**[18F]Fluorothymidine PET for the study of proliferation in breast cancer**

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**Background**

[18F]Fluorothymidine ([18F]FLT) has been developed as a novel marker for studying cell proliferation in oncology. Compared to the most commonly used PET radiotracer (FDG) it is more specific for tumour tissue and shows little uptake in inflammatory tissue. As a nucleoside analogue, it is a substrate for thymidine kinase 1 (TK1), which is upregulated in response to mitogenic signals; it rises late in G1 phase, peaks in S phase, and is targeted for degradation late in M phase. This will be the first study to evaluate the pharmacokinetics of [18F]FLT in breast cancer, using semiquantitative and mathematical modelling techniques for data analysis. The parameters will be compared to a standard immunohistochemical measure of proliferation, Ki-67.

**Methods**

Patients with histologically-proven invasive breast cancer and measurable disease ≥ 2.5cm, were eligible for the study. 15 patients with 13 primary tumour areas, 6 nodal metastatic areas, and one pulmonary metastasis were studied, overall, multiple slices from 29 distinct tumour regions were studied. All patients were scanned for 90 minutes after a bolus intravenous injection of [18F]FLT on an ECAT HR+ 962 scanner (CTI/Siemens, Hammersmith Imanet®). Arterial blood samples were analysed by gamma-counting and HPLC. The dose ranged between 153 and 380 MBq (specific activity 25-465 GBq/µmol).

Following immunostaining of formalin fixed core biopsy sections, Ki-67 positive cells were manually counted in 8 fields of view, and divided by the total number of cells to obtain the Ki-67 labelling index (Ki-67 Li).

**Results**

- [18F]FLT uptake was significantly different between tumour and normal tissues for all the index for Ki (r=0.92, p< 0.0001), FRT(r=0.92, p<0.0001), SUV (r=0.79, p=0.002, and AUC parameters analysed (Ki, FRT, SUV, and AUC).
- [18F]FLT localisation was lower in an inflammatory tumour (no 3 below) compared to a lobular tumour (no 1 below), which in tum was lower than a ductal carcinoma (no 2 below).
- [18F]FLT retention was significantly different between tumour and normal tissues for all the parameters analysed (Ki, FRT, SUV, and AUC).

**Conclusions**

- Primary breast cancer and metastases show a wide range of proliferative capacity as determined by [18F]FLT-PET.
- The delivery and retention of [18F]FLT in tumours were higher than those of normal breast and lung tissue (p<0.0001).
- Metabolite-corrected kinetic parameters of [18F]FLT retention are more sensitive than semiquantitative methods such as SUV. Overall both types of analysis are useful in evaluation of [18F]FLT and correlate significantly with Ki-67 (p<0.01).

**Future work**

To evaluate the utility of [18F]FLT for monitoring anti-proliferative treatments in cancer.

**Data Analysis**

\[
SUV = \frac{B_{SA}}{Q_{inj}} \int \sum C_i(t)\, dt, \quad \text{BSA}
\]

(Where \(C_{tiss}\) = concentration of [18F]FLT in tissue, \(t\) is time, denotes convolution, \(\lambda\) = decay constant for [18F] (1.93 x 10\(^{-4}\)), N = number of basis functions in the model, \(\beta\) values were chosen to describe the entire spectrum of expected kinetic behaviour from the slowest possible clearance \(\lambda\), to the fastest measurable dynamic, \(\alpha\) is the intensity of the component at \(\beta\)).

**Graphical (Modified Patlak)**

\[
A \cdot \frac{C_{tiss}}{C_{plasma}} = K, \quad \int C_{tiss} \cdot \beta \cdot \lambda + V
\]

(where A = total tissue radioactivity, \(\cdot [18F]FL\) and metabolites, \(C_{tiss}\) = total blood radioactivity, \(C_{plasma}\) = radioactivity of FLT by metabolism analysis of blood data (HPLC)).

**Results (contd)**

- Large tumours (>5cm) exhibited heterogeneous [18F]FLT uptake (see above)
- [18F]FLT localisation was lower in an inflammatory tumour (no 3 below) compared to a lobular tumour (no 1 below), which in tum was lower than a ductal carcinoma (no 2 below).

**References**

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**SUV**

\[
\text{SUV} = \frac{B_{SA}}{Q_{inj}} \int \sum C_i(t)\, dt, \quad \text{BSA}
\]

**Spectral**

\[
C_{tiss}(t) = \frac{1}{\lambda} \sum C_i(t) \cdot \exp(-\beta \lambda) \cdot \exp(-\alpha \lambda)\]

(Where \(C_{tiss}\) = concentration of [18F]FLT in tissue, \(t\) is time, denotes convolution, \(\lambda\) = decay constant for [18F] (1.93 x 10\(^{-4}\)), N = number of basis functions in the model, \(\beta\) values were chosen to describe the entire spectrum of expected kinetic behaviour from the slowest possible clearance \(\lambda\), to the fastest measurable dynamic, \(\alpha\) is the intensity of the component at \(\beta\)).