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PET of Hypoxia and Perfusion with ^{62}Cu -ATSM and ^{62}Cu -PTSM Using a $^{62}\text{Zn}/^{62}\text{Cu}$ Generator

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Abstract

OBJECTIVE—Copper-diacetyl-bis(N^4 -methylthiosemicarbazone) (Cu-ATSM) and copper-pyruvaldehyde-bis(N^4 -methylthiosemicarbazone) (Cu-PTSM) are being studied as potential markers of hypoxia and perfusion, respectively. The use of short-lived radionuclides (e.g., ^{62}Cu) has advantages for clinical PET, including a lower radiation dose than long-lived radionuclides and serial imaging capability. A $^{62}\text{Zn}/^{62}\text{Cu}$ microgenerator and rapid synthesis kits now provide a practical means of producing ^{62}Cu -PTSM and ^{62}Cu -ATSM on-site. Tumors can be characterized with ^{62}Cu -PTSM, ^{62}Cu -ATSM, and ^{18}F -FDG PET scans during one session. We present the initial clinical data in two patients with lung neoplasms.

CONCLUSION—Hypoxia and perfusion are important parameters in tumor physiology and can have major implications in diagnosis, prognosis, treatment planning, and response to therapy. We have shown the feasibility of performing ^{62}Cu -ATSM and ^{62}Cu -PTSM PET together with FDG PET/CT during a single imaging session to provide information on both perfusion and hypoxia and tumor anatomy and metabolism.

Keywords

granuloma; lung cancer; perfusion imaging; PET/CT; radionuclides; tumor hypoxia

Tumor hypoxia is a critical factor in both the development and treatment of malignant disease. Hypoxia and altered angiogenesis are critical factors in carcinogenesis, and hypoxic tumors are more resistant to both radiation and chemotherapy than tumors that are not hypoxic. Tumor hypoxia has been shown to correlate with poorer prognosis in head and neck cancer and cervical cancer and may have similar negative prognostic implications in other malignancies. For these reasons, there is a compelling interest to develop techniques for imaging tumor hypoxia; these imaging techniques would increase the current understanding of tumor physiology and would have immediate applicability in guiding cytotoxic chemotherapy, radiation therapy, and the use of antiangiogenic agents. PET can provide quantitative information about positron-emitting

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radiotracers. Furthermore, PET/CT technology allows the distribution of positron-emitting radiotracers to be accurately correlated with high-resolution anatomic imaging.

Copper-diacetyl-bis(N⁴-methylthiosemi-carbazone) (Cu-ATSM) has been studied as a marker for hypoxic cells [1], and preliminary clinical studies indicate that this agent may provide diagnostic and prognostic information in certain malignancies and may be predictive of treatment outcome after radiation therapy [2,3]. Copper-ATSM is a small molecule that readily diffuses into cells, where it is selectively bioreduced and trapped within viable cells under hypoxic conditions. A variety of positron-emitting radionuclides of copper can be used for labeling Cu-ATSM [4]: ⁶⁰Cu (half-life [t_{1/2}] = 23.7 minutes), ⁶¹Cu (t_{1/2} = 201 minutes), ⁶²Cu (t_{1/2} = 9.7 minutes), and ⁶⁴Cu (t_{1/2} = 762 minutes).

Using ⁶²Cu-ATSM offers several advantages. The short half-life of ⁶²Cu reduces radiation dose to the patient and allows multiple studies to be performed. For example, a companion PET scan using ⁶²Cu-pyruval-dehyde-bis(N⁴-methylthiosemicarbazone) (⁶²Cu-PTSM) can be obtained during the same imaging session. Like ATSM, PTSM freely diffuses into cells, but without the selectivity for hypoxic cells; therefore, PTSM is a surrogate marker of perfusion. The disadvantage of using a short-lived radionuclide is that the radiotracer must be synthesized shortly before injection in the patient.

