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# Chondrosarcoma radiotherapy with helical delivery and analysis of MR guidance

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## ABSTRACT

**Purpose:** To screen cell and metabolic qualities of chondrosarcoma of thoracic spine through the span of standard 6-week chemoradiation treatment on helical delivery with compound trade immersion exchange - MRI; and to recognize the most suitable process for CEST could decide consequent restorative reaction. **Material and Methods**: Twelve patients with recently analyzed chondrosarcoma were selected, and CEST-MRI was obtained promptly previously (Day0), 2 weeks (Day14) and a month (Day28) into treatment, and multi month after the finish of treatment (Day70). A few CEST measurements, including charge exchange proportion and region under the bend of CEST tops relating to atomic Overhauser impact and amide protons (MTRNOE, MTRAmide, CESTNOE, and CEST Amide separately), polarization exchange (MT), and direct water impact were examined. Normal tissue volume with target volume coverage was analyzed with plans yielding mean low dose. Absence of early movement was resolved as no expansion in tumor size or intensifying of clinical side effects as per routine post-chemoradiation serial auxiliary MRI. **Results :** Changes in MTRNOE (nonprogressors = 1.35 ± 0.18, progressors = 0.97 ± 0.22, P = .006) and MTRAmide (nonprogressors = 1.25 ± 0.17, progressors = 0.99 ± 0.10, P = .017) between pattern (Day0) and Day14 brought about the best detachment of nonprogressors from progressors. Besides, the pattern (Day0) MTRNOE (nonprogressors = 6.5% ± 1.6%, progressors = 9.1% ± 2.1%, P = .015), MTRAmide (nonprogressors = 6.7% ± 1.7%, progressors = 8.9% ± 1.9%, P = .028), MT (nonprogressors = 3.8% ± 0.9%, progressors = 5.4% ± 1.4%, P = .019), and CESTNOE (nonprogressors = 4.1%ċHz ± 1.7%ċHz, progressors = 6.1%ċHz ± 1.9%ċHz, P = .044) could distinguish progressors even before the beginning of the treatment.

**Key Words:** Chondrosarcoma, MRI, Treatment planning, CT, radiotherapy

## Introduction

Magnetic resonance imaging (MRI) is rarely used in assessing response of chondrosarcoma to therapy. Current response evaluation criteria [1]rely on structural changes in tumor size, which take months to occur. Considering the poor prognosis of chondrosarcoma patients [2], a biomarker of response that could identify progressive tumor early after completion of, during, or even before treatment (through characterizing tumor aggressiveness) could have significant clinical utility.

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Several functional MRI biomarkers, such as magnetic resonance spectroscopy, magnetization transfer (MT), diffusion-weighted MRI, and dynamic contrast-enhanced MRI, have been investigated in assessing chondrosarcoma response at 1 to 3 months after therapy [3]. This post chemoradiation time point is the accepted standard for response evaluation in clinical practice. However, very few studies have explored the potential for advanced MRI-based biomarkers during the course of chemoradiation in humans [4]. As chondrosarcoma treatment advances into the era of daily MRI-guided radiation therapy [5], the ability to perform daily imaging of tumors and exploring the potential to perform true adaptive radiation therapy and biologic response-based planning is imminent. A massive coordinated effort to standardize and explore novel sequences that are non–contrast-based is urgently in need. This study explores the potential for chemical exchange saturation transfer (CEST) imaging to be a

novel non–contrast-based imaging biomarker able to monitor and quantify metabolic changes secondary to treatment effects.

