Principles of Positron Emission Tomography and Radiopharmaceuticals

PET Guidance of Therapy for BNCT and in vivo B-10 imaging

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Highlights

Which is the role of Positron Emission Tomography in BNCT?

1) Assist to define a treatment dose planning according to real boron distribution within the target volume

2) Optimizing boron carrier infusion (*timing versus T/N extraction*) using kinetic modelling in vivo (*non invasively*)

3) Unique method for screening candidates undergoing BNCT on the basis of personalized $^{10}$B T/N extraction curves

4) Drug development in preclinical trials and early phases in patients for BNCT
Molecular Imaging in Drug Development
Positron Emission Tomography: Basics
PET Basics

Molecular Imaging in Drug Development
Positron Emission Tomography: Basics
Molecular Imaging Modalities: PET as quantitative tool

The main advantages of PET are:

1) its ability to simultaneously measure many slices of the body;
2) to use radiolabelled biological molecules which detect biochemical changes in tissue;
3) its accuracy in measuring the radioactivity concentration in the body by accurately correcting for physical degrading factors.
Molecular Imaging Modalities

The main disadvantages of PET are:

1) PET operates with isotopes of short half-life, and needs a cyclotron in the vicinity;

2) this modality necessitates several radiolabelled tracers, imaging protocols, data analysis software and kinetic models etc. . . ., which mobilize large resources and a big team of specialists in many fields

3) the measured signal with PET depends on the limited amount of the radioactivity injected in the patient, hence the PET detectors have to be large enough to collect photons and to allow images of good statistics.
PET images are analyzed by defining regions of interest (ROI) and **extracting radioactivity versus time curve** for the selected region, **to calculate the average of the studied physiological parameter in a specific anatomical region**.
FDG is the most common tracer for PET: 90% of today PET studies are ‘sugar’ studies!

Anatomy of glucose metabolism employing CT-PET
Positron Emission Tomography is a functional imaging method.

**Static AND Dynamic images**

Dynamic images (Time Activity Concentration Curves)

*TAC give information about the tissue like:*

- Perfusion
- Endothelial permeability
- Vascular volume fraction
- Transport across cell membrane
- Binding and enzyme activity

The dynamic information are converted to functional information *(PARAMETRIC IMAGE were each voxel value represent a physiological parameter)*
PET is a quantitative tool

How to study the characteristics of tissue?

- Alternatives for model calculation:
  - Ratio
  - SUV (Standardised Uptake Value)
  - Multiple Time Graphical Analysis (Logan or Gjedde-Patlak plot)
  - Compartment models

Radioactivity concentration (tissue or plasma) can be easily converted to drug concentration
PET Basics

PET scanner can deliver quantitative images of radioactivity

\[ \text{Bq/voxel} - \text{kBq/ml} \]

The chemical identity of the labeled molecules in ONLY known at the moment of injection.

*Metabolism in blood, in tissue region of interest need to considered!*

Dynamic studies and blood sampling are not necessary in the clinical setting and may be replaced by a shorter acquisition protocol in the steady state and calculation of tissue uptake ratios which have proved to be sufficient for diagnostic purposes.
Standardized uptake value SUV

- Simple, semi-quantitative measure (g/ml)
- Regional radioactivity concentration (kBq/ml) normalized by injected dose (GBq) and subject weight (kg)
- Average SUV in entire body = body density
- Blood sampling not needed
- Example: measuring amino acid methionine uptake in tumour studies, commonly used for $^{18}$F-FDG

\[
SUV = \frac{\text{Decay Corrected dose}}{\text{cm}^3 \text{tumor volume}} = \frac{\text{Dose injected}}{\text{body weight of the patient (g)}}
\]
Tracer delivery and transport

**Compartmental model** assumes that injected isotope exists in the body in a fixed number of physical or chemical states (compartments) with specified interconnections among them.

Physiologically the flux of material represents transport from one location to another or a chemical transformation or both.

