Differentiation between Radiation Necrosis and Tumor Progression Using Chemical Exchange Saturation Transfer

Hatef Mehrabian1,2, Kimberly L. Desmond2, Hany Soliman3,4, Arjun Sahgal2,3,4, and Greg J. Stanisz1,2,5

Abstract

Purpose: Stereotactic radiosurgery (SRS) is a common treatment used in patients with brain metastases and is associated with high rates of local control, however, at the risk of radiation necrosis. It is difficult to differentiate radiation necrosis from tumor progression using conventional MRI, making it a major diagnostic dilemma for practitioners. This prospective study investigated whether chemical exchange saturation transfer (CEST) was able to differentiate these two conditions.

Experimental Design: Sixteen patients with brain metastases who had been previously treated with SRS were included. Average time between SRS and evaluation was 12.6 months. Lesion type was determined by pathology in 9 patients and the other 7 were clinically followed. CEST imaging was performed on a 3T Philips scanner and the following CEST metrics were measured: amide proton transfer (APT), magnetization transfer (MT), magnetization transfer ratio (MTR), and area under the curve for CEST peaks corresponding to amide and nuclear Overhauser effect (NOE).

Results: Five lesions were classified as progressing tumor and 11 were classified as radiation necrosis (using histopathologic confirmation and radiographic follow-up). The best separation was obtained by NOE_APT (NOE_APT, necrosis = 8.9 ± 0.9%, NOE_APT, progression = 12.6 ± 1.6%, P < 0.0001) and Amide_MTR (Amide_MTR, necrosis = 8.2 ± 1.0%, Amide_MTR, progression = 12.0 ± 1.9%, P < 0.0001). MT (MT, necrosis = 4.7 ± 1.0%, MT, progression = 6.7 ± 1.7%, P = 0.009) and NOE_LIC (NOE_LIC, necrosis = 4.3 ± 2.0% Hz, NOE_LIC, progression = 7.2 ± 1.9% Hz, P = 0.019) provided statistically significant separation but with higher P values.

Conclusions: CEST was capable of differentiating radiation necrosis from tumor progression in brain metastases. Both NOE_APT and Amide_MTR provided statistically significant separation of the two cohorts. However, APT was unable to differentiate the two groups. Clin Cancer Res; 23(14): 3667–75. ©2017 AACR.

Introduction

Brain metastases occur in 20% to 40% of all cancer patients and impacts quality of life and survival (1, 2). Stereotactic radiosurgery (SRS), which involves delivering a high dose of radiation focally to the tumor (either in a single dose or in a few fractions), is an established treatment option for patients with a limited number of brain metastases. SRS is associated with increased local control and a survival advantage as compared with treatment with whole brain radiotherapy (WBRT; refs. 2, 3). However, in certain subpopulations of patients, there is a higher rate of distant brain failures when treated with SRS alone as compared with WBRT (4, 5). The other major drawback of SRS is a greater risk of radiation necrosis within the treatment field, which typically occurs months after SRS (6).

Radiation necrosis (reported in up to 22% of all patients; ref. 3) is the most common morphologic alteration after SRS and can cause significant neurologic morbidity depending on its location in the brain (7, 8). Pathologically, radiation necrosis is seen as a region of coagulative necrosis that affects the white matter in the irradiated area (9). However, the underlying mechanism of radiation necrosis is unknown and its definition varies among studies (9).

Both tumor progression and radiation necrosis appear as an enlarging enhancing region on post-gadolinium T1-weighted MRI and increased vasogenic edema on T2-weighted FLAIR MRI (3, 10, 11). Treatment for tumor progression is significantly different from that of radiation necrosis. Patients with radiation necrosis are typically treated first with dexamethasone (12), and there may be a reduction in volume of the enhancing lesion. However, up to 20% of patients with radiation necrosis do not respond to steroids, and patients may be operated or treated with bevacizumab (13–15). Patients with tumor progression are not observed with serial scans and medical therapy. Tumor progression is typically treated with surgery, further radiation, or a switch to systemic therapy. Therefore, distinguishing progression versus radiation necrosis is a major clinical dilemma.

Figure 1 shows a clinical case of a brain metastases patient that presented with an enlarging, enhancing mass after single-dose radiation necrosis.