A ⁶²Zn/⁶²Cu generator that produces ⁶²Cu from a longer-lived parent (⁶²Zn, t_{1/2} = 9.3 hours) has been developed. Delivery of the ⁶²Zn/⁶²Cu generator can be scheduled on the day of imaging, and thus the generator provides a practical means of producing this short-lived radionuclide on-site. Radio-synthesis kits have also been developed for rapid and convenient production of ⁶²Cu-ATSM and ⁶²Cu-PTSM from the generator. Together, these devices provide a convenient means for obtaining clinical hypoxia and perfusion PET scans during a single imaging session. Additional PET studies using other radiotracers, such as ¹⁸F-FDG (FDG), can be performed after the ⁶²Cu PET studies.

Materials and Methods

⁶²Cu-ATSM and ⁶²Cu-PTSM Synthesis

Copper-62 was produced using a ⁶²Zn/⁶²Cu generator (Proportional Technologies). A rapid synthesis kit (Proportional Technologies) was used to provide the radiolabeled ⁶²Cu-ATSM and ⁶²Cu-PTSM. The use of ⁶²Cu-ATSM and ⁶²Cu-PTSM for human studies was approved by the Duke Medical Center Radioactive Drug Research Committee. The generator (Fig. 1) was scheduled for delivery on the day of PET scanning.

Patients

For this preliminary clinical study, two patients with lung nodules (> 1 cm) suspicious for malignancy were enrolled. PET was performed to evaluate these lesions before surgical resection. The purpose of this research study was to determine the feasibility of imaging lung tumors using the ⁶²Zn/⁶²Cu generator and to compare the imaging findings with surgical pathology. The clinical protocol was approved by our institutional review board, and written informed consent was obtained from both patients. Regional PET images of the thorax were obtained using ⁶²Cu-ATSM and ⁶²Cu-PTSM. A routine clinical PET scan using FDG was also obtained in each patient for preoperative staging.

PET

Imaging was performed using a PET/CT scanner (Discovery ST, GE Healthcare) with a 16-MDCT unit. CT-based attenuation correction was used for all PET examinations. PET images were acquired in the 2D mode and were iteratively reconstructed using ordered subset

expectation maximization (OSEM) (30 subsets, 2 iterations) with a 50-cm-diameter field of view and 128×128 matrix.

Before PET, an unenhanced CT scan of the chest was obtained using automated tube current modulation (140 kVp; noise factor of 15; tube current range, 30–200 mA) while the patient suspended respiration in quiet end-expiration. CT was performed using a 3.75-mm slice thickness, a pitch of 1.375:1, table speed of 27.5 mm per rotation, and rotation time of 0.5 second, resulting in an acquisition time of < 10 seconds.

Subsequently, serial PET with ^{62}Cu -ATSM and ^{62}Cu -PTSM was performed over a single bed position to include the pulmonary nodule. Low-dose CT (5 mAs) was performed between the ^{62}Cu -ATSM and ^{62}Cu -PTSM emission studies for attenuation correction to reduce the effect of possible patient motion between scans. Dynamic PET acquisition was performed immediately after IV injection of each radiotracer (^{62}Cu -ATSM, ^{62}Cu -PTSM) in the following sequence (number of frames $\times$ time per frame): 12×10 , 4×30 , 3×120 , and 2×300 seconds. This resulted in a total acquisition time of 20 minutes after each injection. A minimum time interval of 50 minutes was mandated between injections of the two ^{62}Cu compounds to allow adequate decay and minimize background contamination between the hypoxia and perfusion images.

Semiquantitative measurement of ^{62}Cu -ATSM and ^{62}Cu -PTSM accumulation was performed using standardized uptake values (SUVs), which were calculated on the basis of patient total body weight by drawing regions of interest in normal tissues (i.e., lung and mediastinum) and in the lung nodules. For determining the SUV in the lung lesions, a 3D volume of interest was defined as the group of voxels centered around the voxel having $\geq 70\%$ of the maximum SUV.

