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^{18}F-FES Radiation Dosimetry Preliminary Estimates for Preclinical Studies based on Voxelized Phantom

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1. Introduction

Small animals, such as mice, are used in biodistribution studies and innumerous preclinical investigations involving ionizing radiation. Longitudinal preclinical studies with five or more image procedures (MicroCT and/or PET/SPECT) are not uncommon [1-8] However, the accumulated absorbed doses in mice organs and their influence in experimental results is often neglected. Works have shown that even low doses (50 to 500 mGy) can induce biological effects in mice [9, 10]. In such cases, the accurate quantification of absorbed doses in mice organs is very important to evaluate potential radiobiological effects that may interfere with *in vivo* experiments. In this work, we perform a preliminary dosimetry estimates for female mice to be used in preclinical studies using 16α-[^{18}F]-fluoro-17β-estradiol (^{18}F-FES). ^{18}F-FES is a radiolabeled PET imaging agent that has been used to investigate breast cancers with increased expression of estrogen receptors [11, 12].

2. Methodology

[18F]FES Biodistribution in Mice

Protocols used in animal studies were approved by the Ethics Committee on Animal Use (CEUA-IPEN/SP) under registration nº 002/016 CEUA/IPEN/SP: 115/13. Experiments were performed in compliance with guidelines of the National Council Control in Animal Experiments (CONCEA). Female Swiss mice were fasted for 6 h with *ad libitum* access to water before *ex vivo* biodistribution studies. ^{18}F-FES (0.1 MBq/100 μl) was injected through the lateral tail vein of the animals (20–30 g) and five mice at each time point (5, 30, 60, 120 and 180 min after injection) were sacrificed by cervical dislocation. Blood samples were obtained by cardiac puncture. Organs and tissues samples (spleen, bladder, brain, heart, stomach, liver, small intestine, large intestine, muscle, bone, ovaries, pancreas, lungs, kidneys and uterus) were excised, washed and weighted. Radioactivity was measured in an automatic gamma counter [2480 WIZARD; PerkinElmer (Wallac Oy), Joensuu, Finland]. Similarly, female Swiss mice were fasted for 4–6 h before PET imaging with *ad libitum* access to water. Protocols for imaging included an injected dose of 12-15 MBq/100 μl and isoflurane 2% as anesthesia. 15-min static acquisitions with three bed positions were performed. Images were reconstructed using MLEM-3D algorithm.

Animal Dosimetry

Biodistribution data in mice were used to estimate absorbed doses. ^{18}F-FES uptake values (%ID/g) were converted to percentage injected dose per organ/tissue using animal organ/tissue reference masses from FM_BRA, a female mouse computational model described elsewhere[13].

Time-activity curves for each measured organ/tissue were generated. For each curve, time-integrated activity in the source region, Ã (area under the curve), formerly called cumulated activity, was

determined by trapezoidal integration until 180 min after injection. After the last measured time point (180 min), it was assumed that the radiotracer underwent only physical decay with no biological elimination from the source organ. Time-integrated activity coefficient (ã) of each organ was determined by dividing the time-integrated activity in the source region by the injected activity (A_0) according to Eq. (1):

$$\tilde{a} = \frac{\tilde{A}}{A_0} \tag{1}$$

The MIRD formulation (30) was applied to calculate the absorbed doses according to Eq. (2):

$$\mathbf{D}\,(\mathbf{r_T}) = \sum_{\mathbf{S}} \tilde{A}_{\mathbf{S}} * \mathbf{S}(\mathbf{r_T} \leftarrow \mathbf{r_S}) \tag{2}$$

where D(rT) is target organ rT absorbed dose, $\tilde{A}_S$ is time-integrated activity in source organ rS and S(rT← rS) is the dose factor (mean absorbed dose per time-integrated activity in source region). S values for animal organs/tissues were obtained from the FM_BRA mouse voxel model (13).

3. Results and Discussion

Figure 1 shows an ^{18}F-FES-PET rendered image of a female Swiss mouse, 60min after injection. A median 3D filter was applied. Qualitative analysis of PET image indicates a radiopharmaceutical metabolic behavior in accordance with literature: liver metabolism, urinary and bile excretion and high reabsorption of metabolites in small intestine [14]. Liver uptake is lower at this time, but it's contour is still visible. The high reabsorption of metabolites in small intestine is very evident indicating that lower injected activity could be used in future images. Low background uptake was observed for most of the organs. Uterus and ovary presented significant uptake, indicating the ^{18}F-FES affinity to estrogen receptors expressing tissues.

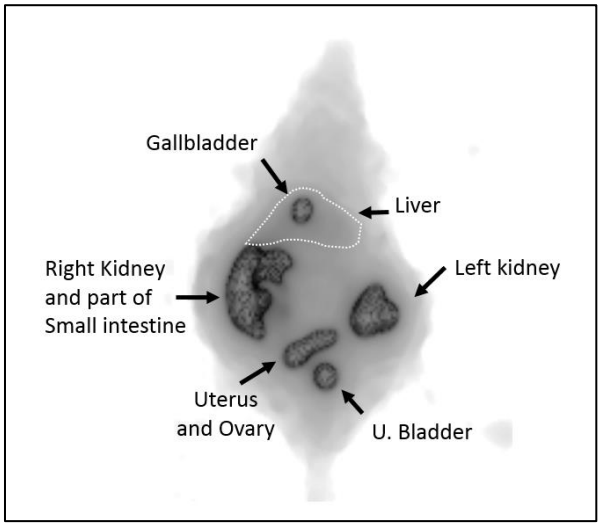

Figure 1: ^{18}F-FES/PET image obtained with AMIDE® software for a female Swiss mouse, 60 min after radiopharmaceutical injection. The main uptake organs are indicated with arrows.