Chemical exchange saturation transfer is sensitive to concentration and exchange of labile protons in the tissue [6]. Ample research in cancer CEST has shown that concentration of certain labile protons changes in tumors. The exchange rate of these protons with water protons, which is sensitive to many micro-environmental factors, such as pH, also changes in tumors. Numerous CEST metrics, including amide proton transfer (APT), have been used in tumor characterization and evaluating chondrosarcoma response to therapy. Zaiss et al showed that tumors have significantly lower CEST signal at the frequency offset corresponding to nuclear overhauser effect (NOE). Sagiyama et al showed, in a rat model of chondrosarcoma, that CEST was capable of predicting response to temozolomide within 1 week. Ma et al successfully differentiated pseudo-progression from true progression in chondrosarcoma using APT 3 months after the treatment. McVicar et al [7] demonstrated the ability of APT in determining response to chemotherapy (tumor acidification with lonidamine) in a chondrosarcoma model in mice as early as 1 hour after treatment. Scheidegger et al compared the CEST signal of chondrosarcoma and normal white matter and concluded that the main contributor to their differences was the MT contrast. The delivery with helical tomotherapy for IMRT is well established in cases requiring durable local control with high doses[8]. As per literature the spinal cord tolerance dose of 45 to 55 Gy is quite below the radiation dose required for chondrosarcoma and helical intensity modulated delivery with tomotherapy is reported to be effective in achieving the prescribed dose with available clinical limitations. The study further reported that sensitive tumor target volume and sensitive normal tissue sparing should be monitored[8].

Chemical exchange saturation transfer is sensitive to treatment-induced changes, such as apoptosis due to radiation therapy [9]or pH normalization caused by temozolomide [10]. These changes occur much earlier than morphologic changes in tumor dimensions and make CEST a promising candidate for early response evaluation. The present study investigates monitoring CEST in chondrosarcoma over the course of a standard 6-week chemoradiation treatment to determine the earliest time point therapeutic response could be evaluated. Assessing response before or within early phases of the treatment may allow for tailoring of the treatment plan to the individual patient's tumor biology and may improve outcome. Recently, researchers at University of Wisconsin, successfully completed the consistency measurements for delineated field strength and baseline procedure measurements with their scan protocol and ultimately monitored the MRI scanner using MR guided RT planning. This approach motivates us to encapsulate MR simulations in the treatment delivery process [11]

## Materials and Methods

Twelve patients with newly diagnosed chondrosarcoma tumor were recruited (13 male, median age 55 years). The study was conducted in accordance with regulations and guidelines of the institutional research ethics board at Sunnybrook Research Institute. Informed consent was obtained from all patients, and all experimental protocols were approved by the research ethics board.

Computed Tomography scans of the chest, abdomen, and pelvis were used to determine cases of metastasis[8]. CT simulated outcomes were exported to pinnacle treatment planning system and as per existing literature, clinical target volume, regions of interest, spinal cord, cord center, esophagus, heart and both lungs were contoured [8]. A 5mm expansion was added to clinical target volume for selecting planning target volume. All patients were treated with intensity modulated radiation therapy (≤2 Gy/day with a boost of < 20Gy to PTV2[8]. Helical treatment delivery plans were generated using a 2.5 cm field width and 0.286 pitch with normal dose calculations grid of 0.309 x 0.309 $cm^2$[8]. Comprehensive longitudinal MR images were acquired at 4 different time points during and after the course of treatment, as follows: (*1*) immediately before the start of the treatment ($Day_0$); (*2*) after receiving 10 treatment sessions ($Day_{14}$); (*3*) after receiving 20 treatment sessions ($Day_{28}$); and (*4*) 4 weeks after the end of the treatment ($Day_{70}$).

Response to treatment was determined at longer than 3 months after the end of the 6-week chemoradiation (between 3 and 8 months after treatment, during which 2 patients were deceased) and was defined as per Response Assessment in Neuro-Oncology criteria (2) through assessing tumor size (ie, stable tumor) on anatomic post-gadolinium (Gd) $T_1$-weighted ($T_{1w}$) and $T_2$-wieighted ($T_{2w}$) fluid-attenuated inversion recovery (FLAIR) MR images, as well as clinical symptoms of the patient. Response Assessment in Neuro-Oncology criteria were used because they are specifically designed to address the issue of pseudo-progression by imposing strict rules on determination of progression within the first 12 weeks of treatment. Response was determined by a senior neuro-oncologist who was blinded to the MRI analysis, whereby patients were classified as early progressors and nonprogressors