Graphical analysis refers to the transformation of multiple time measurements of plasma and tissue uptake data into a linear plot, the slope of which is related to the number of available tracer binding sites.
PET Basics

Aminoacid Analogues

Figure 7 $^{18}$F-labeled amino acid analogs.
# PET for Radiation Treatment Planning

<table>
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<th>PET tracer</th>
<th>Variable</th>
<th>Target</th>
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<td>Clinical PET studies</td>
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<tr>
<td>$[^{18}\text{F}]$Choline</td>
<td>Lipid metabolism</td>
<td>Prostate cancer</td>
<td>Ciernik et al. (2007) [104]</td>
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<tr>
<td>$[^{11}\text{C}]$Choline</td>
<td></td>
<td></td>
<td>Yoshida et al. (2005) [105]</td>
</tr>
<tr>
<td>$[^{11}\text{C}]$Methionine</td>
<td>Lipid metabolism</td>
<td>Brain tumour</td>
<td>de Jong et al. (2003) [106]</td>
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<tr>
<td>$[^{68}\text{Ga}]$DOTATOC</td>
<td>Synthesis of proteins</td>
<td>Brain tumour</td>
<td>Grosu et al. (2006) [107]</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$Fluoromisonidazole ($[^{18}\text{F}]$MISO)</td>
<td>Hypoxia marker</td>
<td>Head-neck cancer; lung-cancer</td>
<td>Ceyssens et al. (2006) [108]</td>
</tr>
<tr>
<td>$[^{11}\text{C}]$Acetate</td>
<td>Cell proliferation marker</td>
<td>Prostate cancer; head and neck</td>
<td>Nariai et al. (2005) [109]</td>
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<tr>
<td>$[^{13}\text{N}]$NH$_3$</td>
<td>Radiation necrosis</td>
<td>Brain tumour</td>
<td>Tsuyuguchi et al. (2004) [110]</td>
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<tr>
<td>Pre-clinical PET studies</td>
<td></td>
<td></td>
<td>Grosu et al. (2003) [111]</td>
</tr>
<tr>
<td>$3'$-Deoxy-$3'$-[^{18}\text{F}] Fluorothymidine ($[^{18}\text{F}]$FLT)</td>
<td>Cell proliferation marker</td>
<td>Murine SCCVII tumours</td>
<td>Milker-Zabel et al. (2006) [112]</td>
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<tr>
<td>4-borono-2-[^{18}\text{F}]fluoro-1-phenylalanine-fructose ($[^{18}\text{F}]$FBPA-F)</td>
<td>Boron carrier in boron neutron capture therapy (BNCT)</td>
<td>Model of Esophageal Cancer. Brain tumour</td>
<td>Thorwarth et al. (2007) [113]</td>
</tr>
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</table>

References:
- Ciernik et al. (2007) [104]
- Yoshida et al. (2005) [105]
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- Milker-Zabel et al. (2006) [112]
- Thorwarth et al. (2007) [113]
- Gagel et al. (2006) [114]
- Thorwarth et al. (2006) [115]
- Eschmann et al. (2005) [116]
- Sun et al. (2007) [117]
- Oyama et al. (2003) [118]
- Dehdashti et al. (2003) [119]
- Xiangsong and Weian (2007) [120]
- Yang et al. (2006) [121]
- Sugiyama et al. (2004) [122]
- Chao (2007) [123]
- Chen et al. (2004) [124]
PET/CT is one of the most rapidly growing areas of medical imaging with many applications

1. Diagnosing malignancy  Differentiating malignant from benign disease
2. Identifying the site(s) of disease  To plan biopsy or surgery especially when cancer is suspected based on clinical biomarkers
3. Detecting the primary tumor  In patients with metastatic disease with an unknown or small primary tumor
4. Grading malignancy  Based on quantifying the amount of radiotracer uptake
5. Staging disease  Whole-body scans would provide the relative uptake of tracer throughout the body
6. Identifying residual disease  Identification of residual viable cell mass after treatment
7. Detecting recurrences  Confirming the sites of recurrent (new) disease
8. Measuring the response to therapy  Objectively assessing the efficacy of specific treatment modalities.
A key issue in RT treatment is how to deliver the prescribed radiation dose to cancer cells, while keeping the dose to normal cells as low as possible.

