}I]IAZG compound may also be

responsible for the varied biodistribution but as thyroid uptake in the animals in this study was not reported it is difficult to determine³⁸. A similar PET imaging agent, [¹²⁴I] – iodoazomycin galactoside, in another study by the same group was shown to have high tumor to whole body ratios in both hypoxic fibrosarcoma and breast cancer models³⁹. Comparisons with [¹⁸F] FMISO showed optimal imaging at later time points (24 hours post injection vs 3 hours post injection for [¹⁸F]FMISO) and higher tumor to normal tissue ratios were obtained. Higher absolute values of tracer accumulation were also obtained with [¹²⁴I] – iodoazomycin galactoside (17% as compared to 5–10% for [¹⁸F]FMISO)³⁹. Considerable deiodination was observed in vivo with this tracer as observed by the amount of radioactivity present in the thyroid in the animals. This data reinforces the notion that hypoxia agent selection may need to be tumor specific.

[¹⁸F]1-(2-fluoro-1-[hydroxymethyl]ethoxy)methyl-2-nitroimidazole (FRP170)

RP170 was recently developed as a new 2-nitroimidazole analog with a hydrophilic side chain in attempts to increase the target to background ratios obtained with [¹⁸F]FMISO. Radiofluorination of this compound yields [¹⁸F]FRP170 which would be expected to yield superior images at earlier timepoints than [¹⁸F]FMISO⁴⁰. A recent study in four healthy male volunteers and three lung cancer patients who underwent dynamic scanning after injection of [¹⁸F]FRP170 revealed rapid elimination through the kidneys and liver with early uptake in lung cancer lesions⁴⁰. Tumor uptake was clearly observed on all lung cancer subjects with contrast increasing over time. The authors concluded that [¹⁸F]FRP170 was almost equivalent to [¹⁸F] FMISO although no match protocols were performed⁴⁰.

The same group has also evaluated [¹⁸F]FRP170 in myocardial tissue in an animal model⁴¹. Visualization of ischemic but viable myocardial tissue was accomplished ex vivo with confirmation of the location of the damaged areas by histology. Further studies would be necessary to confirm the use of [¹⁸F]FRP170 for imaging hypoxic cardiac tissue.

[¹⁸F]2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3-pentafluoropropyl)-acetimide (EF5)

EF5 was first developed as a biopsy based staining agent. A positron emitting version of this compound has been recently developed as an imaging agent of hypoxia. The enhanced lipophilicity of this drug substantially increases its biological half-life and signal from hypoxia-dependent metabolism⁴². EF5 is also reported to be the most stable of the 2-nitroimidazoles studies to date.

In a recent human trial with patients with newly diagnosed head and neck squamous cell carcinoma (HNSCC) the time course of [¹⁸F]EF5 was studied to determine the feasibility of this tracer as a hypoxia imaging agent⁴³. The initial distribution of [¹⁸F]EF5 was found to be dominated by blood flow, whereas binding and uptake at later time points was found to be hypoxia specific. A tumor to muscle ratio of 1.5 was determined to be an appropriate threshold for the presence of clinically significant hypoxia. Additionally, increased [¹⁸F]EF5 uptake was found to be predictive of higher grade tumor and of shorter time to metastasis in patients with soft tissue sarcomas⁴⁴. This was also reported in patients with brain tumors⁴⁵. The authors concluded that [¹⁸F]EF5 could be used to identify patients at high risk for metastases.

One possible drawback to EF5 is that its labeling chemistry is more complex than that for the other ¹⁸F-labeled agents thus possibly leading to reduced availability of this radiotracer⁴⁶.

Copper-based Radiopharmaceuticals for Imaging Hypoxia

^{60,61,62,64}Cu]Copper(II)-diacetyl-bis(N⁴-methylthiosemicarbazone (Cu-ATSM)

Dithiosemicarbazones were discovered to possess antitumor properties in the 1960s. This led to the development of this class of ligands as radiopharmaceuticals due to the simplicity of the chemistry and the availability of copper positron emitting isotopes⁴⁷. Cu-ATSM is a neutral lipophilic molecule which is highly membrane permeable and undergoes reduction and becomes trapped in the cell. This complex has been synthesized with a multitude of copper isotopes with varying half-lives, including ⁶⁰Cu ($t_{1/2}$ = 23.7 min), ⁶¹Cu ($t_{1/2}$ = 3.35 hr), ⁶²Cu ($t_{1/2}$ = 9.74 min) and ⁶⁴Cu ($t_{1/2}$ = 12.7 hr)⁴⁷. ⁶⁰Cu, ⁶¹Cu and ⁶⁴Cu can be produced by proton bombardment of solid targets using a medical cyclotron, while ⁶²Cu is available from a generator similar to that used for ^{99m}Tc⁴⁷.

[⁶⁴Cu]Copper(II)-diacetyl-bis(N⁴-methylthiosemicarbazone (⁶⁴Cu-ATSM) was developed as an alternative to [¹⁸F]FMISO. [⁶⁴Cu] ($t_{1/2}$ = 12.7 h, β^+ = 17.4%) can be produced in high specific activity in reliable quantities and the longer half-life allows for distribution to centers without a cyclotron over longer distances than possible with ¹⁸F. This isotope also decays by β^- and can therefore have potential as both a diagnostic and therapeutic agent⁴⁸.

