MRI Detection of Changes in Tissue Sodium Concentration in Brain Metastases after Stereotactic Radiosurgery: A Feasibility Study

Sherif A. Mohamed, Anne Adlung, Arne M. Ruder, Michaela A. U. Hoesl, Lothar Schad, Christoph Groden, Frank A. Giordano, and Eva Neumaier-Probst

From the Department of Neuroradiology, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany (SAM, CG, EN-P); Department of Computer Assisted Clinical Medicine, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany (AA, MAUH, LS); Department of Radiation Oncology, University Medical Center Mannheim, Heidelberg University, Mannheim, Germany (AMR); and Department of Radiation Oncology, University Hospital Bonn, University of Bonn, Bonn, Germany (FAG)

ABSTRACT

BACKGROUND AND PURPOSE: To date, treatment response to stereotactic radiosurgery (SRS) in brain metastases (BM) can only be determined by MRI evaluation of contrast-enhancing lesions in a long-time follow-up. Sodium MRI has been a subject of immense interest in imaging research as the measure of tissue sodium concentration (TSC) can give valuable quantitative information on cell viability. We aimed to analyze the longitudinal changes of TSC in BM measured with \(^{23}\)Na MRI before and after SRS for assessment of early local tumor effects.

METHODS: Seven patients with a total of 12 previously untreated BM underwent SRS with 22 Gy. In addition to a standard MRI protocol including dynamic susceptibility-weighted contrast-enhanced perfusion, a \(^{23}\)Na MRI was performed at three time points: (I) 2 days before, (II) 5 days, and (III) 40 days after SRS. Nine BMs were evaluated. The absolute TSC in the BM, the respective peritumoral edemas, and the normal-appearing corresponding contralateral brain area were assessed and the relative TSC were correlated to the changes in BM longest axial diameters.

RESULTS: TSC was elevated in nine BM at baseline before SRS with a mean of 73.4 ± 12.3 mM. A further increase in TSC was observed 5 days after SRS in all the nine BM with a mean of 86.9 ± 13 mM. Eight of nine BM showed a mean 60.6 ± 13.3% decrease in the longest axial diameter 40 days after SRS; at this time point, the TSC also had decreased to a mean 65.1 ± 7.9 mM. In contrast, one of the nine BM had a 13.4% increase in the largest axial diameter at time point III. The TSC of this BM showed a further TSC increase of 80.1 mM 40 days after SRS.

CONCLUSION: Changes in TSC using \(^{23}\)Na MRI shows the possible capability to detect radiobiological changes in BM after SRS.

Keywords: Brain metastases, \(^{23}\)Na-MRI, stereotactic radiotherapy, tissue sodium concentration.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
Table 1. Patients’ Demographic Data

| Patient Number | Age (years) | Gender | Primary Tumor                  | Lesion Number | Location      | Concomitant Therapy |
|----------------|-------------|--------|--------------------------------|---------------|---------------|---------------------|
| 1              | 79          | Female | Nonsmall-cell lung carcinoma   | 1             | Frontal left  | _                   |
| 2              | 45          | Female | Mammary carcinoma              | 2             | Frontal left  | _                   |
| 3              | 65          | Female | Bronchial epithelium carcinoma | 3             | Frontal right | Olaparib            |
| 4              | 43          | Female | Malignant melanoma             | 4             | Parietal right| Nivolumab/Relatlimab|
| 5              | 56          | Male   | Renal cell carcinoma           | 5             | Parietal left | Cabozantinib/Nivolumab|
| 6              | 51          | Male   | Spindle cell sarcoma           | 6             | Occipital right| Doxorubicin/Ifofamide|
| 7              | 78          | Female | Cancer unknown primary         | 7             | Frontal right | Trastuzumab         |

Demographic data of the included patients and the location of the evaluated metastases as well as the received concomitant chemotherapy.

metastases after radiotherapy but not in treatment-related changes.13

Tissue sodium concentration (TSC) is a biomarker for cell viability and can be measured with 23Na MRI.14 Changes in sodium/hydrogen (Na+/H+) exchange kinetics are part of the signaling mechanism that initiates cell division.15 Cell division and the acidic extracellular microenvironment of tumor cells are both associated with an increase in intracellular Na+ concentration that has been linked to tumor malignancy.15

