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Quantitative Sodium MR Imaging and Sodium Bioscales for the Management of Brain Tumors

Keith R. Thulborn, MD, PhD, Aiming Lu, PhD, Ian C. Atkinson, PhD, Fred Damen, and John Villano, MD, PhD

Center for Magnetic Resonance Research, University of Illinois at Chicago, Chicago, IL 60612

Abstract

The standard of care for the comprehensive treatment of high-grade primary brain tumors includes surgery, radiation treatment and chemotherapy. Magnetic resonance (MR) imaging is involved in the initial diagnosis for detection and characterization of the lesion, focusing on size, location and its effect on surrounding brain and then on the heterogeneity of the signal characteristics, the presence of hemorrhage, MR perfusion characteristics and integrity of the blood-brain-barrier. These imaging properties have been correlated with tumor grade that has prognostic significance. Functional MRI can be used for presurgical planning and for image guidance of the surgical procedures (biopsy, resection) to minimize disruption of eloquent cortex. The surgical debulking is not considered curative for high-grade tumors but a preliminary step towards improving response to the subsequent treatments. After a short recovery period to allow some degree of healing of the surgical site, radiation planning and treatment begins. The radiation planning uses the X-ray attenuation coefficients from computed tomography (CT) to design the distribution of the radiation used in the treatment plan. Advantage is taken of the better display of tumors on MRI by fusing the MR and CT images. The course of radiation involves fractionated targeted radiation projected along multiple beams at many angles to achieve high dose over the tumor volume and margins while minimizing the dose to surrounding normal brain. The radiation is fractionated, usually administered for 5 days per week over about 6 weeks to a total dose of about 55 Gy. Imaging is not routinely performed during radiation treatment. Symptoms of brain swelling are controlled by use of oral steroids. Chemotherapy at low dose may be delivered during radiation treatment. Full dose, single agent chemotherapy then follows after the completion of radiation and is administered over multiple cycles to maintain tumor control. Follow-up MR imaging studies begin after radiation treatment is completed and are then performed every few months or more frequently depending on the clinical status of the patient. Although this protocol has been developed based on experience from large numbers of patients in multi-center trials, the prognosis has not changed in three decades (20% survival at 2 yrs, [1]). This extremely poor success rate for a not insignificant neoplasm, despite such this comprehensive protocol after decades of experience, suggests that there is a fundamental oversight in the current treatment of this disease. This material provides an imaging perspective of how regional responses of primary brain tumors may be examined during treatment to guide a flexible treatment plan to the response of each patient's tumor, rather than using a fixed rigid protocol based on population studies. Sodium imaging provides a direct measurement of cell density that can be used to measure regional cell

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Corresponding Author Address: Keith R. Thulborn, Room 1307, Center for Magnetic Resonance Research, OCC, MC707, 1801 West Taylor Street, Chicago, IL 60612, kthulbor@uic.edu.

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kill during treatment. These bioscales of regionally and temporally sensitive biological-based parameters may be helpful to measure tumor responsiveness that the oncologists can use to guide treatment for each patient. The suggestions are speculative and still being examined experimentally but are presented to challenge the medical community to be receptive to changes in the standard of care when that standard continues to fail.

Keywords

Brain tumor; Sodium MR imaging; Tissue viability; Bioscales; Treatment protocols; Imaging treatment response

Introduction

The conventional imaging workup for a brain tumor is a proton MR imaging examination with and without gadolinium contrast enhancement. The standard T1- and T2-weighted images define the location and dimensions of the mass. Diffusion weighted imaging defines the extent of vasogenic edema while excluding cytotoxic edema. Perfusion imaging defines the regions of tumor with high vascularity on the relative cerebral blood volume (rCBV) map consistent with high-grade tumor (Figure 1). The role of perfusion imaging in tumor grading is discussed in another chapter of this volume.

These anatomic characteristics are important in defining the proximity of eloquent cortex that should be mapped with fMRI prior to biopsy and surgical resection. The fMRI study is best done with fiducial markers in place over the head so that accurate anatomic registration of the patient's head with the images can be achieved on the neurosurgical workstation to guide the location and size of the craniotomy (Figure 2). The functional maps are best registered over the contrast-enhanced images to aid in distinguishing tumor margins from eloquent cortex. Functional mapping for presurgical planning is also discussed in more detail in another chapter of this volume.

