MEDICAL PHYSICS COMMUNITY · INSPIRATION · INNOVATION · IMPACT

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JOINT AAPM | COMP MEETING

Visualization of Cervical Cancers with MRI-Based Metabolic Imaging

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ABSTRACT

18F-fluorodeoxygluose positron emission tomography (18F-FDG-PET) is clinically useful in cervical cancer. Chemical exchange saturation transfer (CEST) MRI with glucose-based contrast agents has been suggested as a non-radioactive, non-toxic alternative to 18F-FDG-PET. While many CEST studies have utilized D-glucose (D-Glc), it is not directly analogous to FDG as it is fully metabolized rather than accumulating intracellularly. D-glucosamine (D-GlcN), an amino monosaccharide, is phosphorylated like FDG then slowly metabolized, exhibiting favourable uptake kinetics and safety. D-GlcN CEST successfully visualized human breast cancer, but has yet to be applied to cervical cancer. This work aims to assess D-GlcN-CEST as an alternative to 18F-FDG-PET for cervical cancer imaging.

NMR tubes containing 0-20mM D-GlcN in PBS (pH 6.6) were imaged at 7T (Bruker Biospec MRI; 40 mm inner diameter quadrature RF coil) using a CEST-RARE sequence. N=5 NOD/SCID mice bearing orthotopic ME180 xenografts were imaged before and after injection of 1g/kg D-GlcN HCl (Sigma Aldrich) in saline. Tumour ROIs were selected from coregistered T2 anatomical scans. B0 inhomogeneity was corrected through spline interpolation and saturation transfer was calculated through asymmetry analysis (Moritz Zaiss, Matlab2023b).

In the phantom study, the strongest MR signal modulation was observed at ~1 ppm with signal modulation from 0 to 21% across D-GlcN concentrations. Saturation transfer increased linearly with D-GlcN concentration. In the animal study, a small but statistically significant increase in saturation transfer was observed within the tumours.

D-GlcN is a CEST contrast agent with potential utility in cervical cancer visualization. While the observed effect was modest, preliminary phantom and animal studies suggest that D-GlcN can provide non-toxic, non-radioactive MRI contrast in cervical tumours

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INTRODUCTION

- Metabolic imaging with F18-FDG PET is useful in cervical cancer care for staging, treatment planning, and follow up evaluation[1]
- Limitations of F18-FDG PET include:

Radiation Dose | Radiotracer Cost | Specialty Scanner | Low Spatial Resolution | Cyclotron Infrastructure

- CEST is an MRI technique that indirectly detects tracer protons as they exchange with surrounding water protons (Figure 1)
- CEST with glucose-based contrast agents has been investigated for cancer imaging, but literature thus far excludes cervical cancers[2]
- D-glucosamine (D-GlcN) is a CEST-visible, non-toxic, amino sugar, with similar transport properties as F18-FDG (Figure 2)[3]

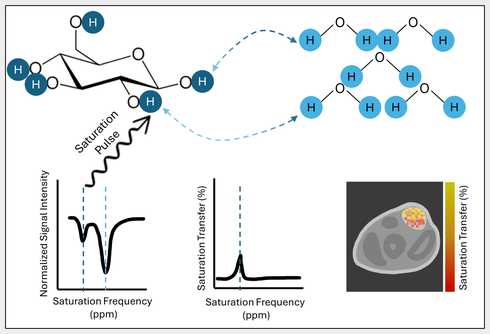

Figure 1. CEST mechanism, where saturated protons are continuously exchanged with water protons, causing a quantifiable drop in water signal. .

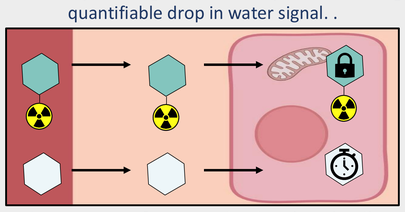

Figure 2. Transport of F18-FDG (top) and D-GlcN (bottom) from vasculature, to extracellular space, to cell, with F18-FDG trapped and D-GlcN slowly metabolized.

METHODS AND MATERIALS

Phantom Experiment

- Phantom consisting of 5 X 5mm NMR tubes containing 0, 5, 10, 15, and 20 mM D-GlcN in pH 6.6 PBS

Animal Experiment

- N=5 NOD/SCID mice bearing ME180 orthotopic cervix tumours3 (5-7mm)[4]
- Z-spectra acquired pre and post injection of 1g/kg D-GlcN HCl in saline

Analysis

- B0 inhomogeneity corrections based on spline interpolation
- Saturation transfer quantified via asymmetry analysis: $$ST\% = \frac{S(-\omega) - S(+\omega)}{S_0} \times 100\%$$

Table 1. MRI parameters for phantom and animal experiments.