In a previous study, it was concluded that TSC measurements with 23Na MRI may identify malignant tumors with regard to intrinsic changes that occur in the tumor’s Na+/K+ pump function.15 Treatments that affect or destroy tumor cell membrane integrity are likely to generate changes in TSC and can be detected with 23Na MRI.16 Studies evaluating TSCs in BM have shown an increase of the total 23Na signal, likely due to dysregulations of the Na+/K+-ATPase.15,17-19 This change in total sodium signal can originate from changes in intracellular sodium concentration or variations in extracellular volume fraction (with constant extracellular sodium concentration of 140 mM),16 mainly because extracellular plasma sodium levels are regulated by the kidneys.16 Therefore, 23Na imaging may prove a useful method in providing an early noninvasive biomarker of tumor response to therapy. However, to the best of our knowledge, no study to date examined and evaluated the longitudinal TSC changes in BM.

The aim of this study was to analyze the longitudinal changes of TSC in BM measured with 23Na MRI before and after SRS.

Methods

Patients

From June 2019 to December 2019, seven consecutive patients were prospectively included (five women and two men; mean age = 59.6 ± 15 years) with 12 untreated BM deriving from six different primary tumors. The primary tumors were as follows: nonsmall-cell lung carcinoma (1), bronchial epithelium carcinoma (1), mammary carcinoma (1), renal cell carcinoma (1), malignant melanoma (1), cancer of unknown primary (CUP-syndrome) (1), and spindle cell carcinoma (1) (Table 1). Five of the 7 patients received concomitant chemother-apy (Table 1). None of the 7 patients received systemic glucocorticoids during the course of the study. Excluded from the evaluation were two small size BM (diameter less than 4 mm) and one hemorrhagic BM.

All patients were scheduled for SRS by Leksell gamma knife with a single ablative dose of 22 Gy to the 50% isodose line; and an average planned target volume of 1.017 cm³.

This study was approved by the Institutional Review Board (reference No.: 2019-630 N-MA), and informed written consent was obtained from all patients. This study was also compliant with all patient confidentiality regulations.

MRI Data Acquisition

All scans were performed at a 3 T MRI system (Magnetom TRIO, Siemens Healthineers, Erlangen, Germany). All patients underwent MRI investigations at four time points: (I) 2 days before SRS at baseline, (II) 5 days after SRS, (III) 40 days after SRS, and (IV) 6 months after SRS.

First, third and fourth scans were synchronized with the routine clinical appointments. For the second scan, an additional appointment was agreed.

Standard MRI protocol was acquired at time points I, III, and IV using a 12-channel head coil and included a 2-dimensional fluid-attenuated inversion recovery spin echo sequence (FLAIR) (field of view [FOV] = 230 mm², voxel size = .9 × .9 × 5 mm³, TR/TI/TE = 9,000/2,500/93 ms, TA = 2 minutes 44 seconds); a 2-dimensional T1-weighted spin echo sequence [TIw] (FOV = 230 mm², voxel size = .9 × .9 × 5 mm³, TR/TE = 330/2.5 ms, Time of Acquistion [TA] = 2 minutes 9 seconds); a DSC MRI perfusion (FOV = 230 × 230 mm², TR/TE = 1,500/46 ms, TA = 1 minutes 14 seconds); and a 3-dimensional gadolinium-enhanced T1-weighted magnetization-prepared rapid gradient echo (MP RAGE) (FOV = 250 mm³, TR/TE = 1,900/2.5 ms, flip angle = 20°, matrix size = 256 × 246, slice thickness = 1.0 mm, and voxel size = 1.0 × 1.0 × 1.0 mm³ = 1).

An initial loading dose of 5 mL of gadoterate meglumine (Dotarem®) was administered and after 5 minutes, was followed by another bolus injection with the remaining dose (for a total of .2 mL/kg) during image acquisition.

23Na MRI scans were additionally acquired at three time points (I-III) using a 1 Tx/1 Rx dual-tuned 1H/23Na birdcage head coil (Rapid Biomedical GmbH, Rimpar, Germany).