Once surgical resection is accomplished, a few weeks are allowed for healing and anatomical stabilization before beginning radiation planning. The radiation treatment uses CT for establishing radiation attenuation coefficients but requires a new MRI study to be merged with the CT to delineate the margins of the surgical bed and residual tumor and regions of normal brain. Radiation exposure to normal brain should be minimized while dose to the tumor bed should be maximized (Figure 3). The functional maps could also be used in this setting but this is rarely done.

Once radiation treatment commences, CT is used to ensure that the alignment of the radiation distribution is accurately maintained. MRI is rarely done during radiation treatment unless there is a dramatic clinical change that requires specific evaluation. After radiation treatment is completed, there is a baseline MRI study to which all subsequent imaging is referred. The full dose chemotherapy begins after radiation is completed and is used across multiple cycles. All follow-up MR examinations should include perfusion imaging as discussed elsewhere in this volume but this is still not done universally. The issue of pseudoprogression (Figure 4, consequence of combined radiation and chemotherapy) with worsening gadolinium contrast enhancement but reduced cerebral blood volume in the few weeks to months after radiation with subsequent resolution is also discussed elsewhere in this volume [2].

Given the comprehensive nature of this combined treatment protocol extending over months to years, why has the prognosis for brain tumors not improved? This poor outcome surely

reflects the failure to gain control over the tumor in the initial stages of treatment. Cancer stem cells or residual malignant cells with longer cell cycle times that make them less vulnerable to even fractionated therapy may initiate recurrence. Radiation damages DNA but radiation sensitivity decreases as the oxygen concentration in the tissue decreases [3]. Thus, poorly vascularized tissue is less sensitive to radiation damage than normal tissues. Necrotic areas of tumors are by definition poorly vascularized and may contain cells that are less sensitive to treatment. Surgical debulking attempts to remove these regions. The radiation sensitivity is greatest at the mitotic phase of the cell cycle [3]. In other phases of the cell cycle, the radiation damage is repaired before the cell is required to undergo mitosis. Such cells proliferate to produce the tumor recurrence observed later by imaging. Multiple mechanisms of different radiobiological sensitivities, heterogeneity of cell types and variable microenvironments presumably underlie current treatment failure.

For a more successful treatment protocol to be found, it would seem reasonable that the variability of each tumor for each patient must be considered. This customization of treatment to the heterogeneity of response promotes the need for rapid feedback about the tumor response across spatial distribution of the tumor as well as a need to treat the tumor of each patient individually and flexibly. The current use of a standard rigid protocol for each patient is to deny the nature of the tumor biology. The current approach of a standard protocol for a particular tumor grade and cell type is a product of multi-center trials taking many years and patients to attempt to reach statistical significance for finding small differences in the average survival of patients. Such protocols are exceedingly difficult and expensive to establish and at the end only provide average effects across a still very heterogeneous patient group [4,5]. The impact of this epidemiological approach to finding the appropriate treatment is, as can be expected for a heterogeneous disease, disappointing [1]. In contrast, adaptive treatment in which the radiation distribution is sculptured to the ongoing tumor responses has much to be recommended in that responsive areas are not over treated and unresponsive areas are provided with additional treatment. Boosted radiation doses could be directed objectively rather than prescribed subjectively by the radiation oncologist.

What means are available to achieve such response monitoring? Clearly, a change in tumor size and texture are usually late events on MR imaging and unsatisfactory for this goal. The desired parameter should be a measure of tissue viability, which may be reflected, in metabolic parameters. Glucose utilization such as reflected in 18-fluoro-deoxy-glucose positron emission tomography may be suggested but this requires that the tumor have with a different metabolic rate from surrounding brain tissue. As brain uses glucose as its primary substrate, discrimination may not be achieved [6]. Another metabolic parameter is tissue sodium concentration (TSC) that reflects sodium ion homeostasis. If a cell loses its ability to maintain a sodium ion gradient across its cell membrane, it ceases to be viable. Thus, TSC can be used as an operational definition of tissue viability. The TSC is the volume fraction weighted mean of the intracellular sodium concentration (ICC ~ 10-12mM) and the extracellular sodium concentration (ECC ~ 145-150mM) [7]. The interstitial volume of the brain is small at about 0.2 leaving a cell volume fraction (CVF) of 0.8 [8].

$$\text{TSC} = \text{ICC} \cdot \text{CVF} + (1 - \text{CVF}) \cdot \text{ECC} \quad (1)$$

