Grant agreement no. 667510

GLINT

Research and Innovation Action
H2020-PHC-2015-two-stage

D7.3 Technical validation of the GlucoCEST technique in human cancers

Work Package:	7
Due date of deliverable:	31/12/2018
Actual submission date:	January 14, 2019
Lead beneficiary:	UCL
Contributors:	UCL
Reviewers:	MPG, TAU

*"This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Grant Agreement No **667510**"*

Project co-funded by the European Commission within the H2020 Programme (2014-2020)		
Dissemination Level		
PU	Public	YES
CO	Confidential, only for members of the consortium (including the Commission Services)	
CI	Classified, as referred to in Commission Decision 2001/844/EC	

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1 Version log

Version	Date	Released by	Nature of Change
V1.0	12/12/2018	Mina Kim	First version
V1.1	18/12/2018	Eleni Demetriou	Revision
V2.1	20/12/2018	Mina Kim	Revision

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2 Definition and acronyms

Acronyms	Definitions
glucoCEST	Glucose Chemical exchange saturation transfer
MTR_{asym}	Asymmetric Magnetization Transfer Ratio
WASAB1	Simultaneous mapping of water shift and B1

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3 Introduction

In order to validate the GlucoCEST technique in human cancers, it is essential to evaluate the results which have been carried out until now. So far, five patients were successfully scanned: 3 lymphoma, 1 prostate cancer, and 1 glioma patients. An additional 3 patients were scanned, however leading to unusable data due to technical issues:

- Patient 1: Due to errors in the software, the targeted frequencies for tumour detection were not properly applied and the data turned out to be unusable.
- Patient 2: A high degree of patient movement was observed in images of the patient's neck. This was caused by breathing, swallowing, and movement during the blood sampling.
- Patient 3: Extravasation of glucose from the cannula had occurred and led to local swelling in the left arm. The scan had to be abandoned.

Therefore, only data from five patients (3 lymphoma, 1 prostate cancer, and 1 glioma patients) are considered in this report.

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4 Report of experimental procedures and results

4.1 Experimental procedures

Glucose Infusion protocol:

- Baseline blood glucose measurements ensured that fasting blood glucose is less than 7 mM/l, random glucose less than 10 mM/l and the highest rise in glucose from baseline during infusion didn't exceed 10 mM/l rise.
- 2 mins-glucose monitoring was carried out in the first 10 mins of scanning and then reduced to every 5 mins monitoring afterwards.
- The glucose infusion ran as minimal time as possible for about 30 min to 1 hour.

Imaging protocol:

- Anatomical localization images and CEST images were acquired once the glucose infusion commenced.
- Imaging protocols are illustrated in Figure 1 and described as follows:
  - CEST:
    - 18 repetitions of 40ms sinc truncated Gaussian pulses (sg_100_100) with a single ms interpulse delay.
    - flip angle: 1200 degrees (~2.5uT effective B1)
    - offsets: [inf inf [-3.36, 3.36, -3.04, 3.04, -2.72, 2.72, -2.4, 2.4, -2.08, 2.08, -1.76, 1.76]*5 times] ppm = 12 offsets* 5 + 2 far away offsets = 62 dynamics in total.
  - WASAB1:
    - block pulse, 5ms (~3.7uT effective B1)
    - offsets: [inf -3.0 -2.7 -2.4 -2.1 -1.8 -1.5 -1.2 -0.9 -0.6 -0.3 0 0.3 0.6 0.9 1.2 1.5 1.8 2.1 2.4 2.7 3.0] ppm.

- The acquired CEST images were post-processed using a custom written software.