In both patients, PET with FDG was also performed using our routine clinical protocol. In patient 1, FDG (0.147 mCi/kg [5.44 MBq/kg]) was injected immediately after the ^{62}Cu -ATSM and ^{62}Cu -PTSM scans, and FDG PET was performed 1 hour after FDG injection. Patient 2 had recently undergone FDG PET (i.e., 1 month before the ^{62}Cu -ATSM and ^{62}Cu -PTSM scans were obtained), so FDG PET was not repeated in that patient.

Both patients underwent surgical resection of their pulmonary nodules the day after the ^{62}Cu -ATSM and ^{62}Cu -PTSM PET studies were obtained. Patient 1 underwent right upper lobectomy, and patient 2 underwent left upper lobe wedge resection. Routine surgical pathology results were obtained of the pulmonary lesions and mediastinal lymph nodes.

Results

Data are presented about the first two patients imaged using the $^{62}\text{Zn}/^{62}\text{Cu}$ generator and the administered doses of ^{62}Cu -ATSM and ^{62}Cu -PTSM in Table 1. Our objective was to inject 5–10 mCi (185–370 MBq) (≈ 0.1 mCi/kg = 3.7 MBq/kg) of activity for each ^{62}Cu scan. The estimated effective dose equivalents from these administered doses were 0.2 rem (2 mSv) for ^{62}Cu -PTSM [5] and 0.1 rem (1 mSv) for ^{62}Cu -ATSM [6]. Because of the clinical schedule, patient 1 was imaged late in the day, and the administered dose of ^{62}Cu -PTSM was limited by ^{62}Cu availability from the generator but still provided satisfactory imaging. A new semiautomated generator system that provides convenient dose preparation in less than 2 minutes with minimal dose to the operator is now available. This updated system should provide 15- to 20-mCi (555- to 740-MBq) doses of both PTSM and ATSM at the end of the day.

Images from patient 1 are shown in Figure 2. The CT and corresponding FDG PET images are shown, along with steady-state ^{62}Cu -ATSM and ^{62}Cu -PTSM PET images obtained in the last 5 minutes of scanning. This patient had a small pulmonary nodule in the right upper lobe with

a maximum SUV (SUV_{max}) of 10.5, which is highly suspicious for malignancy. This lesion also showed high ^{62}Cu -ATSM and ^{62}Cu -PTSM accumulation, suggesting high perfusion and hypoxia. Surgical pathology results proved the mass was an adenocarcinoma.

Patient 2 had an irregularly shaped mass in the left lung (Fig. 3). This nodule also had high FDG accumulation ($SUV_{max} = 8.4$), which is suspicious for malignancy. In contrast to the lesion in patient 1, this lesion showed high ^{62}Cu -PTSM accumulation, suggesting perfusion, but low ^{62}Cu -ATSM uptake, suggesting that the lesion did not have significant hypoxia. At surgery, this mass proved to be necrotizing granulomatous inflammation with no evidence of malignancy.

Time-activity curves for ^{62}Cu -ATSM and ^{62}Cu -PTSM in the two patients are illustrated in Figure 4. The SUVs for both radiotracers are shown as a function of time for normal tissues (lung and mediastinum) and for the lung nodules. All tissues exhibit an initial spike related to the injection bolus, followed by a distribution phase toward steady state. The ^{62}Cu -ATSM scan for patient 2 (Fig. 4C) was shortened to 20 minutes because of patient discomfort. These dynamic studies show that steady-state distribution for these radiotracers is achieved at approximately 10 minutes after injection with little subsequent redistribution. Normal tissues typically achieved a steady-state SUV of 1 or less, whereas the pulmonary nodules with elevated ^{62}Cu -ATSM and ^{62}Cu -PTSM levels were observed to have SUVs in the range of 2–4.

Discussion

The results from dynamic PET acquisition suggest that the distribution of ^{62}Cu -PTSM and ^{62}Cu -ATSM does not change significantly 10 minutes after injection and that imaging between 10 and 20 minutes after injection reflects the steady-state distribution of these radiotracers. A reasonable imaging strategy is to acquire images for 5 minutes beginning 10 minutes after injection of ^{62}Cu -PTSM or ^{62}Cu -ATSM.