**MRI acquisition**

The patients were scanned on a 3T Philips Achieva MRI system with 8-channel SENSE head coil with the following MRI sequences: 3-dimensional (3D) $T_{2w}$-FLAIR data (repetition time [TR]/echo time [TE]/inversion time [TI] = 9000/2800/125 milliseconds, slice thickness = 5 mm, 25 slices, field of view [FOV] = 24 cm × 24 cm) was used to identify an oblique axial slice passing through the largest cross-section of the tumor for CEST imaging. To ensure accurate reproducibility of the CEST slice prescription between multiple scans, specific brain structures were first used to prescribe the 3D-FLAIR sequence. Then the coordinates of the FLAIR slice that passed through the largest cross-section of the tumor was used as the CEST imaging slice. For subsequent scans, the FLAIR scan was prescribed using the same brain structures, so that the 3D-FLAIR coverage would be identical to the earlier scans of the patient. Then the same FLAIR slice number that was used in previous scans was used to prescribe the CEST slice.

Offset frequencies between −750 Hz (−5.9 ppm) to 750 Hz (5.9 ppm) with increments of 25 Hz were used in CEST spectrum data acquisition. Four reference images at 100 kHz (approximately 780 ppm) were acquired at the beginning, and another 4 reference images were acquired at the end of the CEST spectrum data acquisition. These reference images were used for drift correction and CEST spectrum data normalization (12). Chemical exchange saturation transfer data were acquired with radio frequency (RF) power amplitude, $B_1$ = 0.522 μT, and saturation duration, $T_{sat}$ = 970 milliseconds. The RF saturation consisted of 4 block-shaped pulses of 242.5 milliseconds each. There was also a delay of 2.5 milliseconds after each block, during which spoilers were applied in the slice selection direction.

The CEST imaging readout was fast field echo (FFE) with multi-shot turbo field echo (TFE) factor = 20, TR/TE = 7.78/4.5 milliseconds, half scan = 0.8, acquisition matrix = 132 × 95, reconstruction matrix = 144 × 144, FOV = 20 cm × 20 cm, slice thickness = 3 mm. There was also a spectral presaturation with inversion recovery (SPIR) fat suppression (12 milliseconds) after the saturation pulses and before the TFE acquisition. To allow for the magnetization to recover and also to satisfy duty cycle constraints, a delay was included after TFE acquisition, making the time between consecutive saturations equal to 2 seconds. Chemical exchange saturation transfer imaging was performed twice, for a total duration of 4.6 minutes.

$T_2$-mapping was performed on the same slice using a $T_2$-weighted spin echo sequence with 10 echo times (TE = n × 20 milliseconds, n = 1, 2, 10), TR = 3000 milliseconds, FOV = 20 cm × 20 cm, slice thickness = 3 mm, matrix size = 80 × 80, α = 90°. $T_2$-mapping was performed by fitting a mono-exponential function to the data on a voxel-by-voxel basis.

To optimize the process we used the proven approach of measurements with several number of OC inserts, and considerations of signal to noise ratio alongwith uniformity and setup of laser alignment (11). For benchmarking we used MRgRT quality control criteria from existing work on edge spread transition width ranging from 10-90% and signal uniformity restricted within 30 cm of diameter (11).

