GlucoCEST for the detection of human xenografts glioblastoma at early stage.

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Introduction

Tumours avidly consume glucose, a feature used by FDG-PET to discriminate tumour from healthy tissue and an indicator of maximal rates of cell proliferation[1]. GlucoCEST is a newly developed MRI imaging technique with the ability to detect glucose uptake in tissues, based on the chemical interaction of glucose hydroxyl protons and water. As previously reported, glucoCEST and FDG measurements provide equivalent information in various flank tumour models[2]. However, because glucoCEST measures natural glucose[3] as opposed to the modified FDG, information offered by both techniques might vary across tumour types[4]. In addition, performing measurements of glucose uptake in the brain may be challenging due to high background in grey matter, a known issue in brain FDG-PET scans[5].

This work therefore explores the feasibility of using glucoCEST as a tool for early detection of primary brain tumours.

Methods

Human glioblastoma cells were injected intracranially in immune suppressed (NON-SKID) mice (n=2) and allowed 200 days to grow. Prior to glucoCEST measurements mice were fasted for 24 hours in order to reduce and stabilize blood glucose levels. GlucoCEST data were acquired using a modified turbo-flash sequence (TR=2.73ms, TE=1.52ms, flip=5^o, FOV=20x20mm^2, slice thickness=1mm, matrix size=64x64) with a saturation train prior the readout of 80 Gaussian pulses at 1μT (pulse length=50ms, flip=400^o, 91% duty cycle). Saturation was applied at 51 frequency offsets ranging from -4 to 4ppm, giving a temporal resolution of 4 minutes per Z spectrum.

Mice were anaesthetized with 1.3% isoflurane and cannulated via the intra peritoneal route for glucose administration while in the scanner. GlucoCEST baseline scans were performed for 20 minutes followed by glucose administration of 1g/Kg (0.3ml of 10% glucose in saline solution) and 2.5 hours of post-glucose scans.

The glucoCEST signal enhancement (GCE) was calculated as the change in MTR_{asym} pre- and post- glucose administration, integrated between 0.4 and 1.8 ppm. Both high resolution spin echo (SE) anatomical scans (TR=3s, TE=20ms, ETL=6, FOV=20x20mm^2, slice thickness=0.5mm, matrix size=256x256) and histological analysis of human-specific cells (Vimentin) were performed for comparison with glucoCEST images. Two anatomical scans were acquired; one before the glucoCEST experiment and a second one before histology, 15 days later.

Results and Discussion

GlucoCEST data show an overall GCE increase across the entire brain, due to the slight hypoglycaemic state of the mice prior to glucose injection. However, there is a significantly higher increase ($p<0.03$) in regions affected by tumour, detected from 12 minutes after injection (Fig.1).

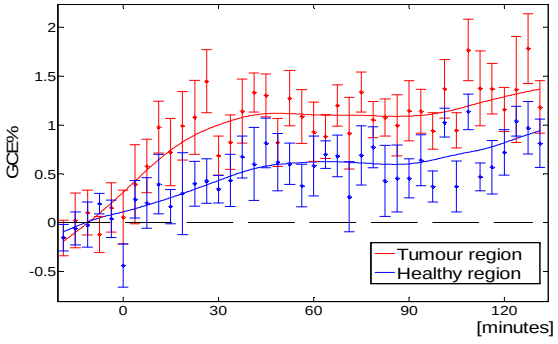

Figure 1: Time evolution of the mean GCE across two different regions (tumour in red, healthy tissue in blue). A significantly higher signal increase is observed in the tumour region followed by glucose administration at t=0 minutes.

The averaged GCE image over the first 20 minutes shows a well demarcated tumoral area. Interestingly, comparison of the GCE image with anatomical and histology images suggests that glucoCEST can identify tumour regions at an earlier stage than the SE images (Fig.2). A possible explanation for this finding is that at early stages of cancer, while brain structures are still not disrupted and the T2 relaxation times are unaffected, tumours cells already proliferate at higher rates with a dysregulated metabolic pattern. Therefore, the GCE image displays features that better match with the anatomical scan 15 days later when disrupted cell membranes in tissue provide T2 weighted contrast. Pixel by pixel analysis shows a weak correlation (R^2=0.13) with GCE versus Anatomical (day15), while no correlation was found (R^2=0.027) with GCE versus Anatomical (day1).

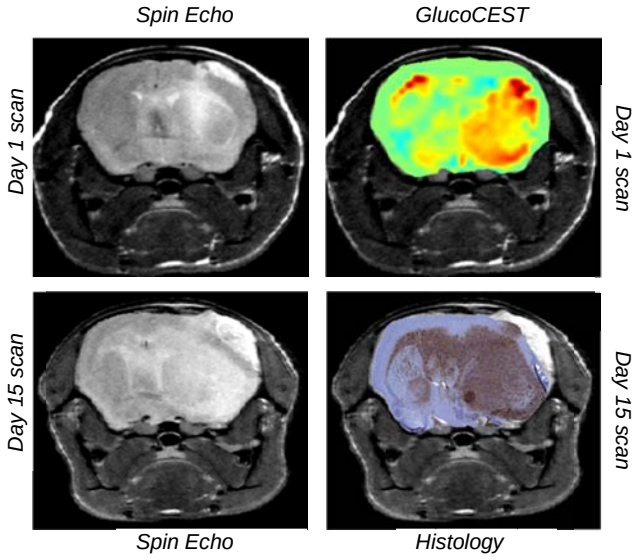

Figure 2: Comparison between glucoCEST, spin echo and histology. At day 1 the SE image is unable to show the full penetration of the tumor, while glucoCEST already displays the features that will be detectable 15 days later with SE.

Conclusion

In this preliminary study, we show that glucoCEST is sensitive enough to distinguish between cancerous and healthy tissue in the brain. Furthermore, due to the particular source of glucoCEST contrast (glucose uptake rather than relaxation times), the technique can depict cancer-affected areas before the appearance of microstructural changes.

Another important strength of the technique is the possibility for dynamic assessment of tumour metabolism, which might be useful as a potential characterization tool of tumour malignancy.

An extensive study is being conducted using different glioblastoma models (3 human xenograft and 1 allograft) to validate these findings and investigate the importance of glucose uptake dynamics for the characterisation of glial tumour grade.

References

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