23Na image acquisition was performed with a 3-dimensional radial density-adapted sequence20 with TR/TE = 100/4 ms, FOV = 300 × 300 × 300 mm³, bandwidth = 100 Hz/Px,
Fig 1. (A) A coregistered axial contrast-enhanced T1-weighted MRI scans; 2 days before SRS (I), 5 days after SRS (II), and 40 days after SRS (III), respectively, showing a metastatic lesion in the right parietal lobe, of a 43-year-old female patient, with almost no change in the longest axial diameter 5 days post-SRS and distinct regression in size 40 days post-SRS (lesion number 6; Table 1 and Table 2). (B) Corresponding axial reconstructed, coregistered 23Na MRI showing the segmented metastatic lesion. The TSC values were computed based on the segmented regions of interests (in red circle).

gradient amplitude of 5.6 mT/m, resulting in an acquisition time of 15 minutes and a isotropic resolution of 4 mm. All 23Na MRI scans were performed after the administration of gadolinium, which has no impact on TSC values.

At the three time points (I-III), an additional gadolinium-enhanced 2-dimensional gradient echo T1-weighted images with TR/TE = 360/8 ms, slice thickness = 4 mm, FOV = 26 cm × 26 cm, matrix size = 256 × 208 was acquired using the dual-tuned 1H/23Na birdcage head coil.

MRI Data Processing

The 23Na images’ reconstruction was performed in MATLAB 2015a (The Mathworks, Natick, MA, USA) using a zero-filling factor of 2, resulting in a 120 × 120 × 120 voxel dataset for a FOV of 241 × 241 × 241 mm3. The algorithm used a Hanning filter in k-space and data were gridded using a Kaiser-Bessel window with the width of 4. No B1+ or B1– corrections were performed as a homogenous field was assumed with a birdcage coil at 3 T.

The 23Na MRIs, the 2-dimensional gadolinium-enhanced T1, and the FLAIR images from the three scans were coregistered to the MP RAGE image acquired on the first scan on which the regions of interest (ROIs) were defined using the statistical parameter mapping software SPM12 (Wellcome Centre for Human Neuroimaging, UCL, London, UK).

The MP RAGE at scan time (I) was used by the radio oncologists for segmentation of the BM and calculated in Leksell GammaPlan (Elekta Instrument AB, Stockholm, Sweden) for radiotherapy treatment plan. In the initial and the follow-up scans, the BMs were segmented by a neuroradiologist. Segmented BMs were exported as DICOM RT files including the ROIs and imported into MATLAB using the computational environment for radiotherapy research (CERR) in MATLAB. Peritumoral edema was defined as areas around the lesions with increased FLAIR signal; these areas were further manually segmented.

Afterward, areas of the contralateral normal appearing brain area were also segmented and then transferred to the 23Na images. The absolute TSC was measured in all three scans (Fig 1). The relative TSC (rTSC) was calculated in the three scans using the following formula:

\[ rTSC = \frac{TSC_{inROI}}{TSC_{contralateral}} - 1 \]

The ROIs for healthy appearing contralateral tissue were created by mirroring the locations of the ROIs containing tumor in relation to the location of the central fissure, except in those patients where the tumor location prevented accurate positioning. In these patients, the ROIs for uninvolved contralateral tissue were placed manually.

Quantification of the 23Na images was performed based on signal intensities (SI) within the patient’s left vitreous humor that is assumed to be constant at 145 mM 23Na. Signal intensity (SI) was evaluated by defining three dimensional ROIs within the vitreous humor. TSC at location x (TSCx) was calculated based on the ROI’s signal intensity:

\[ TSC_x = SI_x \frac{\rho(23\text{Na})_\text{Vitreous humor}}{SI_{\text{Vitreous humor}}} \]

The longest diameter of the tumor was measured in the axial plane where the largest tumor extent was seen in the 2-dimensional gadolinium-enhanced T1w images in the three scans.

The postprocessing of the DSC-Perfusion was performed by a commercial software package: Aycan Osirix Pro v2.04 (Aycan Medical Systems, LLC, Rochester, NY, USA) and IB Neuro v1.1 (Imaging Biometrics, LLC, Elm Grove, WI, USA). After transferring the perfusion weighted images (PWI) to an off-line...
workstation and removing baseline points collected during the first 3 seconds, we generated whole-brain rCBV maps by using all default options including leakage correction: (1) automated detection of brain tissue mask for voxels used in CBV calculation, (2) automated detection of contrast arrival within brain masks to define the prebolus baseline and integration intervals, and (3) leakage correction based on Boxerman et al.25 We normalized all rCBV maps to mean CBV from a 1-cm ROI within the contralateral frontoparietal normal-appearing white matter.