The radiopharmaceutical ⁶²Cu-ATSM was initially reported an agent for delineating hypoxic myocardial tissue in an isolated rat heart model⁴⁹. The reduction of Cu(II) to Cu(I), which is the retention mechanism by which the copper is trapped in hypoxic tissue, was measured by electron spin resonance using non radioactive Cu-ASTM and this study determined that the Cu-ATSM was reduced in hypoxic but not in normal mitochondria. Rapid washout of this tracer from other tissues as well as favorable blood pool clearance may allow for screening for patients with myocardial hypoxia with this agent. Retention of the radiopharmaceutical was increased under hypoxic conditions and in this heart model, the ⁶²Cu-ATSM retention was inversely correlated with ²⁰¹Tl, a known blood flow marker⁴⁹. Additional studies in several canine models determined quantitative and selective Cu-ATSM radiotracer uptake in hypoxic myocardium⁵⁰. This study was performed in order to determine the oxygen deprived myocardial state in both hypoxia and ischemia. The authors concluded that Cu-ATSM was an effective tracer for global hypoxia which was also useful in situations such as myocardial infarction where flow may be limited. This study also demonstrated that Cu-ATSM was not retained in necrotic tissue thus this tracer could differentiate between hypoxic, viable tissue and nonfunctional, dead, myocardial tissue⁵⁰. In addition, these scans were performed only 20 minutes after tracer injection, thus showing differences between hypoxic and normal tissue can be rapidly obtained⁵⁰. In a preliminary human patient study, ⁶²Cu-ASTM PET imaging was performed in 7 patients with coronary heart disease. Increased uptake was observed in one patient with unstable angina⁵¹.

Yuan *et al* evaluated ⁶⁴Cu-ATSM as a hypoxia agent by comparing autoradiography distributions of the radiotracers in animal studies with nonradioactive EF5, a validated hypoxia marker drug⁵². This group studied the uptake and immunohistochemistry in mammary adenocarcinomas, fibrosarcomas and gliomas. While they determined that high tumor to muscle ratios could be observed for the adenocarcinomas and gliomas, this was not the case for the fibrosarcomas⁵². This shows that although Cu-ATSM may be a valid hypoxia agent for some tumor types, this cannot be extrapolated to all tumors and hence this may not be a universal hypoxia marker.

The first report of Cu-ASTM in a human study was with ⁶²Cu-ATSM in 2000 and was conducted in normal subjects and patients with lung cancer⁵³. Intense uptake of the ⁶²Cu-ATSM was observed in all lung cancer patients reaching a plateau within a few minutes after injections. The mean tumor to backgrounds ratio of ⁶²Cu-ATSM was 3.00 with a maximum

of 9.33⁵³. The radiotracer cleared rapidly from the blood and lungs of all normal subjects. In addition to this a negative correlation was observed in three out of four patients between flow and flow-normalized ⁶²Cu-ATSM uptake, indicating that ⁶²Cu-ATSM uptake might be increased by low flow.

Cu-ATSM has also been evaluated in patients with rectal⁵⁴ and cervical cancer⁵⁵. These were correlative studies designed to determine if uptake of ⁶⁰Cu-ATSM was predictive of a response to therapy. In patients with rectal cancer a pilot study indicated that ⁶⁰Cu-ATSM uptake may be predictive of survival but that further studies were needed to confirm this⁵⁴. In a small study in cervical cancer patients the inter-patient ⁶⁰Cu-ATSM uptake was variable and found to strongly correlate with response to therapy and overall survival⁵⁵. A tumor to muscle ratio of 3.5 was determined to be an accurate cutoff for distinguishing patients who did and did not develop disease recurrence after radiation therapy. In addition this study determined that the prognostic information obtained from ⁶⁰Cu-ATSM could not be derived from FDG-PET. Further studies comparing ⁶⁰Cu-ATSM with ⁶⁴Cu-ATSM in patients with cancer of the uterine cervix found that patterns of these radiopharmaceuticals were similar and image quality of the ⁶⁴Cu-ATSM was superior to the ⁶⁰Cu-ATSM⁵⁶. Representative images from this study are shown in Figure 3. The use of this longer lived analogue in this crossover study demonstrated the utility of ⁶⁴Cu-ATSM, which would allow for production and shipping of this radiopharmaceutical to supply large multicenter trials.

Overall this agent shows rapid delineation of tumor hypoxia and higher tumor to background ratios (>>2.0) thus showing advantages over [¹⁸F]FMISO⁴⁷. A current large scale clinical trial with this radiopharmaceutical may shed more light on the advantages of Cu-ATSM.

Conclusion

A recent review concluded “PET imaging with specific hypoxia tracers is becoming a must in radiation therapy planning”¹⁰. With the developments of new therapies in phase three clinical trials to overcome hypoxia in tumors, the testing of predictive assays that can identify patient populations that can benefit from these treatments is necessary⁵⁷. In addition, it has been suggested that dynamic hypoxia measurements during oxygen-modifying treatments could aid in the determination of responding and non-responding patients¹. Reduction of unnecessary treatments in non-responding patients could result in decreased side effects as well as the opportunity to modify the patient treatment regime. Assays are needed for prediction of patient outcome, and as treatment selection tool and for evaluation of treatment response. These techniques may be used to apply hypoxia-directed interventions such as intensity modulation radiation therapy (IMRT) and chemotherapy with hypoxia selective drugs such as tirapazamine¹².

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Figure 1.
Structure of hypoxia PET imaging agents

Figure 2.
Mechanism of Nitroimidazole retention in hypoxic tissue

Figure 3.
Comparison of ^{60}Cu -ATSM and ^{64}Cu -ATSM