The Method of Slopes was used for $B_1$- and $T_1$-mapping (13). Method of Slopes image acquisition consisted of high spatial resolution images with small flip angles (FFE, α = 3°, 14°, TR/TE = 10.7/5 milliseconds, FOV = 20 cm × 20 cm, matrix size = 224 × 224 × 40, slice thickness = 2 mm), as well as low spatial resolution images with large flip angles (FFE, α = 130°, 150°, TR/TE = 50/5 milliseconds, FOV = 20 cm × 20 cm, matrix size = 80 × 80 × 20, slice thickness = 6 mm). The low-resolution, high flip angle images were used for $B_1$-mapping, and the high-resolution, low flip angle data allowed for high resolution $T_1$-mapping [14]

**CEST analysis**

The CEST images, the multi-echo images for $T_2$-mapping, and the FFE images for $T_1/B_1$-mapping were all co-registered to the first acquired CEST image (first reference image of the first CEST spectrum) using affine registration in Elastix (15). Chemical exchange saturation transfer data of each spectrum were first normalized to the reference images acquired at the beginning of the spectrum. Drift correction was performed using the reference images at the 2 ends of the CEST spectrum. $B_0$ inhomogeneity correction was performed by fitting a Lorentzian line-shape to the data surrounding the water resonance ($|\text{offset}| < 1.3$ ppm) and the end tails of each spectrum ($|\text{offset}| > 4.5$ ppm). The spectrum was then shifted to place the minimum on the 0-Hz offset frequency. Any voxel that failed to fit to the Lorentzian line-shape was discarded. Data were then resampled at the offset frequencies of the imaging protocol. The normalized, drift, and $B_0$-corrected spectrums of the 2 CEST repetitions of each voxel were then averaged to generate the final CEST spectrum used in calculating the following CEST metrics.

(*1*) Magnetization transfer ratio (MTR) of amide protons, defined as:

$$\mathrm{MTR}_{\mathrm{Amide}} = \frac{S(ref) - S(3.5\,ppm)}{S(ref)}$$

where *S*(*ref*) represented the reference image (equal to 1 for the normalized CEST spectrum), and $S(\Delta)$ represented the CEST spectrum value at offset frequency $\Delta$ (which was 3.5 ppm for amide protons).

(*2*) The MTR of nuclear overhauser effect (NOE) at −3.5 ppm:

$$\mathrm{MTR}_{\mathrm{NOE}} = \frac{S(ref) - S(-3.5\,ppm)}{S(ref)}$$

(*3*) The conventional amide proton transfer (APT) was defined as:

$$\mathrm{APT} = \frac{S(-3.5\,ppm) - S(3.5\,ppm)}{S(ref)}$$

The signal in CEST spectrum represents a combination CEST effect, MT, and direct water saturation effect (direct effect).

Tumor ROI

The tumor ROI was defined on post-Gd $T_{1w}$ data and was transferred to the CEST images. To achieve this, the 3D volume imaged in post-Gd $T_{1w}$ data was first co-registered to the 3D FLAIR data using affine registration in Elastix (18). It was then interpolated with the voxel resolution of the CEST data, and the oblique axial slice corresponding to CEST was selected (CEST slice matched a slice of the 3D FLAIR data). Two analysis ROIs were then defined and were used in longitudinal evaluation of the CEST metrics: (*1*) ROI type I: the tumor ROI was defined as the enhancing region on the post-Gd $T_{1w}$ slice that was acquired at each scan; (*2*) ROI type II: The tumor ROI was defined as the enhancing region on the post-Gd $T_{1w}$ slice at the baseline scan and was kept constant for the subsequent scans.

In ROI type I, the CEST metrics represented the average CEST properties of the tumor ROI, and thus change in the tumor size was not taken into account. In ROI type II, however, the ROI was defined at the first scan, and if the tumor size changed over time, other tissues (eg, peritumoral tissue) would enter the ROI, thus change in tumor size would affect the average CEST metric value in ROI type II. The ROI type II represented the brain region that received the highest radiation dose (defined in radiation therapy planning stage) throughout the treatment. By investigating both ROI types, a more comprehensive understanding of the CEST metric changes over the course of the treatment was achieved.

Normal tissue

The CEST metrics were also calculated on an ROI of cNAWM. This measurement was performed to monitor the reproducibility of the CEST metrics between patients and also over the course of the treatment (intersubject and intrasubject reproducibility). The cNAWM ROI was defined on an area of uniform signal intensity in the white matter in post-Gd-$T_{1w}$ MRI. Considering the invasive nature of chondrosarcoma cells and the fact that they could migrate far from the tumor (even to the contralateral hemisphere of the brain) (19), the cNAWM was chosen to be on the farthest possible (from tumor) white matter region on the contralateral hemisphere.