After correction for the fractional average water content of normal brain as 0.8, the simple Equation (1) gives the TSC as about 45 mM. This is the value that is measured experimentally in normal human brain tissue [9-12]. This expression can be rearranged in the form of cell volume fraction (CVF), i.e., cell density as:

$$\text{CVF} = (\text{TSC} - \text{ECC}) / (\text{ICC} - \text{ECC}) \quad (2)$$

These parameters of TSC and CVF are termed bioscales in that they are quantitative parameters with a spatial distribution that can be displayed as a map of the underlying anatomy. The term bioscale emphasizes the quantitative nature of these parameters as compared to the term biomarker which is often only a binary indicator of disease being present or not and has no connotation of a spatial distribution. When cells fail to maintain ion homeostasis as is reflected in the TSC bioscale, the intracellular compartment is breached and becomes continuous with the extracellular compartment. This interstitial compartment is maintained at high sodium concentration by the entire systemic homeostatic mechanisms of ion balance through tissue perfusion and diffusion. The increasing TSC bioscale indicates loss of tissue viability and the CVF bioscale reflects the concomitant decrease in cell density. These trends in the bioscales have been used to document loss of tissue viability in the clinical settings of stroke and brain tumors [9-14].

The sodium nucleus has an MR signal that can be imaged albeit challenging due to the low concentration of tissue sodium (~45mM) compared to protons in water (80M) used by conventional clinical MR imaging of the brain. Another further challenge for sodium MR imaging is the lower intrinsic sensitivity (gyromagnetic ratio of the sodium nucleus is about one quarter of that of the proton nucleus) of the sodium nucleus. Additionally, the rapid nuclear relaxation properties of sodium (biexponential T2 with a fast T2 component of less than 3ms and a long T2 component of less than 15ms compared to the monoexponential T2 of brain water protons of about 80ms) due to its quadrupolar nuclear spin of 3/2 require different imaging strategies from protons. These were formidable technical challenges when sodium MR imaging was first proposed for clinical applications in the mid 1980s [15] but these challenges have been surmounted over the last two decades and clinical applications have been demonstrated [16,17]. Although the role of sodium MR imaging in treatment response assessment of brain tumors remains under investigation through NIH funded grants (PHS RO1 CA1295531A1), this report summarizes current preliminary findings to prepare clinicians for future options that may improve their care of patients who currently confront the grim prognosis of high-grade brain tumors.

An example of the sodium images, with corresponding TSC and CVF bioscale maps and the calibration phantom at 3.0 Tesla is shown in Figure 5 for a normal human subject.

The TSC bioscale is derived from the sodium image by using the sodium MR imaging of a calibration phantom under equivalent conditions as the patient to convert arbitrary MR signal intensities into voxel concentrations (mmoles/L wet tissue) or after correction for the tissue water content to tissue water concentrations (mmoles/L tissue water). The phantom has been designed to produce the same electrical loading on the RF coil and is imaged under the same acquisition conditions as the patient. The phantom contains samples of known sodium concentration spanning the biological concentration range. Appropriate corrections for the inhomogeneities in the static magnetic field and RF excitation field are made to the images of both the patient and the phantom. The calibration curve is linear as would be expected (Figure 6). The method at 3.0 Tesla has an error across repeated independent measurements of less than 3% for young normal adults. The value of TSC ca. 45mM gives a CVF of ca. 80% leaving an interstitial compartment of 0.2, which matches well with known value for normal brain [18].

The feasibility of routine sodium imaging in conjunction with the conventional proton MR imaging at 3.0 Tesla was illustrated in Figure 1 for a patient with a brain tumor. The full display of the sodium imaging and its TSC bioscale for this same patient are displayed in

Figure 7 to illustrate human imaging at 9.4 Tesla [19]. The technical details of the flexible twisted projection pulse sequence are described elsewhere and will not be elaborated upon here [16]. Sodium imaging at 3.0 and 9.4 Tesla are similar but with improved spatial resolution possible at the increased sensitivity of higher field at 9.4 Tesla. The nominal resolution of $5 \times 5 \times 5 \text{ mm}^3$ is achieved in less than 9 minutes at 3.0 Tesla whereas a resolution of $3 \times 3 \times 3 \text{ mm}^3$ can be obtained in the same time at 9.4 Tesla. However, it is important to emphasize that the sodium imaging technology is available commercially on current 3.0 Tesla clinical scanners with multi-nuclear capabilities. This 3.0 Tesla resolution is probably adequate for sampling the spatial distribution of responses of tumors to treatment.