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doi: 10.1158/1078-0432.CCR-16-2265

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Radiation necrosis is the most common side effect of stereotactic radiosurgery and has similar characteristics to tumor progression on standard anatomic MRI. Differentiation between these two conditions is a major clinical dilemma for which no imaging technique is able to provide a conclusive solution. Moreover, currently available techniques require long follow-ups and usually involve contrast agent administration. Chemical exchange saturation transfer (CEST) is an MRI technique that is sensitive to endogenous metabolites in the tissue. This study demonstrated that CEST is capable of differentiating radiation necrosis from tumor progression with very high accuracy. Thus, CEST provides a solution for this clinical dilemma in a timely manner and without requiring any contrast agent administration that could be easily translated into routine clinical practice.

Histopathologic confirmation with biopsy is considered the most reliable diagnostic technique; however, biopsy is expensive, suffers from sampling error, puts the patient at risk of harm given the risks of surgery, and is not practical in all cases (depending on lesion location and considering these cancer patients have several competing issues with respect to oncologic management; ref. 16). Although structural MRI metrics have been used to differentiate radiation necrosis from tumor progression [for instance, Kano and colleagues (17) used the correspondence between lesion volume in post-gadolinium $T_1$-weighted MRI and lesion margins in $T_2$-weighted MRI ($T_1/T_2$ match and mismatch) and demonstrated a relatively high sensitivity and specificity], this method is still not diagnostic. In addition to metabolic imaging such as magnetic resonance spectroscopy (MRS) through measuring ratios of choline, N-acetylaspartate and creatine (18), PET (19), and single-photon emission CT (SPECT; ref. 20), there has been increasing interest in functional imaging techniques such as diffusion-weighted MRI [measuring apparent diffusion coefficient (ADC); ref. 21] and perfusion imaging with DSC-MRI [measuring relative cerebral blood volume (rCBV); 22]. None of these imaging techniques have the necessary specificity or sensitivity (16–22) to be definitive, and histopathologic confirmation is considered the gold standard. With surgery being an unattractive option for cancer patients, there is a need for novel imaging approaches to distinguish radiation necrosis from tumor...
progression given the major impact these diagnoses have on patient management.

Chemical exchange saturation transfer (CEST) is a promising new MRI contrast mechanism that has been used in studying the tumor microenvironment through detection of mobile proteins and peptides (23–27). This technique relies on the labeling of endogenous populations of exchanging protons by a radiofrequency pulse at a specific frequency. These pools can transfer their magnetization to the unbound water (through exchange), the extent of which constitutes the MRI image contrast, and by varying the radiofrequency pulse frequency, a spectrum is generated. In the absence of CEST effect, this spectrum is generally considered to be symmetric; however, in its presence, the signal is attenuated at certain frequencies, resulting in chemical-specific negative peaks.

Recently, a chemical exchange MRI technique, based on CEST, called amide proton transfer (APT) imaging has been developed, which detects amide protons of low concentration in endogenous proteins and peptides in tissue (25, 28). It has shown promising results in differentiating radiation necrosis from tumor progression in glioma and necrosis models in rats (29). APT has also been applied to human glioma patients to differentiate high-grade tumors from low-grade ones with encouraging results (30, 31).

Magnetization transfer ratio (MTR) has also been investigated in animal studies to differentiate necrosis from tumor progression without success (32). However, there was a significant difference between the imaging parameters (e.g., duration of saturation pulse and the choice of offset frequencies) that we have used in the current study and the parameters used previously (32). In this prospective study, we evaluated the entire CEST spectrum in differentiating radiation necrosis from tumor progression in patients with brain metastases treated with SRS.

Materials and Methods

Patient population

Sixteen patients with brain metastases, who had earlier been treated with focal single dose or hypofractionated SRS, were recruited. The patients initially responded to SRS (tumor shrinkage), but months later presented with an enlarging, enhancing lesion at the treatment location. The lesion was suspected of being radiation necrosis or tumor progression (details of each patient have been provided in Table 1). Informed consent was obtained from all patients, and the study was conducted under an institutional research ethics board–approved protocol.

In all cases, the MRI scan of this study was performed immediately after detection of the suspicious lesion. The lesions were surgically resected for 9 patients (within a few days after the MRI scan), and histopathologic assessment of the resected lesion was performed. For the other seven lesions, diagnosis of radiation necrosis or tumor progression was rendered clinically by two expert neuro-oncologists. These patients were followed by standard clinical MRI involving T2-weighted FLAIR and post-gadolinium T1-weighted MRI. ADC measurement was also performed for all cases along with CEST. Moreover, SPECT was performed for three cases, MRS was performed for two cases, two cases responded to steroids, and the lesion was stable in the other two cases (details in Table 1). The oncologists considered all these data in all follow-up scans to render the diagnosis of necrosis or progression.

