Imaging of Tumour Hypoxia - which Tracer to Use?

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Preclinical Imaging

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Why is Hypoxia Important?

- failure of radiotherapy
- resistance to chemotherapy
  - lower proliferation and lower drug concentration
- predispose more malignant phenotype
- more likely to be metastatic
“The Ideal Hypoxia Tracer”

High specificity for hypoxia
Low non-specific binding (background uptake)
Fast clearance of non-specifically bound radioactivity
† High contrast PET images

Metabolic degradation undesirable
† Radiolabelled metabolites might participate in unknown biochemical processes…

Nitroimidazoles

**1953:** 2-Nitroimidazole (Azomycin) naturally occurring antibiotic effective against bacteria thriving in a hypoxic environment

(Maeda et al, J Antibiot 1953)

† Several antibiotics; e.g Metronidazole, Ornidazole

**1973:** Investigations of their utility as radiosensitizers in order to increase therapy response

(Adams, Br Med Bull 1973)

† Limited use due to neurotoxicity!

**1979:** Nitroimidazoles proposed to be used as tracers for imaging techniques (PET and SPECT)


† Tracer development started
Mechanism of Nitroimidazoles

Reduction of nitrogroup $\rightarrow$ irreversible binding to macromolecules

$pO_2$ dependent metabolism

Lipophilicity $\rightarrow$ Pharmacokinetics

Side chain determines pharmacological properties!
Strong pre-clinical documentation of hypoxia-specific binding

Large clinical experience

T/B uptake ratios $\geq 1.4$ at 2 hrs or more considered as indicative of hypoxia.

Rasey et al. *Int J Radiat Oncol Biol Phys* 1989

Why then Evaluate other Tracers?

- Slow accumulation in hypoxic tumours
- Low target-to-background contrast
- Significant amount of metabolite products
$^{18}$F-Labelled PET Tracers

- $[^{18}$F$]$FMISO
- $[^{18}$F$]$FAZA
- $[^{18}$F$]$EF5
Other/New Tracers

- $[^{18}\text{F}]\text{FETNIM}$
- $[^{18}\text{F}]\text{FETA}$
- $[^{18}\text{F}]\text{EF3}$
- $[^{64}\text{Cu}]\text{ATSM}$
- $[^{18}\text{F}]\text{HX4}$
## Pharmacology & Experience

Partition coefficient ($P \neq \log P$)

<table>
<thead>
<tr>
<th>Octanol / Water ($\log P$)</th>
<th>FMISO</th>
<th>FAZA</th>
<th>FETNIM</th>
<th>EF5</th>
<th>EF3</th>
<th>FETA</th>
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<tr>
<td>0.40</td>
<td>0.04</td>
<td>0.17</td>
<td>0.60</td>
<td>0.10</td>
<td>0.16</td>
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<td>50%</td>
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<table>
<thead>
<tr>
<th>Metabolites (2h Blood)</th>
<th></th>
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### Available Tracers

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Availability</th>
<th>Experience</th>
<th>Pubmed Total</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>$^{18}$F-FMISO</td>
<td>J</td>
<td>J</td>
<td>42</td>
<td>21</td>
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<tr>
<td>$^{18}$F-FAZA</td>
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<td>L</td>
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<td>15</td>
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<td>$^{18}$F-EF5</td>
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<td>K</td>
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<td>$^{18}$F-FETNIM</td>
<td>J</td>
<td>K</td>
<td>4</td>
<td>2</td>
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</tbody>
</table>
Effect of Lipophilicity on Biodistribution

- $[^{18}\text{F}]\text{FMISO}$ \( \log P = 0.43 \)
- $[^{18}\text{F}]\text{FETNIM}$ \( \log P = 0.17 \)
- $[^{18}\text{F}]\text{EF5}$ \( \log P = 0.6 \)

Summary I

Several tracers in use and new ones are synthesized and evaluated
- preclinical and clinical settings
- different types of tumours
- challenging to compare

Different pharmacological properties
(metabolism, background uptake)
- some tracers clearly more ideal than others

Nitroimidazoles are useful as PET hypoxia tracers
- oxygen dependent accumulation in hypoxic tumours

BUT...
Radiotherapy Planning

- PET/CT and FDG increasingly used for treatment planning
- Application of hypoxia imaging with PET
  ‡ requires a fundamental understanding of the biological processes that affect the uptake of a PET tracer.

Validation of Hypoxia Tracers!
Tumour Heterogeneity

Voxel-by-voxel in 18 primary and metastatic HNSCC at 3h p.i.

High perfusion with good oxygenation

Intermediate

Low perfusion with low oxygenation

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Repetitive Hypoxia Imaging

Future challenges:
- Hypoxia image based RT planning?
- Intense Modulated Radiation Therapy?

Molecular mechanisms behind uptake of hypoxia tracers need to be validated!
Thank you!

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