FAZA-PET Imaging for Tumour Hypoxia

Doug Vines BSc, MRT(N), CNMT, PET, CTIC

Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network.
Techna Institute, STTARR Innovation Centre, and Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada.
I do not have a financial interest, arrangement or affiliation including receipt of honoraria or expenses with a commercial organization that may have a direct interest in the subject matter of my presentation.
Disclosure

$^{18}$F-FAZA ($^{18}$F-Fluoroazomycin arabinoside):

- is not approved by Health Canada (HC) for commercial use.
- it is an investigational product that can only be used under both a HC and institutional REB approved clinical trial.
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Objectives

1. To briefly describe the use of FAZA-PET imaging in cancer.

2. To compare FAZA scan methodologies for different disease types.

3. To summarize methods of FAZA image analysis techniques to determine the hypoxic fraction.
Introduction

Hypoxia:

- lower oxygen levels in solid tumours; biochemical, cellular, microregional, or whole tumour.
- oxygen partial pressure = pO$_2$

<table>
<thead>
<tr>
<th></th>
<th>% O$_2$</th>
<th>mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>21</td>
<td>160</td>
</tr>
<tr>
<td>N tissue</td>
<td>5-9</td>
<td>40-75</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>&lt; 3</td>
<td>0-20</td>
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</table>

[Koch, Evans. Semin NM 2015]
Hypoxia:

- is a negative prognostic factor in cancer

Measurement (direct)

- old “gold standard” = polarographic needle pO2 probe

Limitations of polarographic probe:
1. invasive, difficult access
2. small area, not whole tumour

[Bill McBride, UCLA Dept.Rad.Onc.]
Introduction

PET-CT imaging:

- non-invasive, image whole tumour in 3D
- PET provides quantitative measurements

$^{18}$F-Fluoroazomycin arabinoside (FAZA)

- 2nd generation PET radiotracer to image hypoxia
- compares with hypoxia from histology
History: STTARR Innovation Centre

www.sttarr.ca

Image mice with human derived tumour implants (xenograft)
Mouse FAZA uPET-CT
Dynamic FAZA-PET (0-140 min)
Pancreatic Cancer Xenografts: Comparing *in vivo* uPET image with ex vivo AR / histology

<table>
<thead>
<tr>
<th></th>
<th>In vivo PET</th>
<th>Autoradiography</th>
<th>EF5 / Hoechst</th>
<th>PET Image Histogram (Hypoxic Volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCIP19</td>
<td><img src="image1.png" alt="PET Image" /></td>
<td><img src="image2.png" alt="Autoradiography" /></td>
<td><img src="image3.png" alt="EF5 / Hoechst" /></td>
<td><img src="image4.png" alt="Histogram" /></td>
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<td><img src="image6.png" alt="Autoradiography" /></td>
<td><img src="image7.png" alt="EF5 / Hoechst" /></td>
<td><img src="image8.png" alt="Histogram" /></td>
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<td><img src="image10.png" alt="Autoradiography" /></td>
<td><img src="image11.png" alt="EF5 / Hoechst" /></td>
<td><img src="image12.png" alt="Histogram" /></td>
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</tbody>
</table>

[Trevor McKee]
Histologic tumour section

A= Hypoxia pimonidazole (green)  Perfusion Hoechst (blue)

B= 6 x 5mm²

C

D

E 1 mm blur

F 5 mm blur

[Carlin, Humm. JNM 2012]
Typical PET voxel size for a 192 matrix is 2.6 x 2.6 x 3.3 mm (x,y,z), larger than CT
PET imaging

Absolute quantitative measurement of the radiotracer in tissue = kBq/mL

Semi-quantitative measure:
Standardized Uptake Value = SUV

\[
SUV = \frac{\text{tracer in tissue} \ (Bq/ml)}{\text{inj. dose} \ (Bq) / \text{weight} \ (g)}
\]
FAZA Lung

Same patient (diff Depts) 1 month apart

FAZA (120min)  
SUVmax = 1.5  
FAZA has a much lower tumour-to-bkgd ratio than FDG

FDG (60min)  
SUVmax = 5.6
FAZA imaging

Current imaging/disease sites:
- pancreas 33, cervix 49, lung 22, prostate 11, melanoma 11
- total = 126 patients, future: head & neck, esophageal

Protocol

- Pt. prep
  - NPO
  - hydration

- FAZA inj
  - weight based (5.2 MBq/kg)
  - dynamic
  - static
  - post-inj hydration

- PET-CT
  - dynamic, static @120 min
  - scout
  - CT for AC
  - PET (list mode)
  - optional 4DCT (motion)
FAZA imaging

Pancreas:

Prep: hydration 2hr prior

Injection: arms up angio, qs to 7mL, start scanner, infuse over 10-15s

Scan: dynamic 1 FOV, static 2 FOV (30m) resp gated PET, 4DCT
Scout:
use BB's or mark on the landmark for re-positioning
CTAC: 1 FOV (14.7 cm) dynamic
[Metran-Nascente et al, JNM 2016]
FAZA imaging

Cervix:

Prep: hydration 2hr prior

Injection: butterfly or angio, hydration 10mL/kg within 15 min

Scan: static 2 FOV (20m), repeat CTAC after PET, LV CTAC & 5m PET
CT1: bladder not empty

CT2: repeat CT after void

CT1 week 2: bladder empty
Max Int Proj (MIP)  
single slice (3.3 mm)

FAZA LV

1 FOV  
5 min  
static
FAZA imaging

**Lung:**

- Prep: hydration 2hr prior
- Injection: arms up angio, qs to 7mL, start scanner, infuse over 10-15s
- Scan: dynamic 1 FOV, static 2 FOV (20m) resp gated PET, 4DCT

Time [Min]

- 0
- 20
- 120
FAZA Lung

MIP image, patient with RLL tumour (scale SUV = 3.5)

2 FOV (26.8 cm) 20 min static
It appears there are differences in the spatial distribution of hypoxia within the tumour.
Image Analysis

FAZA images: what is hypoxic? how to measure it?

Tumour-based: $T$-to-$bkgd$ ratios = $T/B$ or $T_{max}/B_{mean}$

what is $bkgd$? non-hypoxic reference tissue; blood or muscle

Voxel-based:

hypoxic volume = volume of $T$ voxels that are deemed hypoxic
hypoxic fraction = fraction of $T$ voxels that are deemed hypoxic

All methods require a classification threshold, it varies in the literature: $>1.2-1.5$ for each voxel, or whole tumour
Hypoxic Fraction:

- Calculated based on method of Mortensen et al. 2012, with pooling of patient's muscles (M) SUV_{mean}.
- Hypoxic threshold = M SUV_{mean} + 3(all M standard dev).

Image Analysis

Hypoxic Fraction = area > threshold in %

Pancreas

[SUV_{muscle}]

[Metran-Nascente et al, JNM 2016]
Image Analysis

Thresholds for hypoxic fraction:

**Noise-based** threshold *(pooled patients)* Mortensen et al 2012
Threshold = \( \text{avg}_{\text{non-hypoxic}} + 3 \times \text{pooled sd}_{\text{non-hypoxic}} \)

**Noise-based** threshold *(individual patient)*
Threshold = \( \text{avg}_{\text{non-hypoxic}} + 3 \times \text{sd}_{\text{non-hypoxic}} \)

**Noise-independent** *(fixed)* threshold
Threshold = \( \text{avg}_{\text{non-hypoxic}} \times 1.4 \)
Image Analysis

Cervix: non-hypoxic reference (glut max muscle)

Tumor (T) contours (Rad Onc)
Calculate $\frac{\text{T}}{\text{M}}$ ratios from $\text{SUV}_{\text{max}}$ (T) and $\text{SUV}_{\text{mean}}$ (Muscle)
Muscles are variable

Variability between patients

10 Cervix patients, 11 different muscles

Variability between different muscles

[Tina Shek]
Blood as non-hypoxic reference

- 18 FAZA Lung scans
- How is FAZA uptake in muscle related to FAZA in blood?
- FAZA concentrations in blood and muscle are correlated

[Brandon Driscoll]
Image Analysis

Cervix: non-hypoxic blood (LV and aorta)

Compare blood sample (gold standard) to image-derived blood (LV) values.
Blood Analysis

- pipette triplicate samples
- measure in \( \gamma \) well counter
- convert cpm to kBq/mL

- standards of known \( ^{18} \text{F} \) concentration to create a standard curve

\[
\text{blood} = \text{kBq/mL} \\
\text{image-derived} = \text{kBq/mL}
\]

validate image (LV) data
18F-FAZA PET-CT precision and accuracy of image-derived blood surrogate reference values.

SNMMI: Sunday June 11, 2017 in Denver

D.C. Vines, B.D. Driscoll, H. Keller, T. Shek, K. Han, D.A. Jaffray
Future

1. Outcome analysis (survival times) of hypoxic patients (tumour and/or nodes) for the cervix and lung studies.

2. Pancreas study: 30 patients with FAZA imaging data pre-surgery to evaluate and correlate with resected tumour histology.
FAZA-PET imaging has been shown to be useful for tumour hypoxia assessment.

The FAZA imaging protocol depends on the disease site.

FAZA image analysis methods for hypoxia determination are still an active area of research.
References