**Dose calculation techniques**
A typical process consists of five major phases: (1) simulation, (2) treatment planning, (3) set-up verification, (4) beam delivery and (5) response assessment.

![The 5 phases of the high-precision RT process](image-url)
PET Helps to define gross tumor volume/planning target volume and differentiate tumor from normal tissue

(1) Where is the tumor located and where are the (macroscopic) tumor margins? PET allows the definition of a target volume based on a biological paradigm (BTV). This study discusses only those tumor entities for which we found available data in the literature about the impact of PET in target volume definition for radiation treatment planning.

(2) What are the relevant biological properties of the tumor visualized by PET? The imaging of hypoxia, angiogenesis, proliferation and apoptosis etc. leads to the identification of different areas of an inhomogeneous tumor mass that can be individually targeted.

(3) What is the exact tumor response to therapy? PET may be used to evaluate the response to different therapeutic interventions. The rapidly expanding number of PET/CT imaging devices will have several advantages for radiation treatment planning and the monitoring of patients.
PET for tumor brain imaging in clinical practice

PET differentiates biologically based treatment paradigms from the anatomically based target volume definition
In 1998 this paper reported a method for quantitative measurement of boronated drug uptake in patients with high grade gliomas, based on the use of \( L-[^{18}\text{F}]^{10}\text{B}-\text{BPA} \) the labeled analogue of \( L-{^{10}\text{B}}\)-BPA.

A three compartment model was used to assess the tumor pharmacokinetics: the concentration of boron in the tumor calculated by the rate constant obtained by PET and the measured \(^{10}\text{B} \) input function was found close to that in the surgical specimen.

Similarity in pharmacokinetics between \( L-{^{10}\text{B}}\)-BPA and the labeled analogue was confirmed.
Case 2171
anaplastic astrocytoma (AIII)

MRI-Gd(+)  
L-\textsuperscript{18}F-FBPA

Fig. 1 Modified three-compartment model of $^{18}$F-$^{10}$B-FBPA and $^{18}$F-$^{10}$B-BPA. A, this model is adapted to a four-parameter model by adding an additional serial tissue compartment with anabolic and reverse process rate constants $k_3$ and $k_4$, respectively. $K_1$ and $k_3$ refer to forward and reverse transport of $^{18}$F-$^{10}$B-FBPA across the blood-brain barrier, respectively. The pharmacokinetics of $^{18}$F-$^{10}$B-FBPA were analyzed using the three-compartment model by $K_1$ (ml/g/min), $k_2$ (min$^{-1}$), $k_3$ (min$^{-1}$), and $k_4$ (min$^{-1}$). B, this model was also adopted to analyze the pharmacokinetics of $^{10}$B-BPA described here. The $^{10}$B-BPA-fructose complex is dissociative and reaches an equilibrium between free molecule and the complex in the diluted condition in plasma. $K_d$ and $K_a$ represent the dissociation and association process of the complex, respectively.

Table 1 Rate constants of $^{18}$F-$^{10}$B-FBPA in patients with gliomas

Rate constants of $^{18}$F-$^{10}$B-FBPA in patients with gliomas, including 17 cases of high-grade gliomas and 4 cases of AIII. The values of the rate constants ($K_1$, $k_2$, $k_3$, and $k_4$) are given as the mean ± SD. Control was established at the corresponding region in contralateral brain in each case.