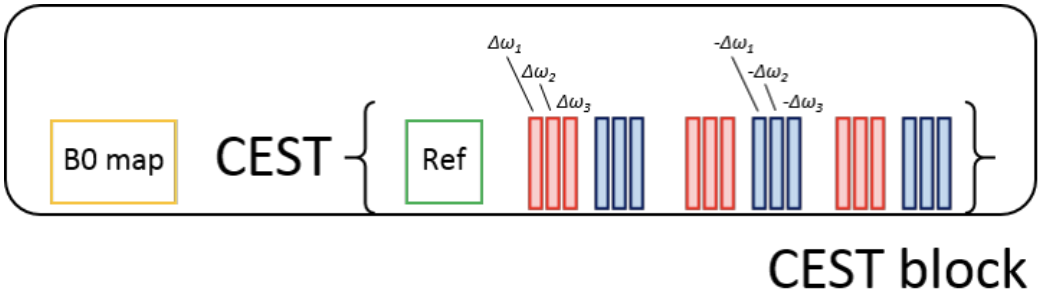

Figure 1: *Diagram of a suggested fast acquisition protocol for glucoCEST*

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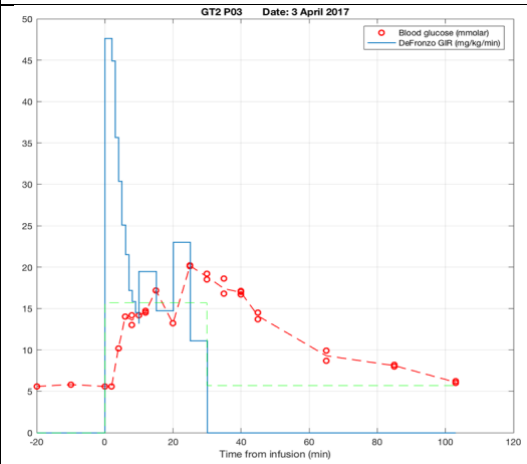
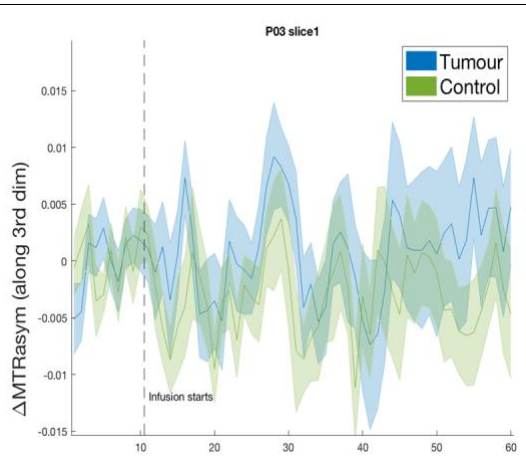
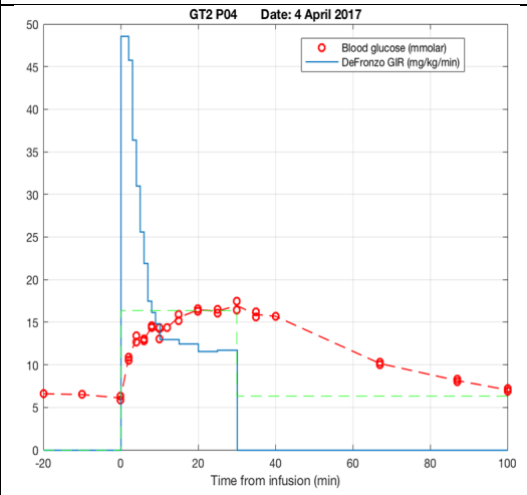
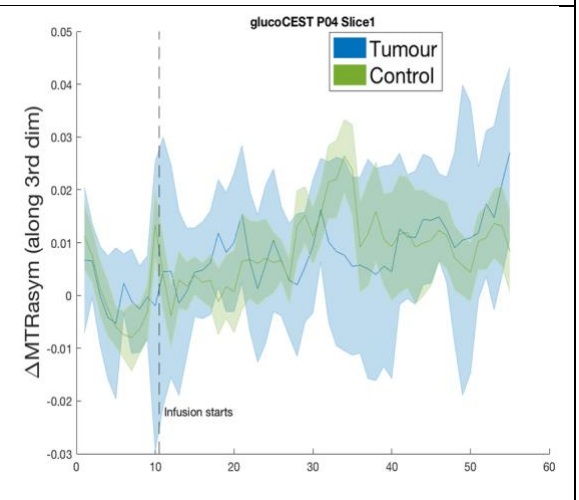
experiments. Three pairs of offset frequencies (positive and negative) are sampled centred around 2.6 ppm. Reference and B0 field maps are also acquired regularly to control for potential field drifts.

4.2 Results

Lymphoma and prostate cancer patients: Image results of three adult lymphoma patients and one prostate cancer patient show no significant enhancement in CEST signal after administration of glucose infusion using Hyperglycemic clamp with DeFronzo's algorithm [1] which significantly improved control over glucose levels and minimize total infusion time (Figure 2).

