PET Study with [11C]Choline and its Derivates in the Human hormone-dependent Prostate Cancer Rat-Xenograft-Tumor-Model PAC120

D. Kukuk[1], O. Raguin[3], H. Wehrl[1], C. Calaminus[1], A. Schmid[1], V. Honndorf[1], S. Wiehr[1], O. Duchamp[3], W. Ehrlichmann[2], J. Mannheim[1], G. Reischl [2] and B.J. Pichler[1]

[1]Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation, University of Tuebingen, Germany; [2]Radiopharmacy, Department of Radiology, Eberhard Karls University Tuebingen, Germany; [3]Oncodesign, Dijon Cedex, France

INTRODUCTION

Prostate cancer is the most prominent oncologic disease in men in the western world. Most prostate cancers show androgen dependency at their beginning, that`s why androgen ablation therapy is the most common therapy.
A big range of biomarkers is available for primary cancer diagnostic as well as therapy monitoring. But in prostate cancer the tracer of choice is still missing.
The aim of this study was to validate [11C]Choline, [18F]FEC and [18F]FCh, three PET tracers specifically developed for prostate cancer imaging, and to compare them with [18F]FDG and [18F]FLT pre and post surgical in the PAC120 human hormone-dependent prostate cancer subcutaneously xenografted in the *Nude* rats.

MATERIAL & METHODS

Dynamic and static baseline PET images of male tumor bearing RH/rnu-rnu rats were acquired on five consecutive days with each tracer. After "baseline" imaging rats were surgically castrated, mimicking an androgen ablation therapy, and thereafter measured again at two different time points.

In addition we measured the apparent diffusion coefficient (ADC) by diffusion-weighted MRI (DW-MRI) and did chemical shift imaging (CSI) of the hormone-dependent PAC120 tumors on a 7.2T MRI scanner, for cross correlating our data. Tumor morphology was monitored by transversal, coronal and sagittal 3D T2-weighted MRI, respiration triggered sequences.

RESULTS

The PET baseline image analysis of the PAC120 tumors showed excellent [11C]Choline uptake with a T/M of 2.19±0.32 and very good uptake with the derivates ([18F]FEC-T/M: 1.54±0.29, [18F]FCh-T/M: 1.79±0.38). A great delineation of the tumors was observed with [18F]FDG (T/M: 4.99±0.84). For [18F]FLT a very low baseline with a T/M of 1.14±0.16 was found.
Effective androgen-ablation therapy through surgical castration is greatly pictured in the first line through [11C]Choline and its derivates as well with the oncologic "Gold-Standard"-tracer [18F]FDG. Thus, we found a significant decrease of the T/M ratio (T/M: 1.31±0.23, p=0.021) three weeks post castration (p.c.) using choline PET imaging. [18F]FEC and [18F]FCh show a highly significant decline of the tracer tumor uptake 3 weeks (p≤0.007) and 7 weeks (p≤0.0006) p.c. compared to baseline measurements as well as with the [11C]Choline (p=0.017). [18F]FDG imaging show highly significant decease (p≤0.0001) of the tracer uptake 3 weeks p.c. (T/M: 2.96±0.64) compared to the baseline scans.
Analysis of the ADC maps revealed a clear increase of the ADC values post castration due to a change in the tumor microenvironment. This effect is characterized by the loss of cellular density because of treatment-induced cell death. Additionally a shift in the CSI data from choline and lactate could be shown.

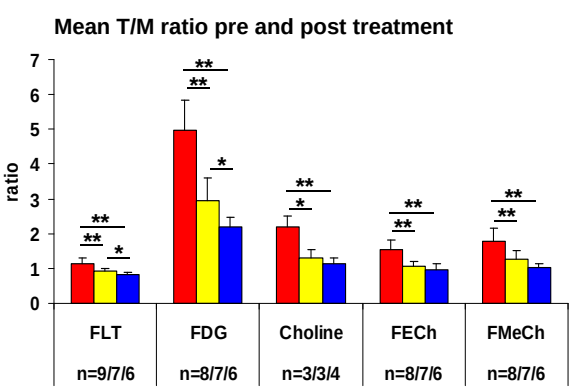

Figure 1: The mean T/M ratios from the investigated tracer [18F]FLT, [18F]FDG, [11C]Choline and [18F]FEC in the PAC120 tumors are shown. All explored tracers showed significant early response to androgen-ablation therapy.