Of the first two patients imaged using ^{62}Cu -ATSM and ^{62}Cu -PTSM, one had malignancy and one had benign disease. As might be expected, the malignant lung nodule had high accumulations of FDG, ^{62}Cu -PTSM, and ^{62}Cu -ATSM. The second patient was found to have granulomatous disease, which is a well-recognized cause of false-positive FDG PET scans. In that case, the high FDG accumulation in the nodule was highly suspicious for malignancy. The high ^{62}Cu -PTSM accumulation suggested the presence of perfusion, but the lack of ^{62}Cu -ATSM accumulation suggested that there was no associated hypoxia in the lesion. In these two cases, the only radiotracer that distinguished benign from malignant disease was ^{62}Cu -ATSM. Although these findings are encouraging, more clinical data are clearly needed to determine the potential implications of multitracers studies and their ability to provide diagnostic and prognostic information.

Copper-ATSM radiotracers have been shown to accumulate preferentially in hypoxic regions of tumor [1]. Copper-PTSM agents have been used to image myocardial and cerebral perfusion [7,8] and blood flow in liver metastases from colorectal cancer [9]. Several copper radionuclides can be used for PET with these radiotracers [4]. To date, most clinical studies have used ^{60}Cu -ATSM. Dehdashti et al. studied 19 patients with non-small cell lung cancer [2] and 14 patients with cervical cancer [3] using ^{60}Cu -ATSM. These studies showed that the additional information provided by ^{60}Cu -ATSM PET scans could be predictive of tumor behavior. Chao et al. [10] showed the feasibility of coregistering ^{60}Cu -ATSM PET scans with CT for planning intensity-modulated radiation therapy treatment. This technique could allow higher radiation doses to be selectively delivered to the regions of the tumor that are most hypoxic and, therefore, that are most resistant to radiation therapy. The major disadvantage

of ^{60}Cu is limited availability because an on-site cyclotron is required to produce these radiotracers.

Copper-64 provides the highest spatial resolution of the copper radionuclides for PET because of its low initial positron energy. However, the beta emission and long half-life result in a relatively high local radiation dose, making ^{64}Cu radiotracers less desirable for clinical diagnostic studies. However, the high spatial resolution makes ^{64}Cu -ATSM and ^{64}Cu -PTSM well suited for imaging in animal experiments, and the beta emission from ^{64}Cu -ATSM could potentially be used to enhance local radiation therapy to hypoxic regions of tumor [11,12].

Using ^{62}Cu radiotracers for PET offers several advantages: The short half-life (9.7 minutes) allows multiple imaging studies to be performed and results in significantly less radiation dose to the patient compared with the other copper radionuclides. In this pilot study, we have shown the feasibility of obtaining ^{62}Cu -ATSM and ^{62}Cu -PTSM PET scans during a single imaging session; these scans independently provide information about hypoxia and perfusion, respectively. For these preliminary studies, we allowed at least 50 minutes (> 5 half-lives) between injections of the ^{62}Cu radiotracers to minimize crosstalk between the two PET scans. This time period could likely be reduced; in addition, the dose of the second ^{62}Cu radiotracer could be increased to further reduce the effect of the background activity from the first scan. In fact, we obtained a third PET scan with FDG in patient 1 immediately after the two ^{62}Cu studies because the 60-minute uptake period after FDG injection is more than adequate for decay of the ^{62}Cu signal.

The short half-life of ^{62}Cu mandates a practical means of producing and synthesizing these radiotracers immediately before injection. The concept of a $^{62}\text{Zn}/^{62}\text{Cu}$ generator was first developed by Robinson et al. [13] and was shown to be a practical means of producing ^{62}Cu -PTSM for clinical perfusion studies [14]. More recently, the $^{62}\text{Zn}/^{62}\text{Cu}$ generator and rapid radiosynthesis techniques for ^{62}Cu -ATSM and ^{62}Cu -PTSM have been refined and put into commercial production [5,14–16]. The generators can be scheduled for overnight delivery to arrive the day of imaging, making clinical studies with these agents a reality.

