PET and SPECT Tracers for Diagnosis and Management of Primary Brain Tumors

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Wolfson Molecular Imaging Centre
Manchester, UK
SNM Annual Meeting, New Orleans
June 14, 2008

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# Glioma Grades and Prognosis

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Median survival</th>
<th>Histological types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cure possible</td>
<td>Pilocytic astrocytoma (children)</td>
</tr>
<tr>
<td>2</td>
<td>10-16 years</td>
<td>Oligodendroglioma</td>
</tr>
<tr>
<td>2</td>
<td>6-8 years</td>
<td>Astrocytoma</td>
</tr>
<tr>
<td>3</td>
<td>3 years</td>
<td>Anaplastic Astrocytoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaplastic Oligodendroglioma</td>
</tr>
<tr>
<td>4</td>
<td>3-24 months</td>
<td>Glioblastoma</td>
</tr>
</tbody>
</table>
Incidence of CNS tumors

Figure 1.1: Numbers of new cases and age specific incidence rates, by sex, brain and other CNS tumors, UK 2003

Low-grade gliomas are among the most frequent tumors in young adults.
Tracers

- **Glucose metabolism**
  - FDG PET: Grading, localization of malignant parts, tumor vs. necrosis

- **Blood flow/volume and ion transport**
  - O-15-water/CO, 99m-Tc-HMPAO
  - 99m-Tc-ECD, 82Rb, 201Tl

- **Amino acids**: Activated transport even in 70% of low-grade tumors; monitoring of therapy and progression; detection of recurrent tumor (vs. necrosis)
  - PET: C-11-methionine, F-18-fluoro-ethyltyrosine (FET), FDOPA, F-18-fluorotyrosine (F-TYR)
  - SPECT: I-123-Iodo-methyltyrosine (IMT)

- **Proliferation markers**: C-11-thymidine, F-18-fluorothymidine (FLT)

- **Intermediary metabolism**: C-11 or F-18-labeled choline and acetate

- **Hypoxia**: F-18-fluoro-misonidazole (FMISO)
Indicators of malignant degeneration

Vascular changes
- Increase of vascularity
  - Endothelial activation: Amino-Acid PET/SPECT
  - Blood volume and blood flow:
    • Dynamic CT, perfusion/diffusion-weighted MRI
    • SPECT, PET
  - BBB breakdown
    • MRI/CT contrast enhancement

Cellular changes
- Increase of glycolysis
  - FDG PET
  - MRS: lactate
- Change of lipid metabolism
  - PET: C11/F18 choline, acetate
  - MRS: increase of choline, altered phospholipid signal
- Increase of cellular proliferation rate
  - Nucleoside PET (requires BBB damage for uptake)
High FDG uptake in lymphoma
FDG PET in Glioblastoma

MRI  Fusion  PET
FDG uptake and prognosis in glioblastoma

Hölzer et al.

JCAT, 1992

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Differentiation of necrosis versus recurrent tumor

Large necrosis without significant glucose metabolism

Small, metabolically active recurrent tumor

MRI fusion FDG PET

MPICologne
Studies on differentiation between recurrent tumor and radionecrosis

<table>
<thead>
<tr>
<th>Tracer</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Lesion type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG</td>
<td>47</td>
<td>75%</td>
<td>81%</td>
<td>Malignant tumor</td>
<td>Chao, 2001</td>
</tr>
<tr>
<td>FDG</td>
<td>15</td>
<td>43% (6/14)</td>
<td>100% (1/1)</td>
<td>Glioma</td>
<td>Thompson, 1999</td>
</tr>
<tr>
<td>FDG</td>
<td>84</td>
<td>73%</td>
<td>56%</td>
<td>Malignant tumor</td>
<td>Ricci, 1998</td>
</tr>
<tr>
<td>FDG</td>
<td>38</td>
<td>88% (15/17)</td>
<td>81% (17/21)</td>
<td>Glioma</td>
<td>Valk, 1988</td>
</tr>
<tr>
<td>FDG</td>
<td>21</td>
<td>81% (13/16)</td>
<td>40% (2/5)</td>
<td>Tumor</td>
<td>Kahn, 1994</td>
</tr>
<tr>
<td>FDG</td>
<td>9</td>
<td>80% (4/5)</td>
<td>100% (4/4)</td>
<td>Tumor</td>
<td>Ogawa, 1991</td>
</tr>
<tr>
<td>FDG</td>
<td>21</td>
<td>64% (9/14)</td>
<td>71% (5/7)</td>
<td>Metastases</td>
<td>Ericson, 1996</td>
</tr>
<tr>
<td>FDG</td>
<td>54</td>
<td>83% (5/6)</td>
<td>96% (46/48)</td>
<td>Metastases</td>
<td>Belohlavek, 2003</td>
</tr>
<tr>
<td>MET</td>
<td>12</td>
<td>100% (5/5)</td>
<td>86% (6/7)</td>
<td>Glioma</td>
<td>Sonoda, 1998</td>
</tr>
</tbody>
</table>