	Glucose Infusion Profile	**MTR_{asym} GlucoCEST signal**
Lymphoma Patient #3		
Lymphoma Patient #4		

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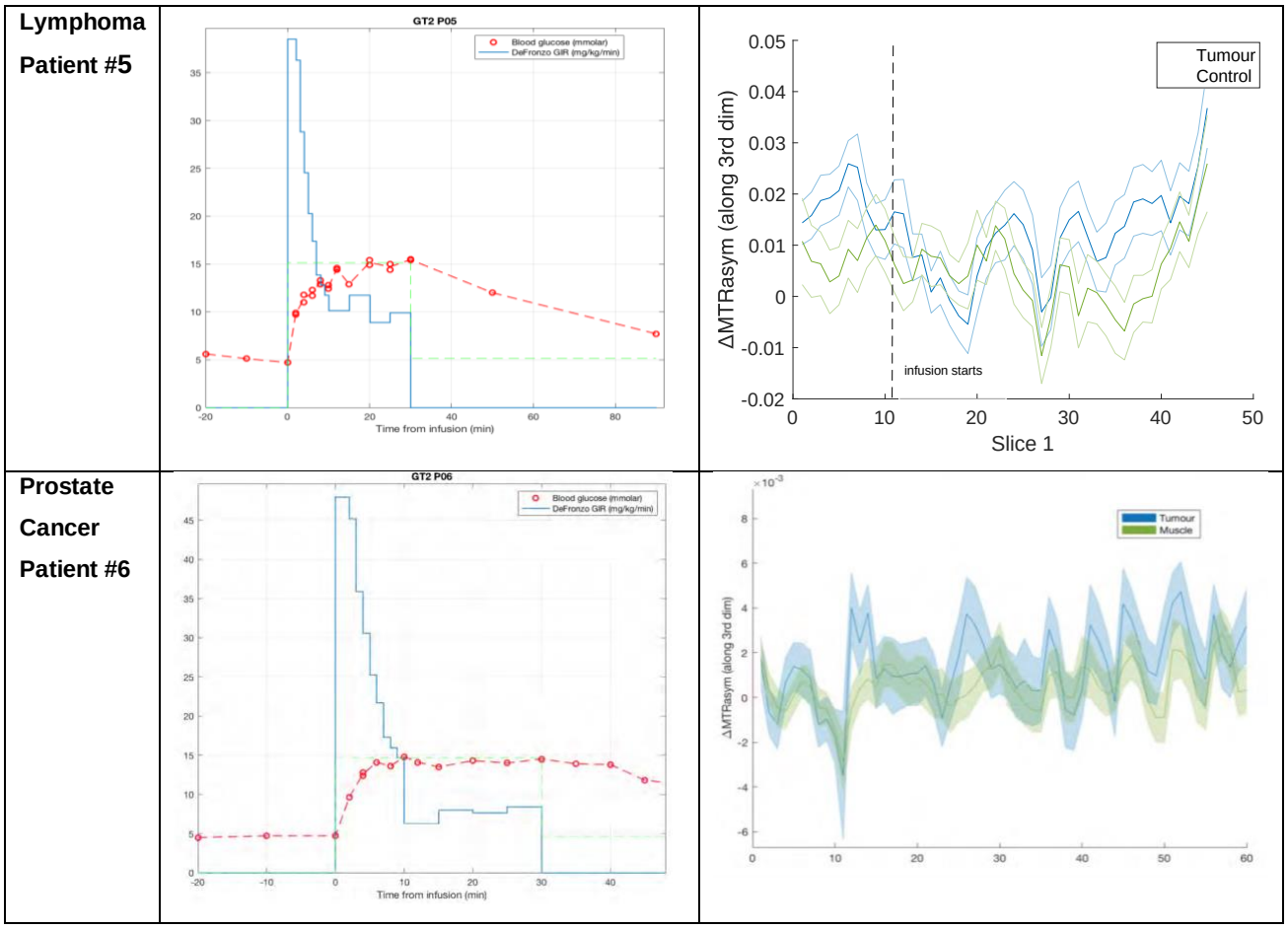

Figure 2: *Glucose Infusion Profile vs. MTR_{asym} GlucoCEST signal of each patient.*

Those negative results from three adult lymphoma patients and one prostate cancer patient are in line with the Deliverable (D) 5.3 which was recently reported by University of Torino. As described in D5.3, the CEST contrast following natural glucose administration is dependent on several conditions such as the amount of the injected dose, the administration route and the magnetic field strength. In particular, clinical scanners (3T) as compared to high field scanner (> 3T) are disadvantageous for CEST detection due to the lower separation in hertz between the exchanging proton pool and the bulk water pool. In D5.3, it was demonstrated that the measured contrast in the tumour region at 3T was lower than the threshold limit of 1%, independent of glucose administration route and injected dose. A likely explanation for these results is linked to the smaller chemical shift difference between hydroxyl protons and bulk water signal at 3T (ca. 125 Hz) that results in higher direct saturation effects and reduced selectivity. As a consequence, CEST signal is less visible and limits *in vivo* detection of natural glucose. In addition, chemical exchange of glucose belongs to the

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intermediate-fast exchange regime resulting to severe coalescence effects and different saturation efficiencies because of changes in relaxation times.

