# CEST MRI to contrast chondrosarcoma tumors: two contrasts in one acquisition

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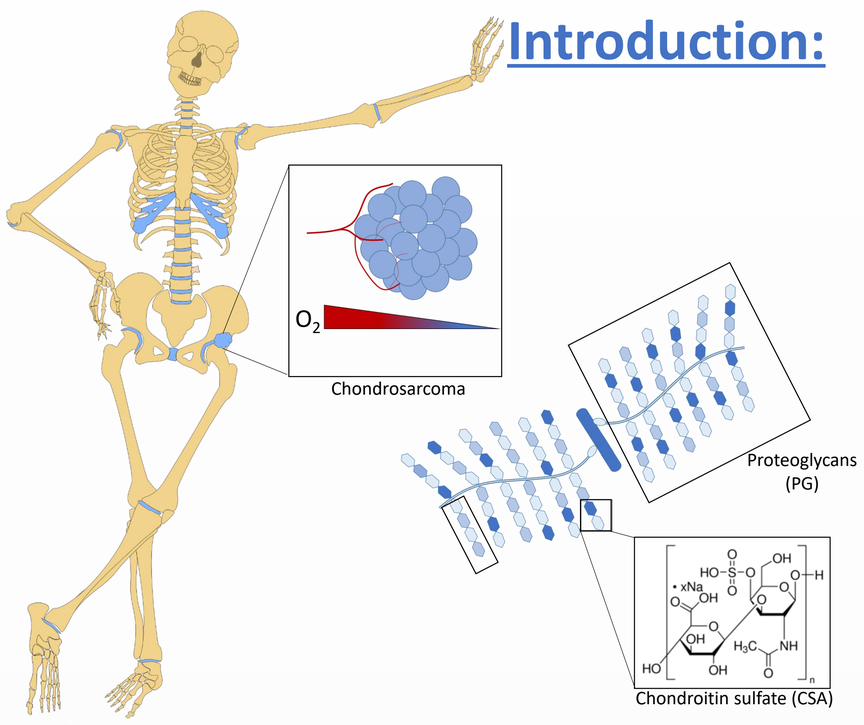
## Introduction:




Chondrosarcoma is a malignant cartilage tumor and represents the second most common primary malignant solid tumor of bone. It accounts for approximately 25% of all bone sarcomas (Bertoni et al. 2002). Poorly vascularized and rich in proteoglycans (PG), chondrosarcomas are considered to be chemo- and radio-resistant with efficient treatment usually limited to surgical resection with large disease-free margins. If the hypoxic and proteoglycan status of the tumor can be assessed by TEP imaging and scintigaphy, it requires however 2 separated exams.

In this context we propose to develop an MRI strategy based on Chemical Exchange Saturation Transfer (CEST) to simultaneously co-register both hypoxia (pH) and PGs content in vivo.

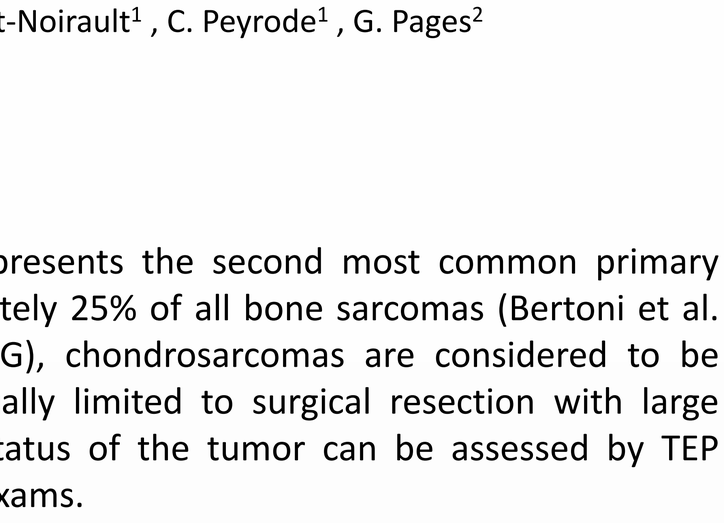
## Materials and methods:

*In vitro phantom*: The work hypotheses were tested in phantoms containing chondroitin sulfate A (CSA) (1, 2.5, 5, 10 20, 40mM) or creatine (pH 6.5, 6.75, 7.0, 7.25, 7.5) to validate PGs and pH imaging, respectively.

*In vivo model of chondrosarcoma*: Nude NMRI mice (n=6) aged 4–5 weeks old were implanted with human chondrosarcoma HEMC-SS xenograft ($3x10^6$ cells in 50µL PBS) in para tibial position. After 8 weeks growth xenograft were characterized in terms of proteoglycan content and hypoxia by CEST MRI. *In vivo* imaging was performed on anesthetized mice (1.5% isoflurane in air/$O_2$ 70/30, v/v, mixture).

