Clinical PET Imaging using Cu-62 ATSM:

Feasibility of Hypoxic Imaging for Malignant Tumors and Cerebral Ischemic Diseases

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Introduction

Copper-ATSM, one of the tracers for hypoxic imaging, is reported to be useful for evaluation of tumor hypoxic tissues and ischemic changes in vascular diseases.

To evaluate feasibility of this new probe for clinical PET studies, images of $[^{62}\text{Cu}]\text{ATSM}$ were compared with $[^{18}\text{F}]\text{fluoro-deoxyglucose (FDG)}$ PET and other conventional PET studies.
I. Basics of Cu–ATSM
**Cu-ATSM**: diacetyl-bis(N⁴-methylthiosemicarbazone)

**Cu-PTSM**

**Cu-ATSM**

Artery

Cell

microsome

Tumor

Retention

Brain Heart

Retention of Cu-ATSM in various tissues:

- Artery
- Cell
- Tumor
- Brain
- Heart

Chemical Structures:

- Cu-PTSM
- Cu-ATSM

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Microvascular Density vs. Accumulation

Tanaka T et al., Nucl Med Biol. 2006
Clinical PET with Cu-ATSM
(University of Fukui)

Malignant Tumors
- Lung cancer: 16
- Head and neck cancer: 22
- Brain disease: 15
- Heart disease: 4
- Normal volunteer: 6

Cu-62 can be eluted every 50-60 min.

ATSM

Glycine

Delivery from NIRS

$^{62}$Zn/$^{62}$Cu Generator

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II. Imaging of Hypoxic Tumors
Clinical Application of Cu-ATSM (Tumors)

Malignant tumors:


Hypoxic tumor mapping for radiation:


Internal radiotherapy:

- Basic animal studies (PNAS 2001; Cancer Research 2003)
II Tumor study

Lt. Maxillary ca. (Pre-treatment)

CT

PET

Fusion
FDG: gray
Cu-ATSM: color

\[ y = -0.07x + 2.83 \]
\[ r^2 = 0.41 \]
II Tumor study

Lt. Maxillary ca. (Post-treatment)

PET (Cu-ATSM)

MRI

Coronal view

Sagittal view
Hard palate cancer (76M)

Yellow and red lines on CT image indicate high uptake areas for FDG and Cu-ATSM.

Stage IV SCC T4N2M0

Hard palate cancer

Kudo et al. Poster No. 1500 (55th SNM Annual Meeting)
SUV values for all Head & Neck Tumors

FDG Cu-ATSM Fusion

Slope = -0.26 ± 0.28
Correlation coefficient = 0.45 ± 0.24 (p < 0.001)

N = 22

% SUV values (SUVROI / SUVmax x 100)
Summary: Cu-ATSM PET for Malignant Tumors

Accumulation of Cu-ATSM would be able to visualize hypoxic, slow growing regions of the tumors, that represents resistant tumor tissue to various therapies. This information would be useful for clinical diagnosis to predict prognosis of patients before treatment.
Imaging Method for Cerebral Study

Cu-ATSM ($\sim$500MBq)

Transmission (10 min)

Emission (Dynamic scan)
(10 sec x 12; 60 sec x 8; 5 min x 2)

Early phase
(0 - 3 min)

CBF image

Delayed phase
(10 - 20 min)

Retention image
Low – moderate accumulation = viable
High accumulation = critical (electron-rich)

Assessment of viability?
Chronic Ischemia (57F, Lt. MCAS)

**MR**
- MRA

**PET**
- $^{15}$O-PET
  - CBF
  - CMRO$_2$
  - OEF

III Brain study
Chronic Ischemia (Lt. MCAO)

**MR**
- FLAIR

**PET**
- $^{15}$O-PET
  - OEF
  - Early
- $^{62}$Cu-ATSM
  - Delayed
  - Delayed/Early

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Acute-Subacute Stroke (54M)

MR
- MRA
- DWI
- T2WI

PET
- $^{62}$Cu-ATSM
  - Early
  - Delayed
  - Delayed/Early

Low
- Brain study

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Acute-Subacute Stroke (follow-up)

III Brain study

MRA

3 months

DWI

T2WI

FLAIR

T2WI
III  Brain study

**MELAS (43F, acute-subacute-chronic strokes)**

<table>
<thead>
<tr>
<th>MRI</th>
<th>PET</th>
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<tbody>
<tr>
<td>DWI</td>
<td>$^{62}$Cu-ATSM (delayed retention)</td>
</tr>
<tr>
<td>T2WI</td>
<td>$^{18}$F-FDG (glucose)</td>
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</tbody>
</table>

Early (CBF)

**Brain study**
### Summary of PET findings

<table>
<thead>
<tr>
<th>Phase</th>
<th>18F-FDG (glucose)</th>
<th>62Cu-ATSM delayed phase (retention)</th>
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</thead>
<tbody>
<tr>
<td><strong>Acute (reperfused)</strong></td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td><strong>Subacute</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viable</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td>↘</td>
<td></td>
</tr>
<tr>
<td>Chronic infarction</td>
<td>↓↓</td>
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Cu-ATSM can predict critical damage of ischemic change.

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Summary

Tumors

- High retention → hypoxic, slow growing
  - = viable & resistant

Brain (, Heart)

- Moderate retention → viable and reversible
- High retention → critical & irreversible damage
Conclusion

Cu-ATSM PET is a promising method for clinical diagnosis by representing hypoxic resistant tumors to predict prognosis and effects of treatments, as well as differentiating viable regions from critical and irreversible damage in the ischemic vascular disease.
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