	Phantom	Animal
System	7T Bruker Biospec	
Readout	RARE	
RARE Factor	80	32
TR/TE (ms)	10000/5	
FOV/Matrix	20x20mm/80x80	32x16mm/64x32
Saturation Scheme	2μT , 5s	
Saturation Offsets	±3.5ppm, 0.25ppm intervals	±4.5ppm, 0.25ppm intervals

RESULTS

- In the phantom, ST% ranged from 6-21% for 5-20mM D-GlcN, with a linear dependence on concentration (Figure 3)
- Maximum ST% was observed at ~1ppm, consistent with D-GlcN-CEST literature
- In the animal experiment, there was a small but significant increase in ST% within the tumour (Figure 4)
- On average ST% increased by 0.6%
- One mouse (M4) exhibited high endogenous ST% prior to injection and did not exhibit a significant increase
- ST% maps show contrast between the tumour and surrounding tissue (Figure 5)
- High ST% is also observed in the bladder, likely due to urea having a similar chemical shift

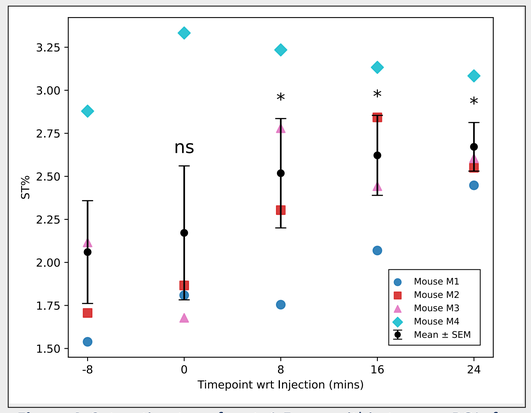

Figure 4. Saturation transfer at 1.5ppm within tumour ROIs for pre-injection (-8 mins) and subsequent post-injection timepoints, with small but significant increase from baseline post 8 minutes (p=0.3019, 0.011, 0.0337, 0.0168).

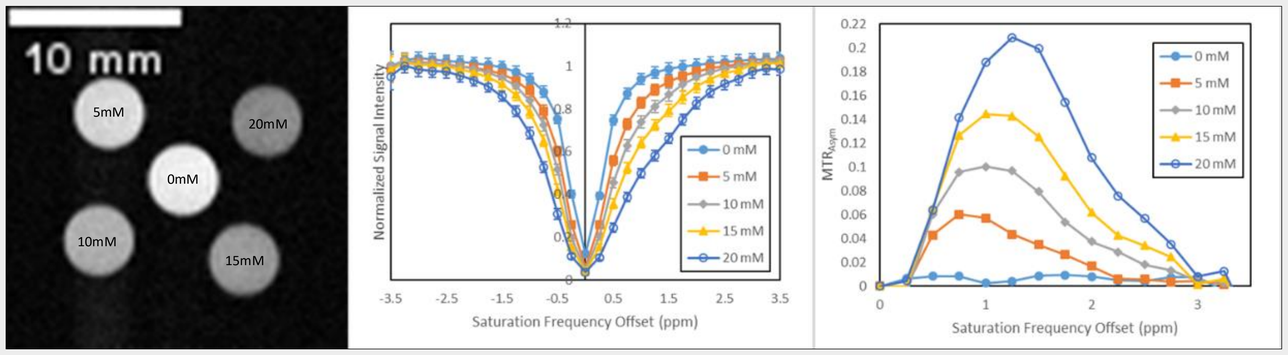

Figure 3. CEST phantom image at 1 ppm with D-GlcN concentrations labeled (left), D-GlcN z-spectrum (center), and D-GlcN MTRasym spectrum (right).

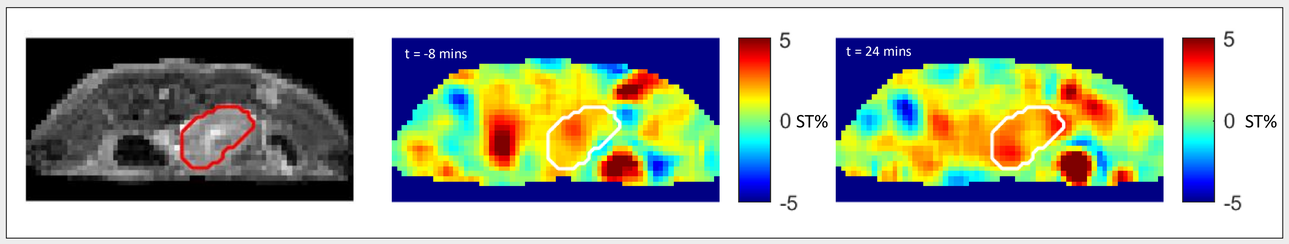

Figure 5. T2-weighted anatomical scan with tumour ROI in red (left). 1.5 ppm ST% map pre-injection with tumour ROI in white (center). 1.5 ppm ST% map post-injection with tumour ROI in white, showing increased ST% in tumour.

DISCUSSION

- The phantom and animal experiments discussed act as a proof of concept, suggesting that exogenous D-GlcN can be detected in cervical tumours
- The ST% appeared to still be rising at the last timepoint, suggesting a longer wait time between injection and imaging
- Compared to published D-GlcN-CEST data in murine breast tumours[3], the measured ΔST values were lower
- The relatively low ΔST and high baseline indicate some endogenous contrast that may be reduced by fasting
- Post imaging, tumours were immediately excised and flash frozen for a future NMR metabolomic study and immunohistochemisty
- This work will provide a quantitative measure of D-GlcN and downstream metabolites present in the tumours and provide insight on the underlying biology responsible for the increased GlcN uptake
- This study represent the first CEST trial of exogenous glucose-based contrast agents in a cervical cancer model

CONCLUSIONS

- While the effect remains modest, preliminary phantom and animal studies suggest that D-GlcN can provide non-toxic, non-radioactive MRI contrast in cervical tumours
- Further work will focus on optimizing in vivo imaging through fasting and a longer delay post injection
- Ultimately this project aims to improve cervical cancer care by providing metabolic information in a safe and practical way

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