Figure 2 shows the ^{18}F-FES *ex vivo* biodistribution results in selected organs, where data are expressed as

percentage of injected dose per gram of tissue (%ID/g). Blood ^{18}F-FES concentration significantly decreased from 1.36 %ID/g at 5 min to 0.08 % ID/g at 180 min after injection. High liver uptake at 5 min indicates the hepatic metabolism of ^{18}F-FES, while high small intestine uptake indicate the metabolites reabsorption in this intestine portion, as described in literature [14]. The uptake in uterus indicates the ^{18}F-FES affinity with tissues expressing estrogen receptors. Animal dosimetry preliminary estimates are presented in Table I.

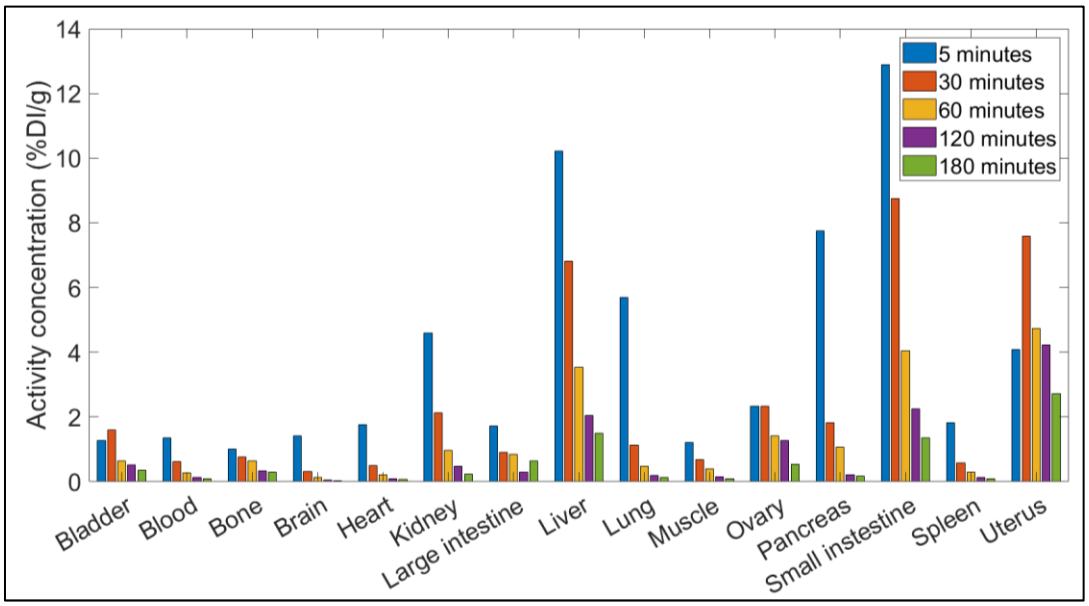

Figure 2: [18F]-FES biodistribution in female Swiss mouse

Table I: ^{18}F-FES preliminary dosimetry estimates in female mouse.

Target organ	Absorbed Dose per Injected Activity (mGy/MBq)	Target organ	Absorbed Dose per Injected Activity (mGy/MBq)
Stomach	22.1	Ovary	10.4
Thyroid	22.1	Urinary Bladder	9.7
Gall Bladder	21.5	Pancreas	9.3
Salivary Glands	21.0	kidneys	8.1
NSST	20.4	Spleen	7.0
Eyes	18.9	Lungs	7.0
Utherus	17.3	Muscle	5.0
Spinal Chord	16.2	Bone	4.8
Liver	14.3	Heart	3.5
Intestine	13.4	Brain	3.0

Non-segmented soft tissues (NSST), eyes, gallbladder, salivary glands, spinal cord and stomach presented high dose coefficients per unit of injected activity. One reason for this high value is that we consider that all decays occur in the mouse and NSST and the above-mentioned organs accumulate all the decays that were not integrated in the organs with biodistribution data, i.e., they were included as "others" biodistribution compartment. Since ^{18}F-FES is a receptor targeted radiopharmaceutical, it is possible that ~15 MBq injections saturated by far all the receptors and a great amount of metabolites, that did not bind, were excreted in the feces (more probable) or in the urine and not decayed in the mouse body. Future biodistribution studies should focus in the evaluations of the optimal injected dose as well as in the quantification of the activity in intestine contents and in the urine. This information could improve the

dosimetry estimations and the image quality. Among the organs with biodistribution data and therefore not affected by the "others" compartment issue, high doses were found for liver and intestine and this fact may be explained due to the ^{18}F-FES hepatic metabolism and the high reabsorption of metabolites in small intestine. Uterus and ovary also presented a high dose when compared to other organs doses. This fact demonstrates the specificity of ^{18}F-FES to estrogen receptor expressing tissue.

4. Conclusions

A preliminary dosimetry data set based on voxelized female animal model was obtained for ^{18}F-FES. The study is not finished yet and some improvements are required to the female mouse model. Also, information about optimal injected activity dose and about activity eliminated through the metabolites should be acquired in order to improve dosimetry estimations and image quality.

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