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Tumor</th>
<th>Primary</th>
<th>CEST (mm)</th>
<th>Follow-up clinical course</th>
<th>Pathology report</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>P01</td>
<td>65</td>
<td>F</td>
<td>Breast</td>
<td>24 Gy/3</td>
<td>2.6</td>
<td>Clinical, stable lesion, response to steroids</td>
<td>Stable lesion</td>
<td>Necrosis</td>
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<tr>
<td>P02</td>
<td>71</td>
<td>M</td>
<td>NSCLC</td>
<td>27.5 Gy/5</td>
<td>3.1</td>
<td>Clinical, stable lesion</td>
<td>Necrosis</td>
<td>Necrosis</td>
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<td>F</td>
<td>Breast</td>
<td>20 Gy/1</td>
<td>1.1</td>
<td>Clinical, stable lesion, response to steroids</td>
<td>Necrosis</td>
<td>Necrosis</td>
</tr>
<tr>
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<td>M</td>
<td>Breast</td>
<td>24 Gy/1</td>
<td>2.6</td>
<td>Clinical, stable lesion, response to steroids</td>
<td>Necrosis</td>
<td>Necrosis</td>
</tr>
<tr>
<td>P05</td>
<td>67</td>
<td>M</td>
<td>RCC</td>
<td>30 Gy/5</td>
<td>2.0</td>
<td>Clinical, stable lesion, response to steroids</td>
<td>Necrosis</td>
<td>Necrosis</td>
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<tr>
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<td>Lung</td>
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<td>Necrosis</td>
<td>Necrosis</td>
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<tr>
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<td>Lung</td>
<td>30 Gy/5</td>
<td>2.0</td>
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<td>Necrosis</td>
<td>Necrosis</td>
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<td>Lung</td>
<td>30 Gy/5</td>
<td>2.0</td>
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<td>Necrosis</td>
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<td>Necrosis</td>
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<tr>
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<td>RCC</td>
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<td>Necrosis</td>
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<td>Necrosis</td>
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<tr>
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<td>59</td>
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<td>24 Gy/1</td>
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<td>Necrosis</td>
<td>Necrosis</td>
</tr>
<tr>
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<td>Lung</td>
<td>30 Gy/5</td>
<td>2.0</td>
<td>Clinical, stable lesion, response to steroids</td>
<td>Necrosis</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma.
MRI acquisition

The patients were scanned on a 3T Philips Achieva MRI system with 8-channel SENSE head coil with the following MRI sequences:

An axial slice passing through the largest cross-section of the lesion was chosen for CEST imaging. A single-shot echo planar imaging (EPI) sequence was used with fast field echo (FFE), TR/TE = 1,971/29 ms, acquisition matrix = 80 × 80, field of view (FOV) = 20 × 20 cm, slice thickness = 3 mm, EPI factor = 67. CEST spectrum images were acquired for offset frequencies between −750 Hz (−5.9 ppm) and 750 Hz (5.9 ppm) at 25 Hz increments. Four reference offsets of 100 kHz (−780 ppm) were acquired at the beginning, and another four reference images were acquired at the end of the spectrum. The radiofrequency saturation consisted of four block-shaped pulses of 242.5 ms each, for a total of 970 ms, radiofrequency amplitude, B1 was equal to 0.52 μT (equivalent to the 1,940 μT experienced by the patient’s body weight followed by a 20-mL saline flush. Then, a bolus of contrast agent (gadobutrol, Bayer Inc.) was injected intravenously at a dose of 0.1 mmol/kg of patient’s body weight followed by a 20-mL saline flush. Then, high spatial resolution postcontrast 3D Axial T1-weighted imaging was performed with the following sequence parameters: TR/TE = 9.5 ms/2.3 ms, α = 8°, FOV = 22 cm × 22 cm, matrix size = 448 × 448 × 113, slice thickness = 1.5 mm. This sequence was used for clinical assessment of tumor volume as well as delineating the lesion region of interest (ROI) on the CEST images.