The application of TSC mapping during radiation is shown for another patient with a right temporal glioblastoma multiforme (GBM) in Figure 8. The clinical imaging indicated that residual tumor was present after surgery.

The standard radiation treatment plan used was about 55Gy to the tumor as shown in Figure 3. Quantitative sodium imaging was performed before and weekly during the radiation treatment as shown in Figure 9. The images were aligned to the pre-radiation images in post-processing at sub voxel accuracy so that the time courses of TSC could be examined in each voxel across the brain. The realignment was performed in k-space rather than the image domain to avoid blurring of the images. Representative time courses shown in Figure 10 illustrate TSC responses.

Although these investigations are preliminary, several points are already evident. The TSC bioscale is responsive to radiation effects on a weekly time scale. The responsive regions (pattern C), showing increases in TSC as the cell density decreases, have completed responding by 3 weeks, well before the end of treatment. The unresponsive regions (pattern B) never become responsive. These observations are consistent with the suggestion that the spatial heterogeneity may well be the basis of the failure of standardized protocols. This patient expired from the tumor within a few months of radiation treatment while after requesting that chemotherapy be stopped because of side effects. The perfusion maps over these months confirmed increasing vascularity consistent with continued tumor growth. The adverse effects and the low success rate of the standard treatment should encourage examination of such rigid treatment protocols. Adaptive treatment protocols should be considered if sodium MR imaging proves to be an effective method for monitoring early tumor response.

One advantage of voxel-wise analysis of tumor response is that many voxels can be assessed to provide regional tissue survival statistics for each patient. Such tissue survival characteristics can use the same radiobiologic models used for multi-center trials in which patient survival is used as the outcome. Thus, imaging results from each patient may be able to provide sufficient information to guide the treatment of each tumor. Such personalized care may avoid the use of rigid standard protocols based on mean population statistics and capitalize on individual sensitivity characteristics of each patient's tumor. In some cases, the lack of response may reduce unsuccessful treatment to avoid the adverse effects of those treatments.

Conclusions

Sodium MR imaging, with its TSC and CVF bioscales, has a direct interpretation in terms of tissue viability. These bioscales can monitor the spatial distribution of tissue responses to radiation treatment on at least a weekly basis. Such rapid feedback could be used to guide adaptive radiation treatment for each patient and avoid excessive radiation when no response can be achieved. This approach can potentially minimize unnecessary treatment to avoid

adverse effects for the patient. Similar responses can be monitored for chemotherapy. Although these hypotheses remain under investigation, it is imperative that new strategies be considered for high grade brain tumors where the prognosis remains grim.

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Figure 1.

Representative MR images from the 3.0 Tesla clinical examination of a patient with a large right hemispheric high-grade glioma prior to treatment. Images are from the following acquisition sequences: (top left) non-contrast-enhanced T1-weighted 3D inversion recovery gradient echo, (top middle) contrast-enhanced T1-weighted 3D inversion recovery gradient echo, (top right) magnetic susceptibility-sensitive 2D gradient echo, (bottom left) 3D quantitative 3D sodium image at a nominal resolution of $5 \times 5 \times 5 \text{ mm}^3$ acquired in under 10 minutes, (bottom middle) relative cerebral blood volume map from a dynamic susceptibility contrast MR perfusion study, and (bottom right) 2D T2-weighted FLAIR propeller. The interpretation is a large, heterogeneous mass with cystic and hemorrhagic components and markedly increased (red) relative cerebral blood volume centered in the right parietotemporal region. The lesion has been biopsied. Surgical resection was not considered as an option.

Figure 2.

Functional MRI performed for presurgical planning of a contrast-enhancing abnormality appearing the surgical bed years after treatment for a brain tumor in the left frontal lobe. The activation map from the fMRI using the reading language comprehension paradigm is presented superimposed over the contrast-enhanced 3D T1-weighted inversion recovery gradient echo images (3D SPGR +C, top row) and over the T2-weighted spin-echo, echo-planar images (AX SE EPI, bottom row) in the axial (left column), coronal (middle column) and sagittal (right column) planes. The planes are cross-referenced with colored lines (blue = axial, green = coronal, yellow = sagittal). Broca's area is cross-referenced (intersection of planes) and is anterior and inferior to the lesion but in close proximity to it so that the surgeon was aware of the potential of producing an aphasia. This location of function was confirmed by intraoperative cortical mapping. The lesion was primarily radiation necrosis as predicted by the low rCBV.