## Results

Data of 3 patients were discarded because of significant motion and imaging artifacts in the tumor ROI. The remaining 16 patients were classified by the blinded neuro-oncologist into nonprogressors (10 patients) and progressors (6 patients) at the time of last follow-up. A few of the patients did not complete all 4 scans and therefore there were the following number of patients at each time point: $Day_0$: 10 nonprogressors, 6 progressors; $Day_{14}$: 10 nonprogressors, 4 progressors; $Day_{28}$: 8 nonprogressors, 3 progressors; $Day_{70}$: 10 nonprogressors, 3 progressors.

For each patient, the CEST metrics were calculated voxel by voxel, and then the average metric value over the tumor and cNAWM ROIs was calculated and used in subsequent statistical analyses.

To minimize operator bias in selecting tumor and cNAWM boundaries, the ROIs were defined on the post-Gd $T_{1w}$MRI and then transferred to the CEST slice (by co-registering the 2 datasets). The reproducibility of the CEST metrics was examined on the cNAWM (reported in Table E-1; available online at www.redjournal.org). For cNAWM, no statistically significant difference was observed between the CEST metrics of any 2 time points (assessed by Wilcoxon rank-sum test) or between progressors and nonprogressors (assessed by unpaired *t*test), demonstrating the stability and reproducibility of the experiments.

The $MTR_{NOE}$ and $MTR_{Amide}$ maps show lower MTR values on the tumor compared with normal tissue and regions of edema. These lower MTR values are mainly due to the low MT effect of the tumor compared with normal tissue. Similarly, $CEST_{NOE}$ is showing lower values for the tumor; however, $CEST_{Amide}$ in the tumor is showing values that are higher than normal tissue (which is expected for the tumor).

The mean and standard deviation of the CEST metrics (segregated into progressors and nonprogressors) are reported for the ROI type I, in which tumor ROI was defined as enhancing region on the post-Gd $T_{1w}$ image at each time point. The parameter pairs that were statistically significantly different between progressors

and nonprogressors are noted with a dagger symbol (†). When focusing on the absolute value of the metrics for tumor ROI only (ROI type I), the $MTR_{NOE}$ (**P** = .015), $MTR_{Amide}$ (**P** = .028), MT (**P** = .019), and $CEST_{NOE}$ (**P** = .044) at baseline ($Day_0$) were statistically significantly different between the progressors and nonprogressors. However, none of the metrics at any subsequent time point were able to differentiate the 2 cohorts. These CEST metrics show that nonprogressors are less metabolically active compared with progressors before treatment.

The distribution (mean and standard deviation) of CEST metrics for ROI type II is reported, in which tumor ROI was defined at $Day_0$ scan and was kept the same for consecutive time points and thus takes the changes in tumor size into account as well. Similar to ROI type I, the absolute value of the metrics at $Day_{14}$, $Day_{28}$, and $Day_{70}$ were unable to differentiate progressors from nonprogressors. This data demonstrates that there is significant difference in CEST metrics of the 2 cohorts before treatment and that they become similar as treatment is administered.

Similar separations were observed when using ROI type II. The ratios ($Day_{14}$ over $Day_0$) of $MTR_{NOE}$(nonprogressors = 1.30 ± 0.19, progressors = 0.93 ± 0.31, *P* = .02) and $MTR_{Amide}$ (nonprogressors = 1.20 ± 0.20, progressors = 0.92 ± 0.27, *P* = .05) differentiated the 2 cohorts. This data demonstrates that there is no significant change in the direct effect at any time point, showing that treatment is not changing $T_1$ or $T_2$ values of the tumor. The MT metric did not change for progressors; however, in nonprogressors there was an increase in this metric as early as 2 weeks into the treatment, which stayed relatively unchanged (slightly decreased) at the last 2 scans. The CEST signals also stayed unchanged for progressors, showing that treatment was not inducing any metabolic changes in the tumor. However, for nonprogressors the increase in CEST metrics could be due to inflammatory response to the tumor cells being destroyed by the treatment; it could also stem from pH normalization by temozolomide.