CEST preprocessing

All CEST spectrum images were registered to the first acquired image of the first repetition of CEST sequence using affine registration in Elastix (36). B0 inhomogeneity correction was performed by fitting a Lorentzian line-shape to the data points surrounding the direct effect (offset < 1.3 ppm) and the end tails of the spectrum (offset > 4.5 ppm). The spectrum was then shifted so that the minimum was at 0 Hz, and the spectrum was resampled at the same offset frequencies as the imaging protocol. Any voxel whose spectrum failed to fit to the Lorentzian line-shape was discarded from the analysis.

Correction for signal drift, which occurs as a result of drop in performance of radiofrequency amplifier or coil (37, 38), was also performed using the reference images at the two ends of each spectrum and assuming a linear drift during the spectrum acquisition. Then, the drift-corrected CEST spectrum of each voxel was normalized with respect to the first reference image at the beginning of the spectrum. For each voxel, the four normalized spectra were then averaged to produce the final CEST spectrum data, which was used to calculate the CEST metrics.

CEST metrics calculation

Several CEST metrics were calculated:

(i) The CEST spectrum was decomposed into a constant MT effect (for the offset frequencies from −5.9 to 5.9 ppm) and four Lorentzian line-shapes corresponding to amide (3.5 ppm), nuclear Overhauser effect (NOE; −3.5 ppm), amine (2 ppm), and bulk water (0 ppm) as follows (38):

\[ S(\Delta) = 1 - \left( \frac{MT + \sum_{i=1}^{4} A_i}{1 + \left( \frac{\Delta - \omega_i}{\gamma_i} \right)^2} \right) \]

where \( S(\Delta) \) was the CEST image at offset frequency \( \Delta \), and \( [A_i, \Delta_i, \omega_i] \) were the amplitude, center frequency, and width of each Lorentzian line-shape, respectively. Lorentzian peak decomposition was then performed and the AUC of CEST peaks (with units of % Hz) corresponding to the NOE and amide (NOE \(_{\text{AUC}}\) and Amide \(_{\text{AUC}}\)) were calculated.

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

\[ APT = \frac{S(-3.5\, \text{ppm}) - S(3.5\, \text{ppm})}{S(\text{ref})} \]

where \( S(\text{ref}) \) was the reference image and \( S(3.5\, \text{ppm}) \) was the image corresponding to 3.5 ppm offset frequency in the final CEST spectrum data.

(iii) Amide MTR defined as:

\[ \text{Amide}_{\text{MTR}} = \frac{S(\text{ref}) - S(3.5\, \text{ppm})}{S(\text{ref})} \]

(iv) NOE MTR defined as:

\[ \text{NOE}_{\text{MTR}} = \frac{S(\text{ref}) - S(-3.5\, \text{ppm})}{S(\text{ref})} \]

(v) Direct effect quantified by:

\[ \text{Direct effect} = \sqrt{\frac{T_1}{T_2}} \]

where \( T_1 \) and \( T_2 \) were the average longitudinal and transverse relaxation times over the lesion ROI. This measure of direct effect is proportional to the full width at half maximum of the water saturation spectrum, which is defined by:
Results

A measure of direct effect \(\sqrt{T_1/T_2}\) was calculated by using the average \(T_1\) and \(T_2\) values over the lesion ROI. The SE of this metric was determined by calculating the SE of the ratio of two normal distributions (corresponding to \(T_1\) and \(T_2\)).

In Fig. 3, the NOE\(_{\text{STR}}\) and Amide\(_{\text{STR}}\) maps of the entire brain for both patients in Fig. 2. The lesion ROIs on CEST maps were determined using the post-gadolinium \(T_1\)-weighted FLAIR images.

Figure 3 shows the NOE\(_{\text{STR}}\), Amide\(_{\text{STR}}\), and APT maps of the entire brain for both patients in Fig. 2. The lesion ROIs on CEST maps were determined using the post-gadolinium \(T_1\)-weighted FLAIR images.

The signal changes observed in CEST experiments with MRI reflect the combination of multiple effects (MT, CEST, and direct effect). Thus, to fully understand the root of these signal changes and determine which metric is responsible for the observed changes, it was necessary to decompose the CEST spectrum and investigate each effect. The \(\sqrt{T_1/T_2}\) was measured to account for the direct water effect; and Lorentzian decomposition was performed to isolate the CEST effect. MT on the other hand reflects the combination of direct effect, MT, and CEST.