Importance of B0 correction: B0 correction was proven to be essential in order to correct for field drifts during the glucoCEST experiment (Figures 3 and 4).

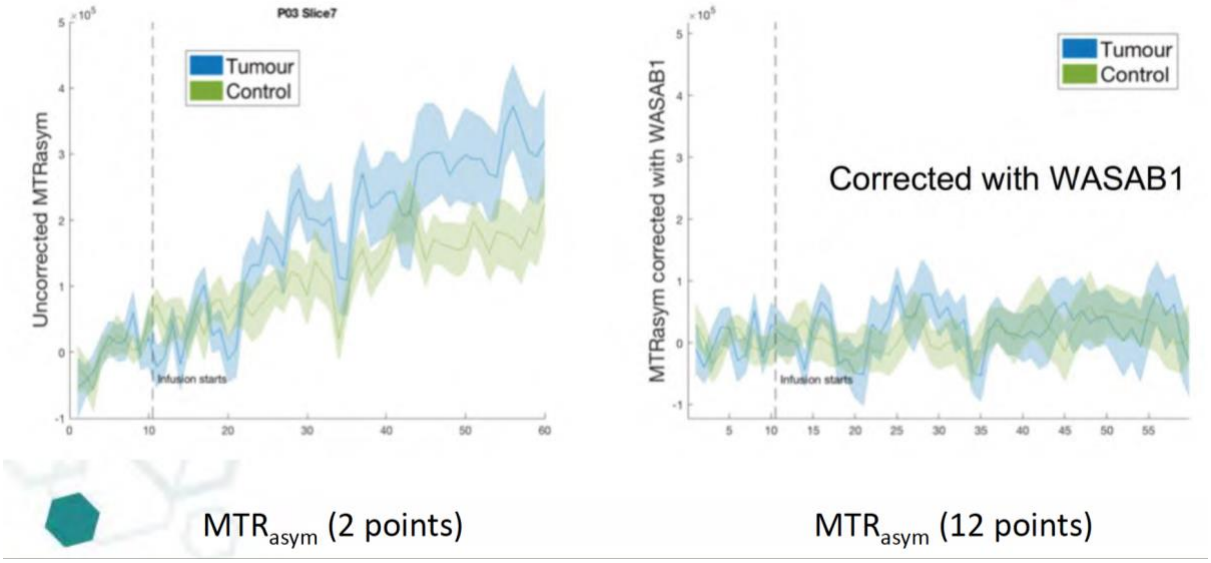

Figure 3: *MTR$_{asym}$ GlucoCEST signal before WASAB1 correction (left) shows field drifts in a Lymphoma patient (#3). After B0 correction (right) shows no significant enhancement in MTR$_{asym}$ signal.*