There are a few disadvantages associated with using ^{62}Cu radiotracers. Currently, $^{62}\text{Zn}/^{62}\text{Cu}$ generators are produced on an as-needed basis, and patients must be scheduled several days in advance of imaging. The generators are relatively expensive, and the 9.3-hour half-life of the parent ^{62}Zn limits the useful life of the generator to 1 day. These costs will significantly decrease if demand for the ^{62}Cu compounds increases to the point at which generators can be produced routinely. Per-patient costs could also be reduced by scheduling several patients for ^{62}Cu PET studies on the day of generator delivery. One generator will support 20 or more dose preparations during 1 day of use, and these doses can be produced at frequent intervals of 30–45 minutes between elutions.

Further investigation is needed to determine the efficacy of Cu-ATSM for imaging hypoxia compared with other radiotracers, such as ^{18}F -fluoromisonidazole and ^{18}F -EF5 (2[2-nitro- ^1H -imidazol-1-yl]- N -[2,2,3,3,3-pentafluoropropyl] acetamide). Our group has shown that the correlation of Cu-ATSM with hypoxia is tumor-dependent in rodent tumor models [17]. Similar findings were recently reported by Matsumoto et al. [18], who found differences between the distribution of ^{64}Cu -ATSM and ^{18}F -fluoromisonidazole for measuring hypoxia in a murine squamous cell carcinoma model.

In this preliminary clinical study, both ^{62}Cu -ATSM and ^{62}Cu -PTSM achieved steady-state distribution within 10–15 minutes after injection, and the short half-life of ^{62}Cu mandates early imaging. O'Donoghue et al. [19] compared early and late imaging of ^{64}Cu -ATSM with ^{18}F -fluoromisonidazole in rat tumor models. Although early imaging of ^{64}Cu -ATSM correlated with ^{18}F -fluoromisonidazole in the FaDu tumor model, ^{64}Cu -ATSM needed to be performed

much later (16–20 hours) to achieve a distribution similar to ^{18}F -fluoromisonidazole in the R3327-AT tumor model. One hypothesis to explain these differences is that the distribution of Cu-ATSM may be limited in certain tumors by reduced delivery of the radiotracer because of poor perfusion. Hypoxic regions within these tumors would not accumulate Cu-ATSM on earlier imaging (10–20 minutes after injection) but may become visible if imaged much later (16–20 hours after injection).

Correlation of Cu-ATSM images with Cu-PTSM images may be important to distinguish cases in which tumor perfusion is low compared with surrounding tissue, but high fractional uptake of Cu-ATSM that reaches the tumor is seen. In such cases, the tumor uptake of Cu-ATSM may not stand out relative to surrounding reference tissue, even in cases in which the tumor is quite hypoxic, so the ATSM/PTSM ratio may be a useful parameter. In view of these findings, the ability to perform both ^{62}Cu -ATSM and ^{62}Cu -PTSM imaging during the same session becomes a significant advantage.

Conclusion

Hypoxia and perfusion are important parameters in tumor physiology and can have major implications in diagnosis, prognosis, treatment planning, and response to therapy. We have shown the feasibility of performing ^{62}Cu -ATSM and ^{62}Cu -PTSM PET together with ^{18}F -FDG PET/CT during a single imaging session to provide information about perfusion and hypoxia and about tumor anatomy and metabolism. Serial imaging with the short-lived ^{62}Cu radiotracers is possible because of the development of a $^{62}\text{Zn}/^{62}\text{Cu}$ generator and rapid synthesis kits. Another advantage of using short-lived radionuclides is the ability to perform imaging both before and immediately after a therapeutic intervention, such as hyperthermia, to measure the acute effects of treatment on hypoxia; the results of a 2006 study by Myerson et al. [20] in a rodent tumor model using ^{64}Cu -ATSM suggest potential utility in this application.

We have shown the feasibility of using generator-produced ^{62}Cu -ATSM and ^{62}Cu -PTSM for clinical PET. Data from the first two patients enrolled in a preclinical pilot study are presented, and the PET findings are correlated with surgical pathology. We are encouraged by these preliminary results, although further investigation is needed to determine the potential value of these radiotracers in diagnosis, prognosis stratification, and treatment planning of patients with lung and other neoplasms.