Statistical analysis

The CEST metrics were calculated for each voxel in the tumor ROI, and the average values over tumor ROIs were used in the statistical analysis. To determine the statistical significance of the differences between parameter distributions, a two-sample \(t\) test was performed using the average metric values for each lesion. This \(t\) test was selected as the number of cases in the radiation necrosis and tumor progression cohorts were not equal. The \(P\) value was calculated to determine the statistical significance of separation provided by each metric (the significance level was set at \(P < 0.05\)).

Stability of the CEST metrics was assessed using the contralateral normal appearing white matter \(c\text{NAWM}\). An ROI was selected on \(c\text{NAWM}\) and all CEST metrics were calculated voxel-by-voxel and then averaged over the \(c\text{NAWM}\) ROI. The variation of each CEST metric over the entire population was then assessed.

Results

Among the total 16 lesions, five lesions were consistent with tumor progression based on pathology. The remaining 11 lesions were classified as radiation necrosis based on pathology or clinical/imaging follow-up. Nine lesions had surgical management with histopathologic diagnosis of either necrosis or tumor progression (details provided in Table 1). The remaining seven lesions were diagnosed on the basis of lesion history, according to serial imaging follow-up that also included diagnostic imaging techniques such as MRS, SPECT, and perfusion imaging, and both a radiologist and the radiation oncologists reviewed each case independently. The details of these cases are also provided in Table 1.

To assess stability of the CEST experiment and analysis, the CEST metrics were calculated for \(c\text{NAWM}\). Each patient was represented by the average metric value over the \(c\text{NAWM}\) ROI. The distribution (mean and SD) of these metric values for the entire patient population (16 patients) were: NOE\(_{\text{STR}}\),\(c\text{NAWM}\) = 16.7 \(\pm\) 2.4\%, Amide\(_{\text{STR}}\),\(c\text{NAWM}\) = 14.9 \(\pm\) 2.2\%, MT,\(c\text{NAWM}\) = 10.6 \(\pm\) 2.0\%, NOE\(_{\text{AUC}}\),\(c\text{NAWM}\) = 9.3 \(\pm\) 2.4\% Hz, Amide\(_{\text{AUC}}\),\(c\text{NAWM}\) = 1.8 \(\pm\) 0.8\% Hz. The relatively small variations in the CEST metric values for \(c\text{NAWM}\) in different patients demonstrate the stability of the calculated metrics and repeatability of the experiments.

Figure 2 shows a necrosis case and a progressive tumor case (both determined through histologic confirmation). It shows the post-gadolinium \(T_1\)-weighted image of an axial slice of the brain that passes through the lesion (this slice was also used for CEST imaging) as well as its corresponding \(T_2\)-weighted FLAIR slice. It can be seen that both lesions have similar MRI characteristics, that is, enhancement in post-gadolinium \(T_1\)-weighted MRI and edema on \(T_2\)-weighted FLAIR. In Fig. 2B, the \(T_1\) and \(T_2\) maps are shown for both patients. The lesion ROIs on these maps were determined using the post-gadolinium \(T_1\)-weighted and FLAIR images.

Figure 2. A, \(T_1\)–weighted post-gadolinium (Gd) images (left column) and \(T_2\)-weighted FLAIR images (right column) of a patient with progressive tumor (top row) and a patient with radiation necrosis (bottom row). B, The maps of longitudinal (\(T_1\)) and transverse (\(T_2\)) relaxation time corresponding to the patient with tumor progression (top row) and the patient with radiation necrosis (bottom row). The lesion ROI is outlined with the white contours.

Table 2 reports the distribution (mean and SE) of each metric for each patient. A measure of direct effect \(\sqrt{T_1/T_2}\) was calculated by using the average \(T_1\) and \(T_2\) values over the lesion ROI. The SE of this metric was determined by calculating the SE of the ratio of two normal distributions (corresponding to \(T_1\) and \(T_2\)).

In Fig. 3, the NOE\(_{\text{STR}}\) and Amide\(_{\text{STR}}\) maps of the entire brain for both patients in Fig. 2. The lesion ROIs on CEST maps were determined using the post-gadolinium \(T_1\)-weighted FLAIR images of the brain. The voxels that were excluded from analysis are shown with zero metric values (black points in NOE\(_{\text{STR}}\) and Amide\(_{\text{STR}}\) maps).