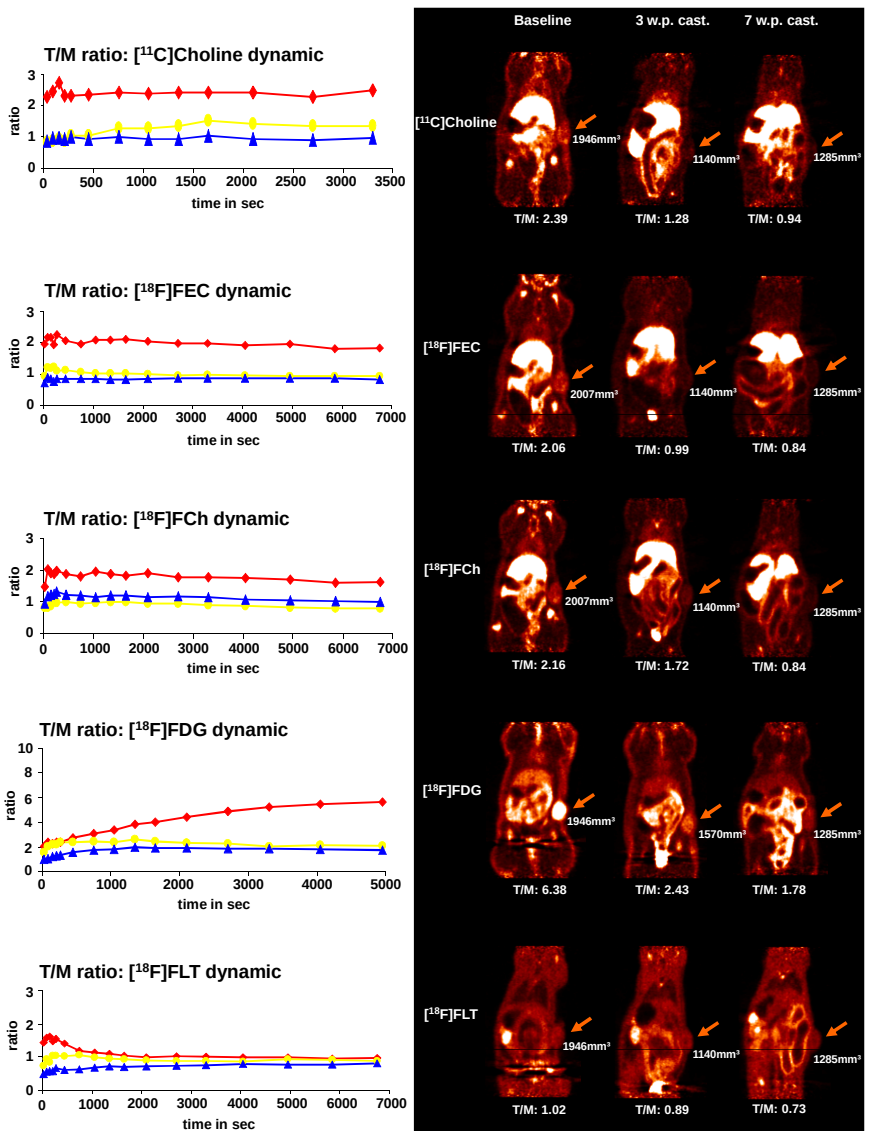

Figure 2: Left side shows representative T/M ratio dynamic curves of each tracer in the PAC120 tumors pre and post castration. Right side illustrates static PET images of PAC120 tumors with [11C]Choline, [18F]FEC, [18F]FCh, [18F]FDG and [18F]FLT pre and post castration.