With histopathological verification in all cases
Hpermetabolism in complex focal seizure with clouded consciousness and involuntary movements of right arm

Intracerebral hemorrhage probably due to amyloid angiopathy

MPI Cologne
FDG PET for brain tumours

• Diagnosis of lymphoma (very high uptake)
• Detection and localisation of malignant gliomas
  – Selection of target point for biopsy to maximise diagnostic yield
  – Recurrent high-grade tumour (vs. necrosis)
  – Malignant degeneration of low-grade glioma
Limitations for using increased FDG uptake as indicator of malignancy

• High glucose metabolism in normal grey matter
  – Dependent on neuronal function
  – Further increase in focal epilepsy
• Glycolytic activity of macrophages
  – Wide range of glucose metabolism in inflammatory lesions
• Tumor uptake not strictly related to malignancy
  – Higher uptake in oligodendroglioma than in astrocytoma
  – High uptake in some benign tumours: Schwannomas, rapidly growing meningiomas
  – Low uptake in some malignant lesions: Micronecrosis in GBM, metastasis
Amino acid tracers

• Transport only
  – by large neutral amino acid carrier (L-type)
    • F-18-fluoro-ethyltyrosine (FET)
    • SPECT: I-123-Iodo-methyltyrosine (IMT)
  – by asymmetric carrier (A-type)
    • aminoisobutyric acid, ACPC

• Transport and complex metabolism
  – C-11-methionine
  – F-18-Fluoro-DOPA

• Transport and protein incorporation
  – C-11 tyrosine, leucine
  – F-18-fluorotyrosine (F-TYR)
C-11-Methionine Uptake is related to Histological Grade and Tumor Type

Results in 83 untreated and histologically verified gliomas

<table>
<thead>
<tr>
<th>Glioma Type</th>
<th>WHO-grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Astrocytoma (including glioblastoma)</strong></td>
<td>2.0±0.6 (2)</td>
</tr>
<tr>
<td><strong>Oligoastrocytoma</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.8±0.4 (14)</td>
</tr>
<tr>
<td><strong>Oligodendrogliaoma</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5±0.5 (6)</td>
</tr>
</tbody>
</table>

ASTROCYTOMA
grade 2:
MRI and
C-11-
methionine
PET

MPI
Cologne

transaxial  coronal  sagittal
Recurrent astrocytoma (grade 2):

Preoperative fusion of MRI and methionine PET
Integrated positron emission tomography and magnetic resonance imaging–guided resection of brain tumors: a report of 103 consecutive procedures

Benoît Pirotte, M.D., Serge Goldman, M.D., Ph.D., Olivier Dewitte, M.D., Ph.D., Nicolas Massager, M.D., David Wikler, M.S., Florence Lefranc, M.D., Nordeyn Oulad Ben Taib, M.D., Jacques Brotchi, M.D., Ph.D., and Others.

Departments of Neurosurgery, Neuropsychology, and Neuroradiology, Unit, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

TABLE 5
Contribution of PET scanning guidance to tumor resection in 103 procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Total No. of Cases</th>
<th>Focused Resection</th>
<th>Extended Resection</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET-PET</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGG</td>
<td>59</td>
<td>13 (22)</td>
<td>39 (66)</td>
<td>52 (88)</td>
</tr>
<tr>
<td>HGG</td>
<td>23</td>
<td>8 (35)</td>
<td>10 (43)</td>
<td>18 (78)</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGG</td>
<td>4</td>
<td>0 (0)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>HGG</td>
<td>17</td>
<td>11 (65)</td>
<td>1 (6)</td>
<td>12 (71)</td>
</tr>
</tbody>
</table>
Astrocytoma Grade II: 
Relation between C-11-methionine and tumor cell density

Low cellularity in area with low methionine uptake

High cellular and vascular density in area with increased uptake of methionine
High uptake of C-11-methionine in glioma infiltration zone

astrocytoma WHO grade III

Growth of Glioblastoma

C-11-methionine after tumor resection

C-11-methionine follow-up day 141

FDG day 140

"hot spot" in FDG corresponds to new tumor
Non-responding Anaplastic Oligoastrocytoma after Therapy with ACNU and PCV

C-11-methionine PET

MRI and PET scans showing T1, T2, and C-11-methionine positron emission tomography (PET) images. The images were acquired at MPI/Uni Cologne.

