# Bicarbonate as a theragnostic CEST agent for glioma models

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**Introduction**

Due to upregulated aerobic glycolysis, tumours have an acidic extracellular pH (pHe) [1]. This acidic environment promotes invasion and enhances metastasis, offering cancer a selective evolutionary advantage [2]. It has been shown that the administration of sodium bicarbonate increases the pHe of cancerous tissue, leading to reduction of metastasis and tumour invasion [3].

Changes in pH can be detected *in-vivo* by CEST MRI [4]. The goal of this study is to assess the CEST signal response of brain gliomas following the administration of an intra-peritoneal (IP) bolus of sodium bicarbonate.

**Methods**

Human glioblastoma cells ($3x10^6$) were inoculated intracranially in immune suppressed (NON-SKID) mice and non-inoculated mice were used as controls (n=6).

Mice were anaesthetized with 1.3% isoflurane and cannulated via the intra peritoneal route for bicarbonate administration while in the MRI scanner. CEST baseline scans were performed for 20 minutes followed by administration of 0.3ml of 8.4% bicarbonate solution and 1 hour of post-bicarbonate scans.

Anatomical scans were acquired with high resolution spin echo (SE) sequence (TR=3s, TE=20ms, ETL=6, FOV=20x20mm$^2$, slice thickness=0.5mm, matrix size=256x256).

CEST data were acquired using a modified turbo-flash sequence (TR=2.73ms, TE=1.52ms, flip=20$^o$, FOV=20x20mm$^2$, slice thickness=1.5mm, matrix size=64x64) with a saturation train prior the readout of 80 Gaussian pulses at 1.3μT (pulse length=50ms, flip=540$^o$, 91% duty cycle). Saturation was applied at 59 equally spaced frequency offsets ranging from -4.5 to 4.5ppm, giving a temporal resolution of 5 minutes per Z spectrum.

The CEST signal enhancement due to bicarbonate (BiCEST) was calculated as the change in $MTR_{asym}$ pre- and post- bicarbonate administration, integrated between 0.5 and 4 ppm.

**Results**

After bicarbonate administration, control mice show no CEST response whereas mice with glioma display regional increase of BiCEST signal. This signal increase peaks around 30 minutes post bicarbonate administration.

BiCEST signal appears to be enhanced in regions with no consolidated tumour, whereas a lower signal is observed in areas of already formed gliomas (see Figure 1).

Figure 2 shows the same glioma mouse as in figure 1, scanned 15 days later. Areas that were enhanced in the previous CEST scan show no signal once the tumour is consolidated (right side of the brain).

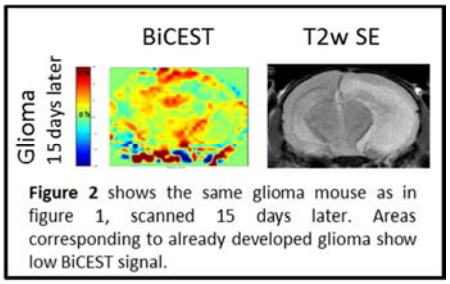


**Figure 2** shows the same glioma mouse as in figure 1, scanned 15 days later. Areas corresponding to already developed glioma show low BiCEST signal.

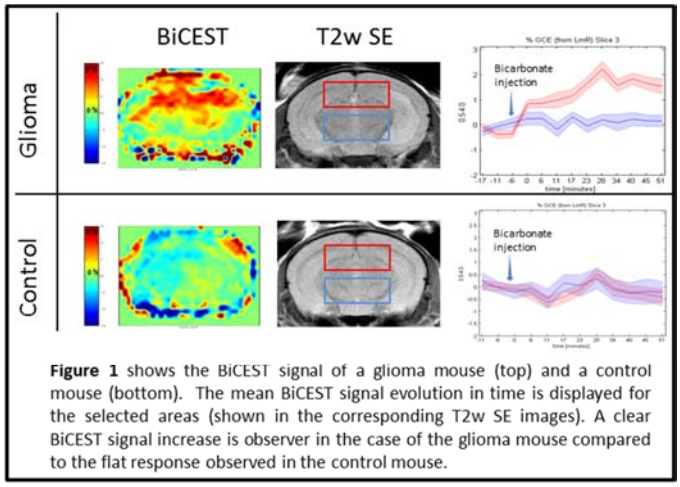


**Figure 1** shows the BiCEST signal of a glioma mouse (top) and a control mouse (bottom). The mean BiCEST signal evolution in time is displayed for the selected areas (shown in the corresponding T2w SE images). A clear BiCEST signal increase is observer in the case of the glioma mouse compared to the flat response observed in the control mouse.

**Discussion/Conclusion**

The acidic extracellular environment offers an open path through which cancer can progress. Administration of bicarbonate causes an alkalinization of this acidic environment which could delay tumour progression and in the same time allow the detection of cancer at early stage with CEST.

This preliminary study shows the potential of bicarbonate as a theragnostic CEST agent for the treatment and early assessment of gliomas.

**References**

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