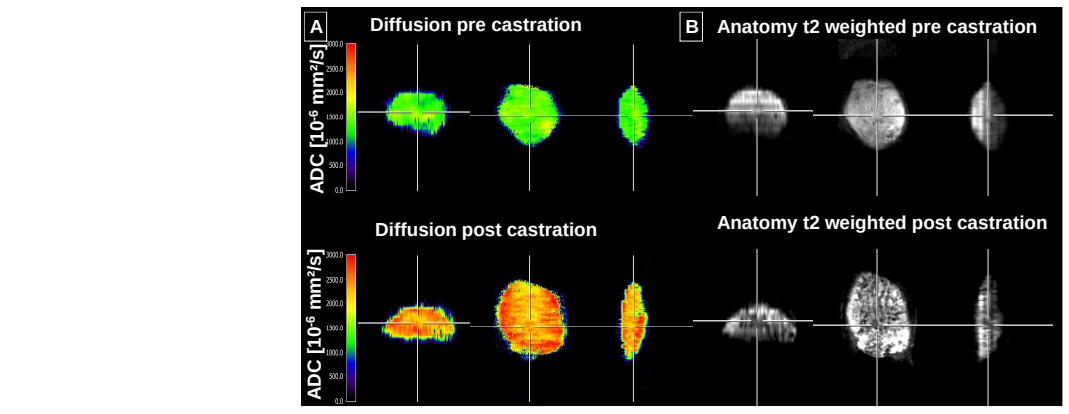

Figure 3: A: The ADC map in the PAC120 tumor assessed by MRI from the same animal is shown pre and post treatment with a clear response to androgen-ablation therapy. B: Even the anatomy alone demonstrates a collapse of the tumor microenvironment.

DW-MRI was acquired using a HASTE MR sequence. The sequence parameters were as follows: TR 5000ms, TE 121ms, voxel size 0.31x0.31x0.1mm, FoV read 40mm; averages 4, slices 14,. Diffusion encoding gradients were applied for b-values from 150 to 1000 s/mm² (150, 300, 500, 800, 1000) along the coronal direction (phase encoding direction). Only one direction of diffusion encoding was selected, because most non-neural tissue exhibits isotropic water diffusion.

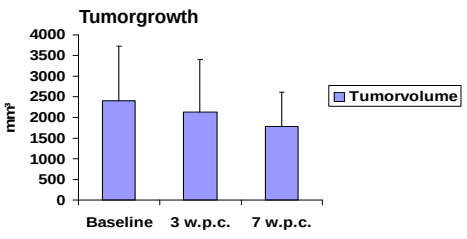

Figure 4: Tumor volumes of the PAC120 tumors xenografted in nude rats, pre and post castration.

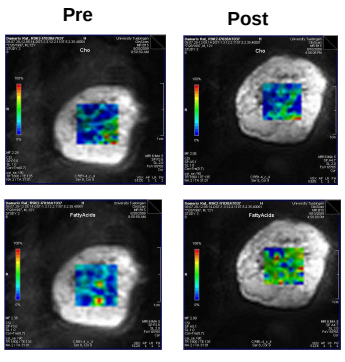

Figure 5: Representative colour maps from CSI measurements of choline and fatty acids. The resonances of these metabolites occur at distinct frequencies or positions in the spectrum. These signals can be converted into colour maps. Shown are colour maps of choline and fatty acids pre and post castration. For choline is seen to this timepoint (2wp) bearly a change in the CSI. But with fatty acids CSI is already monitoring a therapy effect such as an androgen ablation therapy. The applied CSI sequence had the following parameters: voxel size 1.33x1.33x1.33mm, TE 135ms, TR 1800ms, Volume of interest size: 8x7x8mm³.

CONCLUSION

These data show for the first time a significant response to androgen ablation therapy using PET imaging with [11C]Choline and its derivates in an *in vivo* model of human hormone-dependent prostate cancer xenografted in *Nude* rats. Additionally, we have shown an excellent data correlation with ADC and CSI parameters as well as immunohistochemistry. Conclusively the PAC120 tumor-bearing *Nude* rat is a useful *in vivo* model to study new PET tracers for human hormone-dependent prostate cancer diagnostic and therapy efficacy monitoring.

Laboratory for Preclinical Imaging and Imaging Technology of the Werner Siemens-Foundation

Contact:damaris.kukuk@med.uni-tuebingen.de

Eberhard Karls Universität Tübingen