Table 3 reports the mean and SD of the average metric values for each cohort (which were reported in Table 2), as well as their \(P\) value corresponding to the statistical significance of the separation between the two cohorts. Figure 5 graphically shows the metric distributions reported in Table 3.
Discussion

SRS delivers a high radiation dose to the tumor, which increases the likelihood of local control at the expense of the risk for developing radiation necrosis. Differentiating these radiation-induced changes from tumor progression is challenging as both conditions have similar characteristics on standard anatomic MRI sequences (increased enhancement in post-gadolinium T1-weighted and increased vasogenic edema in T2-weighted FLAIR). MR spectroscopy and MR perfusion might be helpful in differentiating radiation necrosis from tumor progression (according to CNS guidelines of National Comprehensive Cancer Network; ref. 39). FDG-PET and SPECT show low tracer update in radiation necrosis and are used to assist its differentiation from progressive tumor (39). Currently, radiologists rely on functional imaging (rCBV, ADC) or metabolic imaging (MRS, PET, SPECf) to differentiate radiation necrosis from tumor progression non-invasively (40). However, none of these techniques have shown sufficient sensitivity or specificity in management of the patients and require validation in large clinical trials, and many of them are also costly and require contrast agent injection (41–43).

CEST measures the concentration and exchange of mobile proteins and peptides in the tissue. Viable tumor has higher cellular content of proteins and peptides compared with necrotic tissue and thus is expected to express a higher CEST signal as compared with radiation necrosis. This feature makes CEST measurements excellent candidates for differentiating the two conditions.

Several CEST metrics were investigated in this study in patients with brain metastases treated with SRS. In Fig. 4, the patients were separated into those with histology and without histology (there were no tumor progression cases without histology). This classification was performed to demonstrate that the radiation necrosis cases that were determined clinically (7 cases) had similar CEST metric values to those determined with histology (4 cases). It also enabled comparing the CEST metric values for the cases with histology only. As shown in Fig. 4, there were statistically significant differences between the necrosis (histology) and tumor progression (histology) cases for both NOE_MTR (P = 0.004) and Amide_MTR (P = 0.005).

As reported in Tables 2 and 3 and Fig. 5, NOE_MTR provided the best separation of the two conditions (NOE_MTR_necrosis = 8.9 ± 0.9%, NOE_MTR_progression = 12.6 ± 1.6%, P < 0.0001). This effect is associated with the fatty acid chains of mobile lipids (which are integral components of the cell membrane; ref. 44) and originates