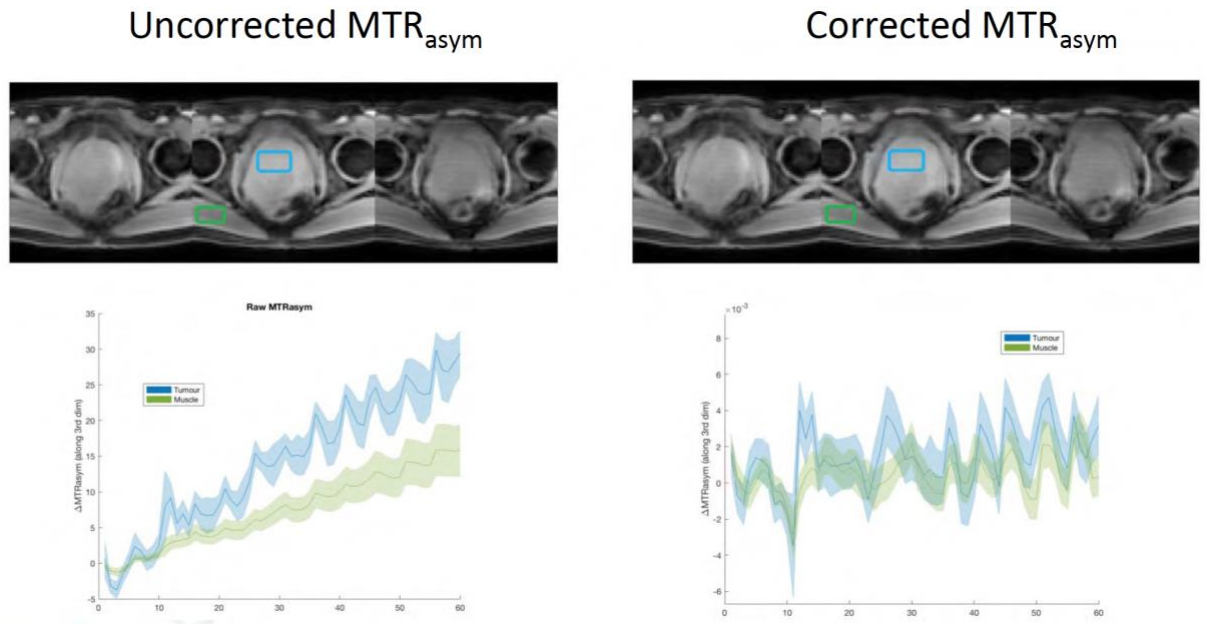

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Figure 4: *MTR_{asym} GlucoCEST signal before WASAB1 correction (left) shows field drifts in a Prostate Cancer patient (#6). After B0 correction (right) shows no significant enhancement in MTR_{asym} signal.*

Glioma patient: Image results of one adult glioma patient show enhancement in CEST signal after administration of glucose infusion using Hyperglycemic clamp with DeFronzo's algorithm [1] as shown in Figure 5.

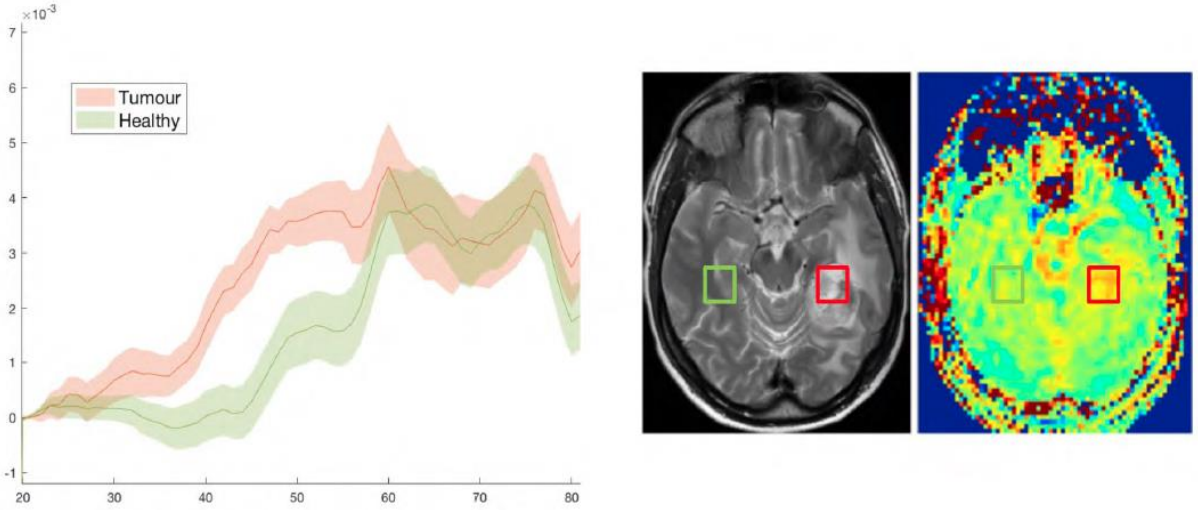

Figure 5: *MTR_{asym} plots of a glioma patient (#7) after B0 field drifts correction (left) show significant enhancement in GlucoCEST signal. Corresponding images of the patient brain are shown on the right.*

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5 Conclusions

The negative results from three adult lymphoma patients and one prostate cancer patient stem from low sensitivity and reduced selectivity at the field strength (3T) of a clinical scanner. It has been shown that B0 correction is essential to correct for field drifts during the glucoCEST experiment. Positive signal was observed only in the glioma patient. It has been demonstrated that the signal-to-noise ratio is not high enough to obtain a signal outside the brain possibly due to lower glucose delivery and outside cancer types with large vascular components. Therefore, the future study will focus on primary brain tumour (glioma) based on these preliminary results.

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Bibliography / References

[1] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol. 1979 Sep;237(3):E214-23.

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