Statistical Analysis

Statistical analyses were conducted with MATLAB 2015a (The MathWorks, Inc, Natticks, USA). A P-value of ≤ .05 was considered to indicate statistical significance.

Descriptive analysis of variables was presented as mean ± standard deviation (SD). Longitudinal changes in TSC and lesions diameters were presented in percentages.

All variables: lesions’ diameters, the TSC as well as the rCBV followed normal distribution as tested by the one-sample Kolmogorov-Smirnov test. A paired student t-test was used to compare the difference between the TSC values in metastatic lesions and that in normal-appearing contralateral brain tissue.

The differences in the longest axial diameter, TSC, and rCBV were compared for all lesions between the baseline and the follow-up scans post-SRS using the paired t-test.

Pearson’s correlation test was performed to evaluate the correlation between the rCBV and rTSC in the scans I and III.

Results

Local Tumor Response

At the baseline scan (I), the mean of the longest diameter of all nine lesions was 9.8 ± 3.3 mm. At scan (II), 5 days post-SRS, the mean of the largest axial diameter of all lesions was 9.7 ± 3.5 mm (P = .91). At (III), 40 days post-SRS, eight of the treated nine BMs showed a mean of 60.6% ± 13.3% decrease in the longest axial diameters (mean 3.8 ± 2.6 mm) (P < .001) and one BM showed a 13.4% (1.3 mm) increase in the largest axial diameter (Table 2). At the 6-month follow-up, five of the eight regressive lesions were not detectable. Three lesions showed further 25%, 15%, and 37% decrease in the largest axial diameter, respectively. The one progressive lesion showed a 2.4% decrease in the largest axial diameter 6 months after SRS.

Evaluation of rCBV in the Treated BMs

At time point (I) [prior to SRS], the mean TSC of all nine lesions was 73.4 ± 12.3 mM, mean rTSC 53% ± 19%. At time point (II), 5 days post-SRS, the mean TSC of all nine lesions was 86.9 ± 13.1 mM, mean rTSC 78% ± 15% (P = .002). At time point (III), 40 days post-SRS, eight regressive lesions showed a mean TSC of 65.1 ± 79 mM, rTSC 35% ± 14% with a mean 25% ± 9% decrease in TSC in comparison to the first follow-up scan (II) (P < .001) and a mean 9% ± 9% decrease in comparison to the baseline scan (I) (P = .04). The BM that presented with an increase in the axial diameter showed a TSC of 84.7 mM and rTSC of 96% at scan (III), 40 days post-SRS follow-up, with a 30.1% increase in comparison to time point (II) and a 41.6% increase in comparison to the baseline scan (I) (Table 2; Figs 3 and 4).

Evaluation of rCBV in the Treated Lesions

All of the evaluated metastatic lesions had an increased rCBV at baseline (range 1.5-11.5, mean 4.9 ± 3.5). At (III), 40 days post-SRS, the mean rCBV for all lesions was 1.4 ± .7 (P = .027). The lesions that showed regression in the longest axial diameter had a mean rCBV of 1.4 ± .7 at (III) (P = .042). The one lesion that demonstrated an increase in the maximal axial diameter showed a rCBV of 2.8 at (III) (Table 2; Fig 5).

A negative correlation between rCBV and rTSC at baseline was observed (r = -.85, P = .01). At time point (III), 40 days post-SRS, a positive correlation between rCBV and rTSC was noted (r = .65, P = .05).
Evaluation of TSC in Peritumoral Edema

The TSC in the peritumoral edema was evaluated in all patients at all time points. At (I), the mean TSC was 73.2 ± 18.9 mM, whereas the mean TSC in the contralateral normal-appearing brain tissue was 48 ± 5.9 mM; mean rTSC in the peritumoral edema was 51% ± 25% (P = .001). At (II), the mean TSC was 82.9 ± 18.4 mM, mean TSC in the contralateral normal-appearing brain tissue was 48.7 ± 6.3 mM; mean rTSC in the peritumoral edema was 69% ± 23% (P = <.001) with a mean 14% ± 10% increase (P < .001) between the (I) and (II). At (III), the mean TSC was 57.1 ± 7.7 mM; mean TSC in the contralateral normal-appearing brain tissue was 48.6 ± 6.1 mM; mean rTSC in the peritumoral edema was 18% ± 18% (P = .01) with a mean 28% ± 21% decrease between scan (II) and (III) (P = .004) and 18% ± 23% decrease between scan (I) and (III) (P = .04) (Fig 6).
Fig 3. Boxplot of the TSC (mM) values of the eight (8) regressive lesions (1-7 and 9 [Tables 1 and 2]) at baseline, 5 days post-SRS, and 40 days post-SRS.