Table 2. The mean and SE of each metric for all lesions

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Lesion type</th>
<th>NOE_MTR (%)</th>
<th>Amide_MTR (%)</th>
<th>APT (%)</th>
<th>MT (%)</th>
<th>NOE_AUC (% Hz)</th>
<th>Amide_AUC (% Hz)</th>
<th>√T1/T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>L01</td>
<td>P</td>
<td>12.5 ± 0.5</td>
<td>11.7 ± 0.4</td>
<td>−0.9 ± 0.2</td>
<td>7.0 ± 0.4</td>
<td>10.3 ± 0.7</td>
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<td>L02</td>
<td>N</td>
<td>8.9 ± 0.3</td>
<td>8.3 ± 0.4</td>
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<td>9.6 ± 0.2</td>
<td>8.9 ± 0.2</td>
<td>−0.8 ± 0.1</td>
<td>5.3 ± 0.1</td>
<td>5.5 ± 0.3</td>
<td>0.3 ± 0.1</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>L05</td>
<td>N</td>
<td>8.4 ± 0.4</td>
<td>8.0 ± 0.4</td>
<td>−0.4 ± 0.1</td>
<td>4.5 ± 0.2</td>
<td>2.7 ± 0.4</td>
<td>0.9 ± 0.2</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>L06</td>
<td>P</td>
<td>12.1 ± 0.6</td>
<td>11.2 ± 0.7</td>
<td>−0.9 ± 0.5</td>
<td>6.3 ± 0.4</td>
<td>5.6 ± 1.2</td>
<td>1.3 ± 0.6</td>
<td>4.5 ± 0.8</td>
</tr>
<tr>
<td>L07</td>
<td>N</td>
<td>7.1 ± 0.4</td>
<td>6.6 ± 0.3</td>
<td>−0.5 ± 0.1</td>
<td>3.8 ± 0.2</td>
<td>3.3 ± 0.5</td>
<td>2.2 ± 0.5</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>L08</td>
<td>N</td>
<td>10.5 ± 1.4</td>
<td>7.9 ± 1.3</td>
<td>−2.7 ± 0.5</td>
<td>6.3 ± 0.9</td>
<td>7.0 ± 1.4</td>
<td>1.4 ± 0.8</td>
<td>2.0 ± 0.2</td>
</tr>
<tr>
<td>L09</td>
<td>N</td>
<td>9.1 ± 0.3</td>
<td>9.7 ± 0.3</td>
<td>0.6 ± 0.3</td>
<td>6.2 ± 0.3</td>
<td>2.3 ± 0.9</td>
<td>1.5 ± 0.7</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>L10</td>
<td>P</td>
<td>15.4 ± 0.3</td>
<td>14.4 ± 0.2</td>
<td>−1.0 ± 0.1</td>
<td>9.5 ± 0.3</td>
<td>7.9 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>L11</td>
<td>N</td>
<td>8.1 ± 0.7</td>
<td>9.0 ± 0.7</td>
<td>0.9 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>2.5 ± 1.6</td>
<td>3.9 ± 1.3</td>
<td>2.9 ± 0.3</td>
</tr>
<tr>
<td>L12</td>
<td>P</td>
<td>8.4 ± 0.4</td>
<td>7.2 ± 0.2</td>
<td>−1.1 ± 0.3</td>
<td>4.4 ± 0.2</td>
<td>4.1 ± 0.7</td>
<td>1.0 ± 0.2</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>L13</td>
<td>N</td>
<td>9.6 ± 0.1</td>
<td>9.4 ± 0.1</td>
<td>−0.2 ± 0.1</td>
<td>5.2 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td>4.2 ± 0.3</td>
</tr>
<tr>
<td>L14</td>
<td>P</td>
<td>12.1 ± 0.6</td>
<td>13.3 ± 0.6</td>
<td>1.2 ± 0.4</td>
<td>5.5 ± 0.4</td>
<td>5.9 ± 0.9</td>
<td>6.5 ± 1.2</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>L15</td>
<td>N</td>
<td>8.7 ± 0.2</td>
<td>7.5 ± 0.2</td>
<td>−1.2 ± 0.1</td>
<td>3.6 ± 0.2</td>
<td>8.0 ± 0.4</td>
<td>4.1 ± 0.3</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>L16</td>
<td>N</td>
<td>9.2 ± 0.1</td>
<td>7.9 ± 0.1</td>
<td>−1.3 ± 1.0</td>
<td>4.6 ± 0.1</td>
<td>5.7 ± 0.3</td>
<td>1.2 ± 0.1</td>
<td>3.2 ± 0.3</td>
</tr>
</tbody>
</table>

Abbreviations: N, necrosis; P, progression.
from dipole–dipole interactions (NOE; ref. 45) rather than chemical exchange. Others have argued that this effect is a combination of dipole–dipole interactions and chemical exchange where the dipolar component is dominant (46).

Similar results were observed for the AmideMTR where a good separation of the two patient cohorts was observed (AmideMTR, necrosis = 8.2 ± 1.0%, AmideMTR, progression = 12.0 ± 1.9%, P < 0.0001). This effect originates from the concentration and exchange of amide protons from the backbone of mobile proteins and peptides, which is expected to be lower in necrotic tissue compared with tumor due to reduced metabolism (29).

Both AmideMTR and NOEMTR measurements, in addition to the CEST signal, reflect the effects of MT, which originates from semisolid macromolecules, as well as the direct effect. Thus, CEST spectrum decomposition was performed and $\sqrt{1/T_1^{-2}}$ (a measure of the direct effect) was calculated to investigate the contribution of each factor.

The AUC of the NOE peak (NOEAUC), which represents the CEST effect of this peak, was lower in radiation necrosis compared with tumor progression with statistically significant differences (NOEAUC, necrosis = 4.3 ± 2.0%, NOEAUC, progression = 7.2 ± 1.9%, P = 0.019). This agreed with the previous findings (38), which demonstrated that the higher CEST effect in tumors reflects their higher metabolism (compared with necrotic tissue). This separation provided by NOEAUC, however, was weaker than that of the NOEMTR, suggesting that the other factors (MT and direct effect) were also responsible for the large MTR contrast and that these factors exhibit similar trends as the NOEAUC.

It was not possible to separate the MT effect from the direct effect using the current MRI experiments (additional MRI sequences are required to quantitatively investigate and separate the MT effect) was calculated to investigate the contribution of each factor.

The MT contrast (calculated from CEST spectrum decomposition) demonstrated a large and statistically significant difference between radiation necrosis and tumor progression (MT, necrosis = 4.7 ± 1.0%, MT, progression = 6.7 ± 1.7%, P = 0.009). This contrast is the combination of direct effect and MT effect. Considering the direct effect was not significantly different between the two groups, we hypothesize that the MT effect was mostly responsible for this large and statistically significant difference.

