International Journal of Radiation Oncology biology • physics

www.redjournal.org

Physics Contribution

Water Exchange Rate Constant as a Biomarker of Treatment Efficacy in Patients With Brain Metastases Undergoing Stereotactic Radiosurgery

Hatef Mehrabian, PhD,[*,†] Kimberly L. Desmond, PhD,[†] Sofia Chavez, PhD,[‡] Colleen Bailey, PhD,[§] Radoslaw Rola, MD, PhD,[‖] Arjun Sahgal, MD,[†,¶] Gregory J. Czarnota, PhD, MD,[*,†,¶] Hany Soliman, MD,[¶] Anne L. Martel, PhD,[*,†] and Greg J. Stanisz, PhD[*,†,‖]

Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; †Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada; ‡Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; §Computer Science Department, University College London, London, United Kingdom; ‖Neurosurgery and Pediatric Neurosurgery, Medical University, Lublin, Poland; and ¶Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Received Sep 9, 2016, and in revised form Dec 12, 2016. Accepted for publication Jan 2, 2017.

Summary

Cells undergoing apoptosis experience an increased intracellular to extracellular water exchange rate. A water exchange quantification technique for clinical DCE-MRI was developed and applied to 19 brain metastases patients treated with stereotactic radiosurgery (SRS). The intra−extracellular water exchange rate

Purpose: This study was designed to evaluate whether changes in metastatic brain tumors after stereotactic radiosurgery (SRS) can be seen with quantitative MRI early after treatment.

Methods and Materials: Using contrast-enhanced MRI, a 3-water-compartment tissue model consisting of intracellular (I), extracellular-extravascular (E), and vascular (V) compartments was used to assess the intra−extracellular water exchange rate constant (k_{IE}), efflux rate constant (k_{ep}), and water compartment volume fractions ($M_{0,I}$, $M_{0,E}$, $M_{0,V}$). In this prospective study, 19 patients were MRI-scanned before treatment and 1 week and 1 month after SRS. The change in model parameters between the pretreatment and 1-week posttreatment scans was correlated to the change in tumor volume between pretreatment and 1-month posttreatment scans.

Results: At 1 week k_{IE} differentiated ($P<.001$) tumors that had partial response from tumors with stable and progressive disease, and a high correlation ($R=-0.76$,

Reprint requests to: Hatef Mehrabian, PhD, Sunnybrook Research Institute, 2075 Bayview Ave, Room S6-05, Toronto, ON M4N 3M5, Canada. Tel: (416) 480-6100, ext. 2455; E-mail: hatef.mehrabian@sri.utoronto.ca

This study was funded by following grants: Terry Fox Research Institute (TFRI project 1034) and Canadian Cancer Society Research Innovation (CCSRI 701640).

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

http://dx.doi.org/10.1016/j.ijrobp.2017.01.016

identified partial response patients within 1 week after treatment and also predicted the extent of tumor shrinkage at 1 month. Thus, intra−extracellular water exchange rate is a promising biomarker of brain metastases response to SRS.

$P<.001$) was observed between early changes in the k_{IE} and tumor volume change 1 month after treatment. Other model parameters had lower correlation ($M_{0,E}$) or no correlation (k_{ep}, $M_{0,V}$).

Conclusions: This is the first study that measured k_{IE} early after SRS, and it found that early changes in k_{IE} (1 week after treatment) highly correlated with long-term tumor response and could predict the extent of tumor shrinkage at 1 month after SRS.

Introduction

Brain metastases have a significant impact on patient quality of life and survival. In the course of cancer illness up to 40% of patients develop brain metastases (1). Stereotactic radiosurgery (SRS) is a useful tool to treat brain metastases and has been found to improve patient outcomes, including survival, in patients with single metastases (2). Evaluation of tumor response to SRS is carried out using the Response Assessment in Neuro-Oncology-Brain Metastasis (RANO-BM) criteria (3) which relies on the changes in tumor size. However, it may take weeks or months before significant changes in tumor size take place. Moreover, early changes in tumor size do not always correlate with later outcomes (4), and very few studies have attempted (with limited success) to evaluate treatment response with quantitative MRI within a few days after treatment (5-7). Thus, more robust markers of response are desired that can quantify early molecular or cellular changes in the tumor, such as those seen in apoptosis (8, 9). Identifying nonresponders early after treatment and avoiding delays to salvage treatments may lead to better treatment outcomes.

Stereotactic radiosurgery induces DNA damage in tumor cells, which leads to programmed cell death (apoptosis). It has been shown in vitro (10) and in animal models (11) that cellular apoptosis can be detected by MRI (within 48 hours after treatment) through quantification of the water exchange rate constant between intracellular and extracellular compartments, k_{IE} (10-12). The water exchange rate increases in apoptotic cells owing to the increased surface-to-volume ratio of the cell either by transformation of the cell into a less spherical shape or decreased volume overall (10, 13) and, to lesser extent, owing to increased cellular membrane permeability to water molecules (10).

There exist several techniques to measure the water exchange rate constant between intracellular and extracellular compartments (11, 12, 14-17). Landis et al (18) and, more recently, Bailey et al (11) applied a 2-compartment tissue relaxation model to contrast-enhanced MRI with multiple injections of contrast agent (CA), to calculate water exchange rate. Multiple injections of CA make these techniques time-consuming and difficult to translate into clinic. Other approaches that can be more easily applied to the in vivo dynamic contrast-enhanced (DCE)-MRI have also been proposed. Yankeelov et al (17, 19) and Springer et al (14) use a 2-compartmental model of water exchange between the intracellular and extracellular compartments and incorporate a tracer kinetic model (Tofts-Kety model [20]) into the apparent longitudinal relaxation rate constant's measurement (while ignoring the contribution of the tumor's vascular compartment).

In the present study we use a modified approach for evaluating the intracellular to extracellular−extravascular water exchange rate constant from clinical DCE-MRI data using a combination of a 3 water compartment tissue model and a vascular signal separation technique called independent component analysis (ICA). The ICA-based separation (21-24)provides the MRI signal of vascular and extracellular−extravascular compartments using the standard, clinically used DCE-MRI datasets and yields sufficient signal measurement to fit to the water exchange model.

The focus of this study was to evaluate this novel imaging approach as an early biomarker of tumor response to SRS. We hypothesized that shortly after SRS, the intra−extracellular water exchange rate constant, which is a surrogate of tumor apoptosis, can differentiate between responders and nonresponders.

Methods and Materials

Three-pool relaxation model

Each voxel in DCE-MRI was assumed to be composed of 3 water compartments: vascular (V), extracellular−extravascular (E), and intracellular (I), and a 3-water-compartment relaxation model (Fig. 1) was used. Each compartment in a voxel was assumed to contain a fraction of the voxel's total water content proportional to its volume fraction ($M_{0,V}$, $M_{0,E}$, $M_{0,I}$). Water was assumed to transfer from the intracellular, I, to extracellular−extravascular compartment, E, with exchange rate constant, k_{IE}. The water exchange between vascular, V, and extracellular−extravascular, E, compartments was assumed to be negligible ($k_{VE} = k_{EV} = 0$). Detailed description of the