Fig 4. Linear illustration of the longitudinal TSC changes in the treated BMs at all time points: (I) baseline, (II) 5 days post-SRS, and (III) 40 days post-SRS.

Fig 5. Boxplot of the rCBV values of all metastatic lesions at baseline and 40 days post-SRS (Table 2).

Fig 6. Boxplot of the TSC values in the peritumoral edema (blue) and the corresponding TSC values in the contralateral normal appearing brain tissue (orange) at baseline, 5 days post-SRS, and 40 days post-SRS in all metastatic lesions.

Discussion

The aim of this prospective study was to evaluate the feasibility of longitudinal $^{23}$Na MRI in detecting early changes in BM after SRS.

We found that eight out of nine BM had a clear reduction in size or vanished at 40 days follow-up after SRS with 22 Gy. In the same time interval, one of the nine BM showed a 13.4% size increase with an increasing central necrosis without significant change in perifocal edema. At time point II, 5 days after SRS, only one BM demonstrated an early size regression, three lesions showed an insignificant increase in size, whereas the other five BMs showed no change in diameter. Patel et al$^{26}$ reported a series of 500 BM treated with SRS in which one-third of the lesions had a transient size increase after treatment, starting as early as 6 weeks, which could be observed up to 15 months post-SRS. Furthermore, it was previously shown that radiation-sensitive metastases can show volume shrinkage early after SRS (<30 days); however, shrinkage of radiation-resistant metastatic tumors may take longer than 30 days.$^5$ Given that early volume expansion may be relatively common, the value of short interval conventional imaging and a 3-month response assessment, as carried out in many early phase studies, is called into question.$^{27}$

All nine metastatic lesions in our study showed an elevated TSC at baseline compared to the contralateral normal appearing brain area with a mean of 73.4 ± 12.3 mM (mean rTSC 53% ± 19%). These values correlate well with data published by Ouwerkerk et al who reported an elevated TSC with a mean of 105 ± 24 mM in malignant brain tumors.$^{15}$ It is believed that the elevated TSC is due to significant alterations in sodium metabolism in brain tumors and increased intracellular sodium concentration in rapidly dividing cells.$^{28}$ On the other hand, sodium extracellular volume fraction is also believed to be increased due to tumor neovascularization and increase in interstitial space,$^{15}$ which could possibly be quantified by measuring triple-quantum signal changes.$^{29}$

The mean TSC in the healthy appearing contralateral brain tissue in our patients was between 40.2 and 60.0 mM, which coordinates with the normal TSC values in white matter (20-60 mM) as stated in previous studies.$^{30}$
The eight lesions with tumor size reduction at time point III all showed a further increase in TSC at time point II shortly after SRS followed by a significant decrease at time point III below the initial TSC values. Considering the two different main types of radiation-induced cell death, apoptosis and mitotic cell death or mitotic catastrophe, the short-term TSC increase can be predicated to the induced endothelial-cell apoptosis followed by autophagy. Apoptosis amount for the majority of ionizing radiation induced cell death characterized by cell shrinkage and increased cell membrane permeability. The subsequent enlargement of the extracellular volume explains the increased sodium concentration at an early stage. On the other hand, the drop of TSC 40 days after SRS can be purported due to the arrest of active cell division as response to radiation. Nevertheless, it can also be explained due to the tumor shrinkage with a consecutive decrease in malignant cells and overall interstitial space.

The only lesion with a slight size progression at time point III (and development of central necrosis at 6-month follow-up) behaved differently already at time point III with a further increase in TSC.