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Fig. 1. Photograph shows $^{62}\text{Zn}/^{62}\text{Cu}$ generator with synthesis kits for production of ^{62}Cu -ATSM (Cu-diacetyl-bis[N⁴-methylthiosemicarbazone]) and ^{62}Cu -PTSM (Cu-pyruvaldehyde-bis[N⁴-methylthiosemicarbazone]).

Fig. 2.

71-year-old woman with adenocarcinoma (patient 1).

A, Axial CT scan shows 1.6×1.2 cm right upper lobe pulmonary nodule.

B–D, Corresponding axial PET images obtained using ^{18}F -FDG (**B**), Cu-pyruvaldehyde-bis(N^4 -methylthiosemicarbazone) (^{62}Cu -PTSM) (**C**), and Cu-diacetyl-bis(N^4 -methylthiosemicarbazone) (^{62}Cu -ATSM) (**D**) show high accumulation of all three radiotracers in lesion.

E, Photomicrograph of surgical pathology specimen reveals moderately differentiated adenocarcinoma with acinar and papillary features. (H and E, $\times 100$)

Fig. 3.

58-year-old man with granuloma (patient 2).

A, Axial CT scan shows spiculated 2.8×1.8 cm left upper lobe pulmonary nodule.

B, Corresponding axial PET images obtained using ^{18}F -FDG (**B**), Cu-pyruvaldehyde-bis (N^4 -methylthiosemicarbazone) (^{62}Cu -PTSM) (**C**), and Cu-diacetyl-bis(N^4 -methylthiosemicarbazone) (^{62}Cu -ATSM) (**D**) show high accumulation of FDG and PTSM but relatively low ATSM accumulation in nodule.

E, Photomicrograph of surgical pathology specimen shows necrotizing granuloma with prominent giant cell response and no evidence of malignancy. (H and E, $\times 100$)

Fig. 4.

Copper-diacetyl-bis(N^4 -methylthiosemicarbazone) (^{62}Cu -ATSM) and copper-pyruvaldehyde-bis(N^4 -methylthiosemicarbazone) (^{62}Cu -PTSM) time-activity curves. Representative regions of interest in lung and mediastinum were also evaluated. Steady-state distribution is achieved 10–15 minutes after injection for both radiotracers.

A and B, Standardized uptake values (SUVs) for ^{62}Cu -ATSM (**A**) and ^{62}Cu -PTSM (**B**) in adenocarcinoma (patient 1).

C and D, SUVs for ^{62}Cu -ATSM (**C**) and ^{62}Cu -PTSM (**D**) in granulomatous disease (patient 2).

TABLE 1

Patient Data

Characteristics	Patient 1	Patient 2
Sex	F	M
Age (y)	71	59
Weight (kg)	70.5	65.5
Surgical pathology	Adenocarcinoma	Granuloma
^{18}F -FDG SUV _{max}	10.5	8.4
^{62}Cu -PTSM		
Administered dose (MBq)	141 ^a	329 ^b
SUV		
Tumor	3.63	1.73
Mediastinum	0.88	1.01
Lung	0.99	0.58
^{62}Cu -ATSM		
Administered dose (MBq)	255 ^c	307 ^d
SUV		
Tumor	2.71	1.00
Mediastinum	1.02	1.06
Lung	0.36	0.24

Note—For copper-pyruvaldehyde-bis(N⁴-methylthiosemicarbazone) (^{62}Cu -PTSM) and copper-diacetyl-bis(N⁴-methylthiosemicarbazone) (^{62}Cu -ATSM) studies, standardized uptake values (SUVs) based on total body weight were measured 20 minutes after radiotracer injection. SUV_{max} = maximum standardized uptake value.

^a 2 MBq/kg.

^b 5 MBq/kg.

^c 3.6 MBq/kg.

^d 4.7 MBq/kg.