The ratios of CEST metric values at $Day_{28}$ or $Day_{70}$ over baseline did not provide a statistically significant separation of the 2 cohorts. This could potentially be associated with having very few progressors participating in the later follow-up scans.

In the present longitudinal evaluation of human chondrosarcoma response to therapy, CEST data of patients at multiple time points was obtained before, during, and after the end of the 6-week standard chemoradiation treatment. The objectives were to (*1*) investigate the potential of CEST in evaluating chondrosarcoma response to treatment; (*2*) determine the earliest time point at which CEST could identify nonprogressors; and (*3*) identify the CEST metrics (if any) that were able to characterize tumor aggressiveness before the treatment.

The CEST metrics were first calculated on the cNAWM region of each patient. As reported in Table E1 (available online at www.redjournal.org), there was no statistically significant difference between the CEST metrics on cNAWM between consecutive time points, and there was a small variation in the metric values. These results show there was no intersubject or intrasubject variability, which demonstrates reproducibility of the experiments and that the differences in measured metrics represent the differences between tumors and are not due to experimental conditions [16]

The main goal of radiotherapy delivery for normal tissue dosimetry in controlled target volume treatment plans met the criteria set by Yadav et al (8). Left lung dose parameters of dose within 68,12,80,10,1.5 (Dmax, Dmean,V5, V20, V40), right lung dose within 18, 14, 81, 15, 4 Gy (Dmax, Dmean, V5, V20, V40), heart dose parameters within 40, 15, 4 (Dmax, Dmean, V25), Esophagus dose parameters with values within 60, 20, 41 (Dmax, Dmean, V20), cord center Dmax < 43 and Dmean < 18 Gy and spinal cord Dmax < 56 Gy and Dmean less the 11 Gy were met (8). These dose constraints helped in establishing the fact that not only modality specific but universal planning constraints were met (including IMRT, Dynamic arc, Tomo, and proton therapy) [8]

The CEST spectrum signal reflects the combination of several effects: direct effect (representing the longitudinal and transverse relaxation times), MT effect (representing the macromolecular content), and CEST effects (generated from labile proteins and peptides). The MTR metrics reported here represent the combination of all 3 components (CEST, MT, and direct effect), the MT metric (derived from Lorentzian decomposition) represents the combination of direct effect and the MT effect, and the CEST metrics represent the actual isolated CEST effects.

To probe the changes in CEST metrics over the course of the treatment, 2 different ROIs were defined to provide a comprehensive assessment of the CEST changes. Region of interest type I focused on the tumor tissue only and reflected the evolution (over time) of CEST metrics inside the enhancing tumor rim. Because radiation treatment planning is performed on the pretreatment tumor margins (gross tumor volume as per the surgical cavity and any residual disease), the analysis region in ROI type II was defined at the baseline scan and was kept fixed for consequent scans.

This ROI received the highest radiation dose in all of the 30 radiation treatment sessions. It also takes into account the tumor size change and white matter infiltration into the initial tumor area over the course of the treatment. The ratio of each metric over its baseline value was used to represent the treatment-induced changes in the tumor.

The baseline ($Day_0$) values of the $MTR_{NOE}$ ($P$ = .015), $MTR_{Amide}$ ($P$ = .028), MT ($P$ = .019), and $CEST_{NOE}$ ($P$ = .044) were capable of differentiating progressors from nonprogressors. All the CEST metrics reported for $Day_0$ of nonprogressors were lower (except for APT), showing they had lower metabolic activity compared with progressors (although direct effect and $CEST_{Amide}$ and APT were not statistically significantly different). Thus, CEST is capable of characterizing chondrosarcoma tumor aggressiveness and identifying patients who will not benefit from standard chemoradiotherapy, even before the start of the treatment. Furthermore, although there were large differences in the CEST metrics at baseline, once the treatment was administered there were no statistically significant differences (at subsequent time points) between the 2 cohorts.