The second main type of cell death induced by radiation is the so-called mitotic catastrophe, a mechanism for the control of cells unable to complete mitosis, by triggering of mitotic arrest and ultimately regulated cell death. Several attempted divisions can occur before sufficient genetic damage is accumulated to trigger mitotic death, underlining the possibility of delayed tumor response after SRS. Injury to the vasculature, caused by clonogenic death of endothelial cells, is thought to be one of the mechanisms of radiation-induced injury. Radiation-induced cell death results in vasogenic edema, ischemia, and hypoxia. Hypoxia results in an upregulation of vascular endothelial growth factor with increased permeability of the vasculature followed by demyelination and tissue necrosis. Hence, the different development in this one lesion might be explained by mitotic catastrophe with delayed development of necrotic tumor response. Another explanation could be the histology, in this case a spindle cell sarcoma, considered to be radioresistant. On the other hand, there were also BMs from melanoma and renal cell carcinoma among our treated lesions, all considered radioresistant tumors behaving like the other examined radiosensitive tumors after SRS. Also several authors pointed out that using SRS showed an equivalent rate of local control of radioresistant BM to that of nonradioresistant BM, with local control rates of 89.9% and 90.1%, respectively, evaluated with a median follow-up of 6 months.

Although all treated lesions showed a rise in the TSC between time point I and II, the lowest rise in the rTSC was observed in a lesion that was concomitantly treated with Trastuzumab. Trastuzumab is believed to cause an increase in cell cycle arrest and the suppression of cell growth and proliferation. Another lesion that also showed a low rise in the rTSC between point I and II was concomitantly treated with Olaparib, an inhibitor of the enzyme poly ADP ribose polymerase, which inhibits the DNA repair of the tumor cell and subsequently decrease cell replication.

On the other hand, lesions that were concomitantly treated with immune modulators like Nivolumab showed higher rise in the rTSC between scan I and II. It is believed that Nivolumab, an IgG4 monoclonal antibody, works as a checkpoint inhibitor, blocking a signal that prevents activation of T cells from attacking the tumor cells. Consequently, this leads to more T cell infiltration in the tissue and induces an immune response.

However, the different mechanism of the concomitant therapies might suggest an explanation of the different percentual increases in the TSC/rTSC after SRS, but our preliminary data are not sufficient to be conclusive.

The high TSC found in FLAIR hyperintense nonenhanced regions is consistent with findings in animal and human MRI studies that show elevated sodium concentration in vasogenic edema and in tumors. The increase in TSC 5 days post-SRS in the peritumoral regions reflects the accumulation of vasogenic edema, which is known to increase following radiation therapy due to the inflammatory process following cell apoptosis. After subsiding of the acute inflammatory process, regression of the peritumoral edema is established in the FLAIR images and is also reflected in the drop of the TSC values at the 40 days post-SRS follow-up with a mean of 57.1 ± 7.7 mM, which is not significantly different from the TSC in normal brain tissue.

SRS is expected to have antiangiogenic effects with severe vascular damage resulting in reduced blood perfusion. Several prior studies have used quantitative MRI to investigate local tumor response after SRS in BM using DSC-derived CBV. These studies have shown that an interval decrease in relative CBV after SRS can be used as a marker of treatment response and to differentiate between tumor progress and pseudoprogression. In this study, in a time interval of 42 days a significant decrease in rCBV was observed in all metastases that were treated with SRS (P = .03). Interestingly, there was a significant negative correlation between rCBV and rTSC before SRS and significant positive correlation between rCBV and rTSC post-SRS. Although the post-SRS positive correlation might be explainable due to radiation-induced devascularization, the negative correlation pre-SRS remains an interesting aspect for further investigation.

A major limitation to our study is the small sample size; a larger cohort would be needed to further validate our results. From a technical perspective, the spatial resolution of the 3-dimensional radial density-weighted 23Na MRI sequence did not allow the analysis of lesions less than 4 mm in diameter. Another limitation is the quantification of the absolute sodium concentration that does not distinguish between intra- and extracellular sodium concentration and therefore does not allow an estimation of the volume fractions as was introduced previously by Madelin et al and Ridley et al.

In conclusion, changes in TSC using 23Na MRI show the possible capability to detect radiobiological changes in BM after SRS.