As reported in Tables 2 and 3 and shown in Fig. 5, all three components of the MTR signals (i.e., MT, CEST and direct effect) were larger in progressive tumor as compared with radiation necrosis. Thus, when these effects were combined (as measured by NOEMTR and AmideMTR), a much better separation of the two groups was achieved with smaller P values. The relatively large MTR effect in radiation necrosis cohort (despite having lower values compared with the tumor cohort) could be associated with the criteria for classifying the patients, as the lesion classified as necrosis contained a small percentage of viable tumor tissue (confirmed by histology in three cases). This could lead to an increase in the MTR signal in these lesions.

The AmideAUC showed a similar trend to the NOEpeak (higher in progressive tumor compared with radiation necrosis); however, the variation in this parameter was large (shown by error bars in Fig. 5), and this difference was not statistically significant. This large variation could be associated with the accuracy of the Lorentzian decomposition of the CEST spectrum at this peak. There exist multiple CEST peaks on the positive offset frequency side of the CEST spectrum, and the amide peak is a narrow peak (compared with NOE peak), and thus, the spectrum decomposition might not be calculating the AmideAUC with high enough accuracy.

APT assesses the asymmetry of CEST spectrum at the offset frequency of amide protons. APT has been shown in preclinical studies in glioma models in rats to be a promising biomarker for differentiation of necrosis from viable tumor (29). However, our results showed that it was not capable of performing such differentiation in brain metastases treated with SRS (APT, necrosis = –0.7 ± 1.0%, APT, progression = –0.6 ± 1.0%, P = 0.89). This could be due to the fact that both amide and NOE measurements have similar CEST contrast for these two conditions (as demonstrated by MTR values in Tables 2 and 3), and thus, the effect diminished.
when the NOE signal was subtracted from the amide signal to generate APT.

It should be noted that the radiofrequency power at which we performed our study was lower than the optimal radiofrequency power recommended for APT measurements (47). However, the NOE effect was large relative to amide effect, which resulted in having negative APT signals in most cases. Higher powers are more efficient in saturating labile protons and producing large CEST effect for amide peak, which results in reversing the CEST asymmetry and higher APT signal (48). However, higher radiofrequency power also increases the saturation of the bulk water signal, which results in reduced CEST signal (49). The impact of this broadening in bulk water spectrum on the amide and NOE signals is more pronounced at lower magnetic field strengths (such as the B₀ = 3 T that was used in this study). These factors influenced the selection of B₁ = 0.52 μT in this study.

Another potential reason for APT being unable to differentiate the two conditions (compared with preclinical studies; ref. 29) was that a considerable portion of the cases that are clinically considered necrosis are comprised of viable tumor, which could be partially responsible for the lack of APT contrast between necrosis and progressive tumor cohorts in this study.

In conclusion, CEST was capable of differentiating radiation necrosis from tumor progression in brain metastases. Both NOEₐᵣᵣ and Amideₐᵣᵣ provided statistically significant separation of the two cohorts. However, APT was unable to differentiate the two groups and provide statistically significant separation. An important advantage of CEST, compared with techniques such as MRS, SPECT, and perfusion MRI, is that the proposed CEST image is relatively fast (less than 9 minutes) and does not require any contrast agent injection. These features make CEST an ideal candidate for being added to clinical practice for differentiating radiation necrosis from tumor progression.

Disclosure of Potential Conflicts of Interest

A. Sahgal reports receiving commercial research grants from Elekta AB and is a consultant/advisory board member for Hoffman-La Roche Limited and Varian Medical Systems. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H. Mehrabian, H. Soliman, A. Sahgal, G.J. Stanisz

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H. Mehrabian, H. Soliman, G.J. Stanisz

Writing, review, and/or revision of the manuscript: H. Mehrabian, K.L. Desmond, H. Soliman, A. Sahgal, G.J. Stanisz

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Mehrabian, G.J. Stanisz

Study supervision: H. Soliman, G.J. Stanisz

Grant Support

This study was funded by Terry Fox Research Institute (TFRI project 1034) and Canadian Cancer Society Research Institute (CCSR 71640). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 9, 2016; revised December 15, 2016; accepted January 6, 2017; published OnlineFirst January 17, 2017.

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