When considering the changes in metrics during treatment, there was statistically significant difference (for ROI type I) between progressors and nonprogressors for $MTR_{NOE}$ ($P$ = .006) and $MTR_{Amide}$ ($P$ = .017) of changes between $Day_0$ and $Day_{14}$. Similar separation (with higher $P$ values) of the progressors and nonprogressors was also achieved for changes between $Day_0$ and $Day_{14}$ in ROI type II (for $MTR_{NOE}$ and $MTR_{Amide}$ with $P$ = .02 and $P$ = .05, respectively). However, the changes in metrics for the later time points ($Day_{28}$ and $Day_{70}$) were not statistically significant different between the 2 cohorts. Nevertheless, considering the ratios and ratio trends(which show the ratios did not change from $Day_{14}$ to later scans), the lack of statistical significance in these later time points could be associated with the fact that very few progressors participated in these scans.

There were large variations in $CEST_{NOE}$ metric in all groups and at all scan time points. This metric was calculated from Lorentzian decomposition of the CEST spectrum. The NOE is a wide peak that ranges between −2 ppm and −5 ppm [17]and encompasses a variety of effects, thus larger variations were observed in its AUC as a result of the treatment.

The $CEST_{Amide}$ signal in nonprogressors was elevated at $Day_{14}$, but it decreased over time, whereas for progressors this metric slightly increased at $Day_{14}$ and continued to increase over the course of the study. $CEST_{Amide}$ (similar to APT) is expected to quantify the concentration and exchange of amide proton in the tumor, which has been shown to increase with the aggressiveness of the tumor (17). However, the difficulties in accurately measuring this metric (due to having a narrow CEST peak) resulted in large variations in its value, which led to $CEST_{Amide}$ not being able to separate the 2 cohorts of patients.

The CEST signal patterns explain the higher APT values in the tumor region, which might be due to higher cellularity of the tumor (as shown by Bai et al (34)). On the other hand, the co-localization of the high APT values with the high $T_1$ values and absence of high APT values in portions of the tumor that had lower $T_1$ values might suggest that these patterns were due to the differences in the $T_1$ and, if $T_1$ differences were eliminated, the high APT value regions might disappear (as demonstrated by Zaiss et al). These points highlight the issues and difficulties in accurately isolating the APT signal particularly in the low-power saturation approaches that were used in this study. Lorentzian decomposition is an alternative approach for measuring the CEST signal of amide protons; however it yielded very noisy $CEST_{Amide}$ map, mainly owing to its narrow and low amplitude CEST peak.

Tumor volume was not capable of separating the 2 cohorts at any of the scan time points which shows a longer follow-up was needed for such differentiation using clinically used metrics. The presented CEST results showed that the best and earliest time point for evaluating chondrosarcoma response to treatment was 2 weeks into the treatment ($Day_{14}$), and the best CEST metrics were the changes in MTR metrics between $Day_{14}$and baseline. Additionally, the largest treatment-induced changes in the CEST properties occurred during the first 2 weeks of the treatment, demonstrating the higher sensitivity of CEST to treatment effects. It is important to note that the CEST metrics at later time points were not able to differentiate the 2 cohorts, or provided weaker separation. Thus, the CEST metrics at early phases of the therapy are the most sensitive to treatment effects.

In case of the progressors (who had more aggressive and highly metabolically active tumors) the metric values over time were relatively unchanged, showing that the treatment was unable to induce significant changes in the tumor. However, for nonprogressors there were significant increases in CEST metrics, showing that the therapy was changing tumor metabolism (particularly at early phases of the treatment). Moreover, the trendsshow that the changes in MTR metrics after $Day_{14}$ mirrored that of the MT metric. This point suggests the CEST response (attributed to the inflammatory response in the tumor and temozolomide-induced pH normalization) was

elevated in the nonprogressors and stayed elevated throughout the therapy. However, the MT metric (governed by the macromolecular content and their access to free water) decreased after $Day_{14}$, which could indicate increased cell death over time.