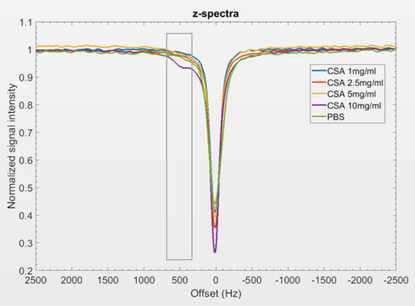
*MRI protocol*: MRI images were acquired at 11.7 T using a 40-mm quadratic volume coil. DWI was first performed to localize the tumor, then WASSR (B1=0,1µT for 1.5s, Δωsat=±1000Hz in 20Hz steps) and CEST Z-spectra (B1=1.5µT for 4s, Δωsat=±3000Hz in 50Hz steps) were acquired based on a RARE protocol. Data were analyzed using an in-house program written in Matlab®R2017a. After correction for B0 inhomogeneity, the CEST maps were generated.

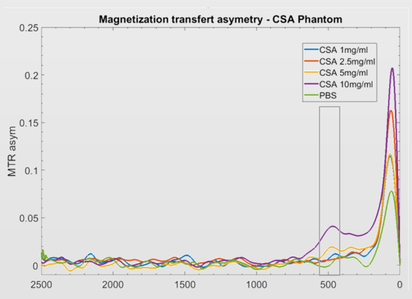
CEST MRI Principle

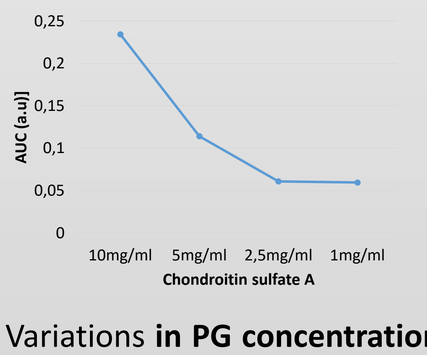



## Results *in vitro* :

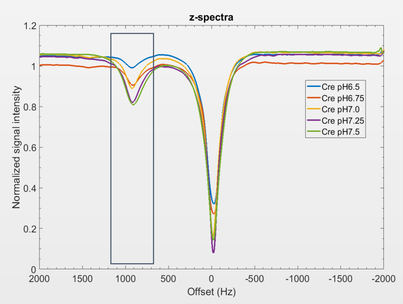
Proteoglycans: Chondroitin Sulfate 4 phantom

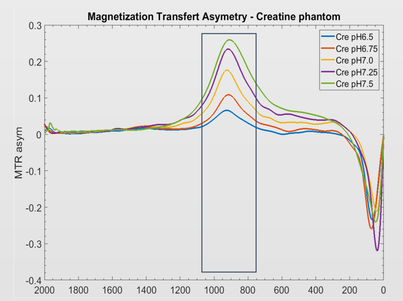


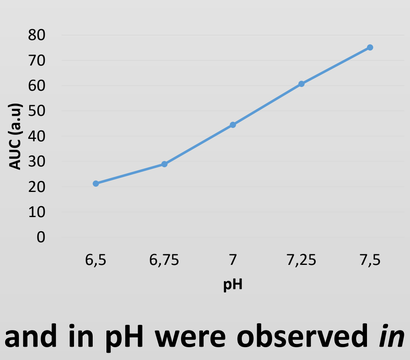




Hypoxia (pH): Creatine phantom



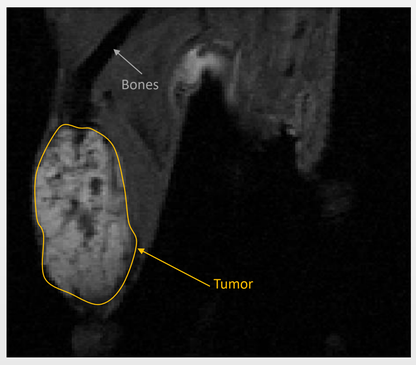



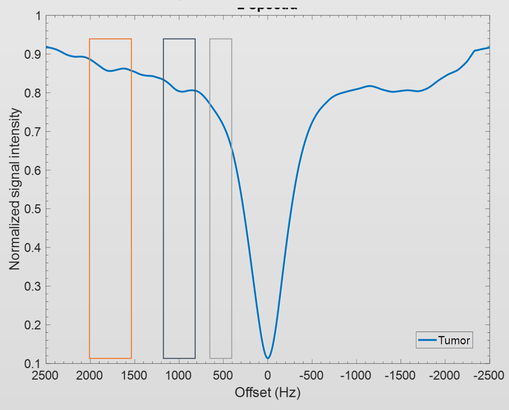

Variations **in PG concentration and in pH were observed *in vitro* by CEST MRI** by monitoring the magnetization transfer ratio asymmetry at 450 (-OH) and 1000Hz (-NH), respectively.