<table>
<thead>
<tr>
<th>Grade</th>
<th>$n$</th>
<th>$K_1$ (ml/g/min)</th>
<th>$k_2$ (min$^{-1}$)</th>
<th>$k_3$ (min$^{-1}$)</th>
<th>$k_4$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM</td>
<td>11</td>
<td>0.040 ± 0.007</td>
<td>0.034 ± 0.009</td>
<td>0.018 ± 0.007</td>
<td>0.011 ± 0.005</td>
</tr>
<tr>
<td>AIII</td>
<td>6</td>
<td>0.039 ± 0.025</td>
<td>0.030 ± 0.013</td>
<td>0.025 ± 0.014</td>
<td>0.011 ± 0.007</td>
</tr>
<tr>
<td>AII</td>
<td>4</td>
<td>0.021 ± 0.006</td>
<td>0.030 ± 0.005</td>
<td>0.025 ± 0.005</td>
<td>0.009 ± 0.009</td>
</tr>
<tr>
<td>Control</td>
<td>21</td>
<td>0.011 ± 0.003</td>
<td>0.025 ± 0.009</td>
<td>0.033 ± 0.015</td>
<td>0.009 ± 0.010</td>
</tr>
</tbody>
</table>

The $^{10}$B concentration is calculated using the rate the rate constants ($K_1$, $k_2$, $k_3$, $k_4$) for brain tumor and the input function for plasma $^{10}$B concentration, on the base of the pharmacokinetic similarities between $L^{-10}$B-BPA and $L^{-18}$F-$^{10}$B-BPA.

With this approach the $^{10}$B concentration is determined at time of neutron irradiation using $L^{-10}$B-BPA.
K1 (measuring amino acid transport) is a major factor governing the accumulation of F-BPA (and BPA).

Kinetic modeling may assist in optimizing timing and length of boron carrier infusion in patients.

Dose planning according to realistic boron distribution within 3D treatment volume.
The long-term outcomes of treatments by investigating the prognostic significance of the metabolic values and ratios of $^{18}$F-$^{10}$B-BPA by PET in patients with gliomas.

**Experimental Design:** subjects were 22 patients who underwent an $^{18}$F-$^{10}$B-BPA/PET study and were followed for at least 4 months thereafter. PET parameters, $K_1$, $k_2$, $k_3$, and $k_4$, were measured before treatment.

Data regarding the tumors, the contralateral normal region, and the uptake ratio of FBPA between the tumor and normal tissue 40 min after injection of the tracer were compared with survival rates after the PET treatment.
Fig. 1  A, MRI of case 10 (A4) showing a tiny enhancing tumor with a surrounding hypointense lesion in the frontal region, and FBPA accumulating intensely in the nonenhancing lesions as well as in the enhancing lesion. Left, enhancing T1 MRI; right, FBPA-PET scan. B, MRI and FBPA-PET of case 8 (GB). MRI demonstrated a heterogeneously enhancing lesion in the posterior temporal region, and FBPA uptake is exceedingly high in the lesion. Left, enhancing T1 MRI; right, FBPA-PET scan.
Submandibular gland cancer, was confirmed that the $^{10}$B-BPA by $^{18}$F-$^{10}$B-BPA before BNCT.

The tumor/normal tissue boron concentration ratio was 2.9. The tumor was irradiated at the Kyoto University Research Reactor with epithermal neutrons 5 MW for 90 minutes.

**Results.** To date there has been continuous complete regression in the tumor and no acute and chronic complications for 1.5 years.
Meningiomas and schwannomas might respond to low-dose BNCT with BPA owing to their growth characteristics.