Results demonstrate that tumors in nonprogressors were less metabolically active (compared with progressors) and, therefore, had lower CEST metrics at $Day_0$. Once the treatment was given, the nonprogressors were less resistant to the treatment, and thus their CEST metrics changed significantly, whereas the progressors were more resistant and the treatment could not affect their CEST metric values. These trends could be attributed to the combination of 2 main factors. (*1*) There was higher treatment-induced cell death in nonprogressors, which induces inflammation and higher pH normalization induced by temozolomide, which increases CEST signal[2].It has been demonstrated that the amount of MT increases with response to treatment (the MT component measured with Lorentzian decomposition was also showing this change semi-quantitatively), because MT is a major component of the MTR metrics ($MTR_{NOE}$, $MTR_{Amide}$), increase in MT (which is mainly governed by the macromolecular content and their access to free water) is also contributing to the increase in MTR metrics.The main limitation of this pilot study was its small sample size. Although the differences between CEST metrics of the 2 cohorts were large, there were only 6 patients with progressive tumors at baseline and only 4 participated in the follow-up scans. A larger number of progressors are needed to increase confidence in the results and establish CEST as a biomarker of chondrosarcoma response to treatment. This pilot study, however, demonstrated the potential of CEST in chondrosarcoma response evaluation and also allowed for determination of the best CEST metrics and the earliest time point CEST could determine chondrosarcoma response to chemoradiation. A subsequent larger study is in progress to confirm these results.

Moreover, CEST sequences are not currently available on clinical scanners, and their application is limited to the research centers with access to the CEST imaging sequence. However, all major MRI manufacturers (Philips, Siemens, GE) are currently working toward making CEST sequences available as standard sequence on their scanners (they all have work in progress sequences at the moment), which will make widespread application of CEST imaging feasible in the near future.

Another major challenge is the long scan time and the fact that a single slice through the tumor was investigated. The imaging slice was selected such that it covered the largest cross section of the tumor, covering 1.1 ($cm^3$) to 5.9 ($cm^3$) of the total tumor volume, which represented 8% to 21% of the total tumor volume of the patients. Advanced 3D CEST sequences with full brain coverage as well as their addition to the product sequences offered by MRI scanner manufacturers are needed for translation of these techniques into routine clinical practice.

This study demonstrated the feasibility of adding CEST sequences to the clinical imaging protocol of the chondrosarcoma patients in a clinically acceptable scan time. A large number of CEST metrics were investigated and their potential in determining chondrosarcoma response to therapy was evaluated. Amongst these metrics, the best performance was achieved by the MTR metrics, which reflect the combination of treatment-induced changes in CEST, MT, and direct effect of the tumor. Future studies could focus on a certain portion of the CEST spectrum to improve metric measurement accuracy and reduce imaging time. From the retrospective analysis of MRI planning parameters as per qc phantom reported doses can help in improvement in both treatment planning as well as treatment delivery and hence can raise the utilization of onboard MR scanners[11]Determining chondrosarcoma response at early phases of the treatment and identifying the patients that will not benefit from standard therapy have the potential for significant clinical utility in the era of MRI-based image-guided radiation therapy. The lack of contrast required for advanced MRI technique such as CEST is a major advantage because with daily MR imaging the patient cannot be administered contrast regularly. The present study also showed the best predictive power and most profound treatment-induced changes occur inside the ROI type I volume as opposed to ROI type II volume. This suggests that plan adaptation can be tailored to the evolving gross tumor volume. By imaging patients daily and before each radiation therapy fraction, the changes in CEST metrics could potentially be used as a biomarker for dose escalation or to guide changes in systemic therapy.

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