References

1. Chen Z, Zu J, Li L, et al. Assessment of stereotactic radiosurgery treatment response for brain metastases using MRI based diffusion index. Eur J Radiol Open 2017;4:84-8.
2. Goryth EA, Rao G, Harvey A, et al. Temporal change in tumor volume following stereotactic radiosurgery to a single brain metastasis. World Neurosurg 2020;136:e328-33.
3. Jakubovic R, Sahgal A, Ruschin M, et al. Non tumor perfusion changes following stereotactic radiosurgery to brain metastases. Technol Cancer Res Treat 2015;14:497-503.
4. Trifiletti DM, Lee CC, Kano H, et al. Stereotactic radiosurgery for
brainstem metastases: an international cooperative study to define
response and toxicity. Int J Radiat Oncol Biol Phys 2016;96:280-8.
5. Da Silva AN, Nagayama K, Schlesinger D, et al. Early brain tumor metastasis
reduction following Gamma Knife surgery. J Neurosurg 2009;110:547-52.
6. Park HJ, Griffin RJ, Hui S, et al. Radiation-induced vascular
damage in tumors: implications of vascular damage in ablative
hyperfractionated radiotherapy (SBRT and SRS). Radiat Res 2012;177:311-27.
7. Iyer A, Harrison G, Kano H, et al. Volumetric response to radio-
surgery for brain metastasis varies by cell of origin. J Neurosurg
2014;121:564-9.
8. Hayashi T, Zadeh G Tumor pseudoprogression following radio-
surgery for vestibular schwannoma. Neuro Oncol 2012;14:87-92.
9. Barajas RF, Chang JS, Sneed PK, et al. Distinguishing recur-
rent intra-axial metastatic tumor from radiation necrosis following
gamma knife radiosurgery using dynamic susceptibility-weighted
contrast-enhanced perfusion MR imaging. AJNR Am J Neurora-
diol 2009;30:367-372.
10. Mehrabian H, Detsky J, Soliman H, et al. Advanced magnetic re-
onance imaging techniques in management of brain metastases.
Front Oncol 2019;9:440.
11. Essig M, Waschkies M, Wenz F, et al. Assessment of brain metastases with
dynamic susceptibility-weighted contrast-enhanced MR imaging:
initial results. Radiology 2003;228:193-9.
12. Sugahara T, Kogoro Y, Tomiguchi S, et al. Posttherapeutic intra-
axial brain tumor: the value of perfusion-sensitive contrast-
enhanced MR imaging for differentiating tumor recurrence from
nonneoplastic contrast-enhancing tissue. AJNR Am J Neuroradiol
2000;21:901-9.
13. Kwee RM, Kwee TC Dynamic susceptibility MR perfusion in
diagnosing recurrent brain metastases after radiotherapy: a
systematic review and meta-analysis. J Magn Reson Imaging
2020;51:524-34.
14. Hilal SK, Maudsley AA, Ra JB, et al. In vivo NMR imaging of sodium-23 in the human head. J Comput Assist Tomogr 1985;9:1-7.
15. Ouwerkerk R, Bleich KB, Gillen JS, et al. Tissue sodium concentra-
tion in human brain tumors as measured with 23Na MR imaging.
Radiology 2003;227:529-37.
16. Schepkin VD, Ross BD, Chenevert TL, et al. Sodium magnetic resonance imaging of chemoatherapeutic response in a rat glioma.
Magn Reson Med 2005;53:85-92.
17. Thulborn KR, Davis D, Adams H, et al. Quantitative tissue sodium concentration mapping of the growth of focal cerebral tumors with sodium magnetic resonance imaging. Magn Reson Med 1990;14:351-9.
18. Thulborn KR, La A, Atkinson IC, et al. Quantitative sodium MR imaging and sodium bioscales for the management of brain tu-
mors. Neuroimaging Clin N Am 2009;19:615-24.
19. Gilles A, Nagel AM, Madelin G. Multipulse sodium magnetic resonance imaging for multicompartment quantification: proof-of-concept. Sci Rep 2017;7:17435.
20. Nagel AM, Laun FB, Weber MA, et al. Sodium MRI using a density-adapted 3D radial acquisition technique. Magn Reson Med 2009;62:1565-73.
21. Paschke NK, Neumann W, Uhrig T, et al. Influence of gadolinium-based contrast agents on tissue sodium quantification in sodium magnetic resonance imaging. Invest Radiol 2018;53:555-62.
22. Thulborn KR, Gindin TS, Davis D, et al. Comprehensive MR imaging protocol for stroke management: tissue sodium concentra-
tion as a measure of tissue viability in nonhuman primate studies and in clinical studies. Radiology 1999;213:156-66.
23. Paschke NK. Quantification accuracy in human 23Na magnetic resonance imaging (Doctoral dissertation). https://doi.org/10.11588/heidok.00028101.