## Results *in vivo* :

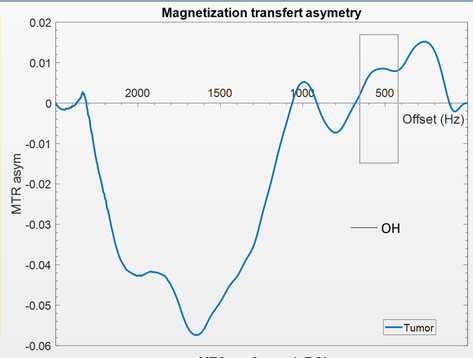
**Diffusion MRI of chondrosarcoma (coronal view)**

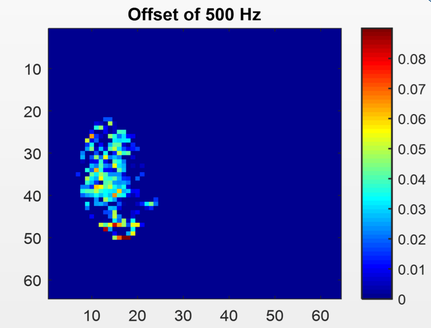



**Z spectra tumor ROI**

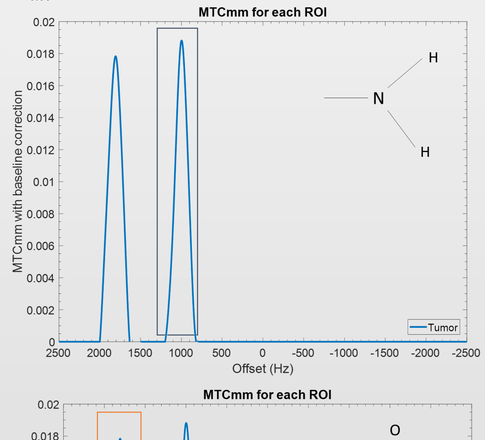


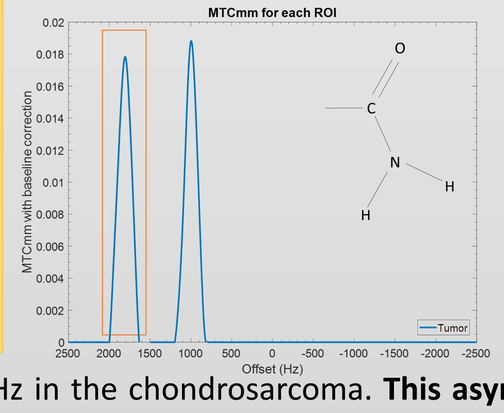

Proteoglycans — Without Baseline correction

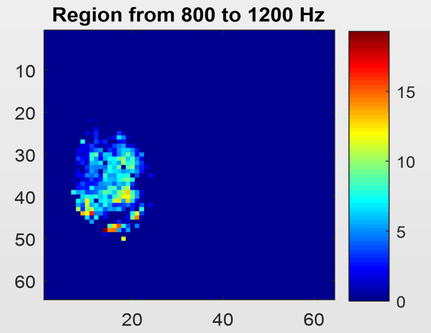



Hypoxia (pH) — With Baseline correction




*In vivo* results showed an asymmetry at 500Hz in the chondrosarcoma. **This asymmetry is expected as during the pathology development the PG concentration increases.** *In vivo*, we also observed changes in asymmetry at 1000Hz (amine group) and 1800Hz (amide group) inside the chondrosarcoma. Theses variations are associated **with acidosis in the hypoxic status** within chondrosarcoma

## Discussion – Conclusion

CEST MRI can be used as a new strategy for non-invasive assessment of chondrosarcoma. Indeed, **CEST MRI offers the possibility to image in the same exam the 2 main characteristics of this tumor: pH and PG contain.** CEST MRI allows identifying and **differentiating zones of hypoxia *in-vivo***. In the next step, comparison with other MRI techniques such as $^{23}$Na MRI (PGs contain) and $^{31}$P MRS (pH) as well as nuclear imaging such as $^{18}$F-MISO and $^{99m}$Tc-NTP15.5 will be done in order to validate the procedure.

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