Figure 3.

The radiation treatment planning fuses the CT and MRI studies (left), especially the perfusion study for high-grade tumors, to generate a radiation distribution (middle) that covers the tumor while minimizing the dose to normal brain. The contour of the head is drawn as the blue outline. The base dose (middle left) is supplemented by an additional boost to the tumor (middle right). The radiation plan (red) can then be superimposed over the contrast-enhanced MR image. The large enhancing tumor in the right temporal lobe is well covered but there is still considerable exposure to the rest of the brain despite targeted treatment.

Figure 4.

Pseudoprogression is demonstrated in a patient across their early treatment in which the tumor shows variation in enhancement (top row) and the relative cerebral blood volume (rCBV) map (bottom row). (a) Prior to surgery and radiation treatment, there is a thin rim of enhancement and increased rCBV. (b) After resection, radiation and low dose chemotherapy, there is increasingly thickened enhancement that then subsequently resolves while the rCBV shows continuous monotonically decreasing rCBV. (b,c,d) Follow-up studies were done every 2-3 monthly after radiation treatment was completed.

Figure 5.

Sodium imaging and its derived metabolic bioscales in a normal subject. (a) 4 partitions from a 3D sodium imaging dataset, (b) TSC map derived from (a), (c) CVF map derived by applying Equation 2 to the TSC map and (d) calibration phantom image used to calibrate the sodium signal intensity into a TSC value. These measurements were performed at 3.0 Tesla at a resolution of $5 \times 5 \times 5 \text{ mm}^3$ in less than 10 minutes.

Figure 6.

(a) Linear calibration curve for the conversion of the intensity (arbitrary scale) from the sodium MR signal to a tissue sodium concentration (mM). The phantom has the same electrical loading on the RF coil as the human head and is also corrected for static magnetic field and RF excitation field inhomogeneities. Similar calibration curves are obtained at 3.0 and 9.4 Tesla. (b) An image through the phantom showing the three calibration tubes with different concentrations (30, 70, 110 mM).

Figure 7.

(a) Sodium images showing the high sodium concentration in the large tumor (arrow) in the right hemisphere of the same patient as in Figure 1. The color bioscale shows TSC from 0 to 150mM with normal brain shown as green (cell density = 0.8) and the tumor as pink indicating a lower cell density. (cell density ~ 0.4-0.6). These images were acquired at 9.4 Tesla at a nominal resolution of $3 \times 3 \times 3 \text{ mm}^3$ in less than 10 minutes.

Figure 8. Conventional proton MR images of a patient after resection of a right temporal GBM. (top left) T1-weighted gradient echo image without gadolinium contrast enhancement, (top middle) T1-weighted gradient echo image with gadolinium contrast enhancement, (top right) magnetic susceptibility-sensitive T2-weighted gradient echo image, (bottom left) rCBV map showing residual areas of increased rCBV, (bottom middle) apparent diffusion coefficient map and (bottom right) T2-weighted FLAIR image.

Figure 9.

Realigned sodium images showing the superimposed accumulated radiation dose (red) for the same patient in Figures 3 and 8. The left image is prior to radiation and each subsequent image to the right is another week of radiation therapy with the far right image being after completion of treatment. The images have been co-registered in post-processing to ensure alignment. The realignment is performed within k-space to avoid blurring that would occur if performed in image space, an important advantage of 3D datasets. The two tubes anterior to the brain are calibration phantoms placed within the field of view to demonstrate reproducible signal intensity. These can be used for quantification but with less accuracy than obtained with a separate calibration phantom.

Figure 10.

Voxel-wise classification of temporal responses of TSC during radiation therapy covering the center of the surgical bed of the lesion of the patient shown in Figures 3, 8 and 9. The 5 categories of responses: **A**: contralateral hemisphere with normal TSC values (green star), **B**: no response with elevated TSC (red solid triangle); **C**: desirable response with cell death shown by increasing TSC (orange solid circle); **D**: decreasing edema with elevated TSC decreasing back towards normal TSC (blue solid diamond) and **E**: elevated TSC decreasing but towards tumor TSC values (magenta solid square). Each voxel can be classified into these responses and related to the subsequent follow-up change in rCBV that revealed recurrence but many weeks later. Response patterns B (red triangle) and E (magenta square) are hypothesized to be predictive of recurrence as they are incomplete responses.