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Evaluation of glioma chemotherapy by C-11-methionine

• Case report: Continuous decline with PCV in oligoastrocytoma (Herholz et al., 2003)

• Responses to 6 cycles of PCV in oligodendroglialoma (n=7, Tang et al., 2005)

• Response after 3 cycles of temozolomide in malignant glioma predicts outcome (n=15, Galldiks et al., 2006)
Recurrent Oligoastrocytoma (now grade 3)

High uptake of C-11-methionine before chemotherapy

Reduction of uptake after 3 cycles temozolomide

MPI/Uni Cologne

Galldiks et al., EJNMMI, 2006

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Decline of Methionine Uptake during Successful Chemotherapy of Anaplastic Oligoastrocytoma

Herholz K et al. (2003) Journal of Neuroimaging, 13, 269-271
Amino acid tracers for gliomas

**Strengths**
- Increased uptake even in most low-grade gliomas
- Clinically useful for
  - Planning and monitoring of therapy
  - Location of most active tumor parts
  - Study of infiltration

**Limitations**
- Not strictly tumor-specific (but still better than FDG)
- Less informative for grading and prognosis than FDG
- Often little uptake in metastases and lymphoma
Thymidine (TdR) and Fluorthymidine (FLT)

While in normal cells TK1 activity is about 10-fold increased only during the DNA synthetic phase, in malignant cells there is a higher and permanent increase of TK1 activity.

In cell culture experiments, FLT uptake correlated well with percentage of cells in S-Phase and TK1 activity in most cell lines, although some cell lines appear to use the TK1-independent salvage pathway for DNA synthesis.

Krohn et al., 2005
Glioblastoma

FLT uptake in contrast enhancing area

Uptake of C-11-methionine extends into infiltration zone

Jacobs et al., JNM, 2006
Recurrent glioblastoma

Jacobs et al., 2006
Correlation between FLT uptake and proliferation index in high-grade glioma

Ullrich et al., Clinical Cancer Research, 2008
Thymidine tracers for brain tumors

Strengths

• Probably most closely linked to proliferation
• Potential for therapy monitoring
• Good target to background signal in malignant gliomas

Limitations

• Uptake dependent on BBB breakdown (very small with intact BBB)
• Unspecific uptake in areas with BBB damage
• Measuring primarily TK1 activity with correlates with proliferation rates in some but not in all tumors
Imaging brain tumor receptors

• Pituitary adenomas (monitoring of therapy)
  – D2 receptors (e.g., by C-11-raclopride, C-11-methylspiperone)
• Meningiomas (esp. recurrent tumors, therapy planning)
  – Somatostatin analogues (Ga-68-DOTATOC, F-18 labelled octreotide analogues)
  – Steroid receptors (F-18 labelled oestrogen and progestin radiopharmaceuticals)
• Growth factor receptors
  – Labeled macromolecules (F-18, Ga-68, Cu-64, I-124) in development
Imaging of gene transfer

- Use of substrates for transferred genes, e.g. 2’-fluoro-2’-deoxy-1-β-D-arabinofuranosyl-5-124I-iodo-uracil (124I-FIAU) and related compounds for imaging HSV-TK

Jacobs et al., Lancet, 2001
Contribution of PET to Development of Chemotherapy

• Measurement of tumor blood flow and BBB permeability for chemotherapy
• Labeling chemotherapeutics (BCNU, temozolomide, gefinitib): Local pharmacokinetics
• Assessment of pharmacodynamics in new drugs
• Assessing multiple drug resistance (C-11-verapamil, Vaalburg et al., 2002)
Radiotherapy

- Improved target delineation in radiotherapy for operated gliomas with C-11-methionine (Grosu et al., 2005)
- Tumors with higher pre-treatment uptake may have a better response to radiation therapy (Ribom et al., 2002) and chemotherapy (Brock et al., 2000)
- Uptake of F-18-misonidazole may indicate presence of radioresistant hypoxic tissue
- F-18-labeled borono phenylalanine for planning of neutron capture therapy (Imahori et al. 1998)
Beyond FDG and blood flow: tracers and targets

- **Amino acids** \((C-11\text{-methionine, } FET \text{ and others})\)
  - Biopsy planning, extent of infiltration, therapy planning
  - Monitoring of therapy and progression, including low-grade gliomas
  - Detection of recurrent tumor

- **Proliferation markers** \((C-11\text{-thymidine, } FLT)\)
  - In high-grade tumors, proliferation, monitoring of therapy

- **Intermediary/lipid metabolism** \((C-11/F-18 \text{ choline, acetate})\)

- **Hypoxia, receptors, gene expression, labeled chemotherapeutics**