* It is necessary to model $[^{18}F]$FBPA uptake kinetics beyond 50 min and compare it with in vivo data on $^{10}$B uptake in tumour after infusion of BPA.
PET models for BNCT and clinical applications

\[^{18}\text{F}]\text{F-BPA-PET in severe form of NF-2}\]

MRI  \[^{18}\text{F}]\text{F-BPA PET}\]

[\textsuperscript{18}F]F-BPA-PET: Boron uptake gradients
SUV25-50min tumour/normal brain

Temporal lobe glioma (gr III)
Boron gradient: 3-3.5

Parietal lobe glioma (gr III)
Boron gradient: 3-4

Boron gradient determined from steady state image
Novel targets for BNCT

**Case:**
A 44-yr man with recurrent poorly differentiated sinonasal carcinoma

Boron Neutron Capture Therapy (BNCT) in locally recurred head and neck cancer

Prerequisite for BNCT:
Uptake of $^{18}\text{F}F$-BPA $2.5 \geq$ surrounding normal tissue

Boron Neutron Capture Therapy (BNCT) in locally recurred head and neck cancer

CT

MRI

[\textsuperscript{18}F]F-BPA PET

BNCT weighted total dose
- 17 Gy (W)
- 7 Gy (W)
- 3 Gy (W)

http://www.turkupetcentre.fi/

©Turku PET Centre, Univ. of Turku, Finland
First case of extensive squamous cell carcinoma in the temporal bone recurring after surgery, conventional radiotherapy, and chemotherapy, which was treated using planned fractionated BNCT

\(^{18}\text{F}\)-BPA PET showed a high T/N ratio of 3.8 at the occipital condyle before the first BNCT of squamous cell carcinoma.
• Conclusions

• T/N ratio of boron concentration can be derived by PET data and used to estimate the boron extraction during BNCT

$^{18}$F-FBPA PET method is appropriate to determine the treatment protocol for BNCT in gliomas and other malignancies (head and neck cancers and melanoma).

• $^{18}$F-FBPA PET can be proposed as imaging tools for different types of malignancy.

• Accurate planning of BNCT may be performed by static images of FBPA PET.

• Other $^{11}$C-MET, $^{18}$F-FET may be studied for screening of candidates for BNCT were $^{18}$F-FBPA is not available

• Use of PET imaging with amino acid probes may contribute very much in following up patients after BNCT.
microPET for small animals studies imaging

Drug Development and Animal Experiments

Example of application:
Brain tumor model in rat (Glioma F98)

Transaxial sections: implanted animal (+), 59MBq $^{18}$F-FDG

Transaxial sections UCLA scale: implanted animal (+), 59MBq $^{18}$F-FDG

(CNR Institute of Clinical Physiology, Pisa)
The pharmacokinetics of $[^{18}\text{F}]$FBPA-F was examined using this dynamic microPET study. A three-compartment model using rate constants (K1, k2, k3, and k4) 

The K1 value in glioma group (three rats) differed from that in normal group (three rats) as shown in Table 

These findings indicate that tracer uptake capacity, associated with tumor malignancy, depends on K1, which is an indicator of the transport process.

microPET can be used to image $[^{18}\text{F}]$-FBPA-F biodistribution in F98 glioma bearing rats in vivo: high tumor-to-normal uptake ratio (3:1).
Aromatic aminoacid analogues mimetic of BPA transport : use of O-(2-[^18F]fluoroethyl)-L-tyrosine in experimental animal model of F98 Glioma

\[ ^{18}\text{F}} \text{FET PET allows the identification of the extent of cerebral lesions in small animal model of F98 glioma bearing rat. } \]

\[ ^{18}\text{F}} \text{FET uptake was found only in the neoplastic tissue while no significant uptake was found in either healthy or sham operated controls. } \]

\[ ^{18}\text{F}} \text{FET images obtained with small animal PET scanner on the animal model of Glioma F98 and control animals (implanted animal without tumor inoculation) (1) Transaxial, sagittal (top right) and coronal (bottom left) images at highest target to background contrast (2) Coronal images of } ^{18}\text{F-FET increased uptake in brain lesion (3) } ^{18}\text{F-FET brain distribution in sham control animal} \]

13th Int. Cong. NCT, Florence Nov 2-7 2008 – L.Menichetti et al.