24. Kokavec J, Min SH, Tan MH, et al. Biochemical analysis of the living human vitreous. Clin Exp Ophthalmol 2016;44:597-609.
25. Boxerman JL, Schmainda KM, Weisskoff RM. Relative cere-
bral blood volume maps corrected for contrast agent extrava-
sation significantly correlate with glioma tumor grade, whereas
uncorrected maps do not. AJNR Am J Neuroradiol 2006;27:859-67.
26. Patel TR, McHugh BJ, Bi WL, et al. A comprehensive review of MR imaging changes following radiosurgery to 500 brain metastases. AJNR Am J Neuroradiol 2011;32:1885-92.
27. Sawlani V, Davies N, Patel M, et al. Evaluation of response to stereotactic radiosurgery in brain metastases using multiparametric
magnetic resonance imaging and a review of the literature. Clin Oncol (R Coll Radiol) 2019;31:41-9.
28. Nagy I, Lustyik G, Lukacs G, et al. Correlation of malignancy with the intracellular Na+:K+ ratio in human thyroid tumors. Cancer Res 1983;43:5395-402.
29. Schepkin VD Statistical tensor analysis of the MQ MR signals gener-
erated by weak quadrupole interactions. Z Med Phys 2019;29:326-36.
30. Madelin G, Regatte RR Biomedical applications of sodium MRI in vivo. Magn Reson Imaging 2013;38:511-29.
31. Thingarajan A, Yamada Y Radiobiology and radiotherapy of brain metastases. Clin Exp Metastasis 2017;34:411-9.
32. Sia J, Szmyd R, Hau E, et al. Molecular mechanisms of radiation-
induced cancer cell death: a primer. Front Cell Dev Biol 2020;8:41.
33. Baskar R, Lee KA, Yeo R, et al. Cancer and radiation therapy: current advances and future directions. Int J Med Sci 2012;9:193-209.
34. Wong CS, Van der Kogel AJ. Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. Mol Interv 2004;4:273-84.
35. Nordal RA, Nagy A, Pintilie M, et al. Hypoxia and hypoxia-
inducible factor-1 target genes in central nervous system radiation injury: a role for vascular endothelial growth factor. Clin Cancer Res 2004;10:3342-53.
36. Yahe A, Nanda T, Jani A, et al. Control of brain metastases from radioresistant tumors treated by stereotactic radiosurgery. J Neuro-
coll 2015;124:507-14.
37. Vu T, Clarey FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol 2012;2:62.
38. Carruthers R, Chalmers AJ The potential of PARP inhibitors in neuro-oncology. CNS Oncol 2012;1:85-97.
39. Riaz N, Havel JJ, Makarov V, et al. Tumor and microenvironment evolution during immunotherapy with Nivolumab. Cell 2017;171:934-49.
40. Hashimoto T, Ikehira H, Fukuda H, et al. In vivo sodium-23 MRI in brain tumors: evaluation of preliminary clinical experience. Am J Physiol Imaging 1991;6:74-80.
41. Schuierer G, Ladebeek R, Barfuss H, et al. Sodium-23 imaging of supratentorial lesions at 4.0 T. Magn Reson Med 2004;10:3342-53.
42. Hoeftnagels FW, Lagerwaard FJ, Sanchez E, et al. Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. J Neurotol 2009;256:878-87.
43. Huang J, Wang A-M, Shetty A, et al. Differentiation between intra-
axial metastatic tumor progression and radiation injury following fractionated radiation therapy or stereotactic radiosurgery using MR spectroscopy, perfusion MR imaging or volume progression modeling. Magn Reson Imaging 2011;29:1001-1001.
45. Koh MJ, Kim HS, Choi CG, et al. Which is the best advanced MR imaging protocol for predicting recurrent metastatic brain tumor following gamma-knife radiosurgery: focused on perfusion method. Neuroradiology 2015;57:367-76.

46. Weber MA, Thilmann C, Lichy MP, et al. Assessment of irradiated brain metastases by means of arterial spin-labeling and dynamic susceptibility-weighted contrast-enhanced perfusion MRI: initial results. Invest Radiol 2004;39:277-87.

47. Madelin G, Kline R, Walvick R, et al. A method for estimating intracellular sodium concentration and extracellular volume fraction in brain in vivo using sodium magnetic resonance imaging. Sci Rep 2014;4:4763.

48. Ridley B, Nagel AM, Bydder M, et al. Distribution of brain sodium long and short relaxation times and concentrations: a multi-echo ultra-high field 23Na MRI study. Sci Rep 2018;8:4357.