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Mapping of global R1 and R2* values versus lipids R1 values as potential markers of hypoxia in human glial tumors: A feasibility study

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ABSTRACT

Availability of an innocuous and repeatable technique for monitoring tumor oxygenation throughout therapeutic course should be a key factor for adaptative therapeutic strategies. We previously qualified lipids R1 as a marker of oxygen level on experimental tumor models. The objectives of the present study were to assess the applicability of measuring lipids R1 in primary central nervous system malignancies in a clinical setting as well as to compare lipids R1 with global (water + lipids) R1 and R2* which are also sensitive to the oxygen environment. 25 patients with brain neuroepithelial tumors were examined on a clinical 3 T MR system. Values obtained within regions of interest contouring contrast-enhanced tumor (C+), unenhanced tumor (C−), peritumoral edema, and normal appearing white matter (NAWM) were compared to those obtained for the normal brain parenchyma of 17 healthy volunteers. Global R1 and lipids R1 values were significantly lower in tumors than in NAWM of patients or healthy brain of normal volunteers. In contrast, R2* values were not significantly different in tumors compared to NAWM or healthy brains. None of them showed significant difference between C+ and C− tumors. Global R1 values within NAWM were significantly different from that of both tumor and peritumoral edema, but lacked sensitivity to differentiate between tumor and peritumoral edema. In turn, lipids R1 measurements enabled discrimination between tumor areas and peritumoral edema. In conclusion, global R1 and lipids R1 deserve further attention as potential markers of tumor hypoxia in primary brain tumors.

1. Introduction

Oxygen deprivation within malignant tumors synergistically results from poor functionality of anarchic neovasculature with subsequent unstable blood supply [1] and from increased oxygen demands by proliferating cells [2,3]. Tumor hypoxia is a well established worsening prognostic factor leading to chemotherapy (CHT) and/or radiotherapy (RT) treatment failure [3–5] e.g. for primary CNS neoplasms which still have short survival rates [6–8]. Therefore, monitoring the hypoxic status of tumors should have a major impact on image-guided adaptative therapeutic strategies [9–13]. Direct quantitative methods, including Eppendorf microelectrodes [14,15], electron paramagnetic resonance (EPR) oximetry [16,17], ^{19}F relaxometry [18], or Overhauser enhanced magnetic resonance imaging (MRI) [19], are either invasive or require the injection of a reporter probe, resulting in inapplicability for routine clinical use. Currently, the reference technique in the clinical setting for whole brain mapping of hypoxia is positron emission tomography (PET) using nitroimidazole-derived tracers selectively accumulating in hypoxic areas after reduction [20], but costs, limited availability and radiation exposure preclude its use in routine clinical practice. Blood oxygen level dependent (BOLD) MR technique is an alternative and innocuous T2* mapping technique sensitive to the relative deoxyhemoglobin/oxyhemoglobin (Hb/HbO_2) ratio within the vascular compartment [21], which has been successfully applied to monitor changes in tissue oxygenation [22–25]. BOLD MRI is sensitive to several factors such as changes in total hemoglobin content [26–28], blood flow and vasculature characteristics [2,29]. Non-invasive estimates of tissue oxygen level variations can also be obtained by standard clinical MR systems using molecular oxygen as endogenous T1-shortening paramagnetic contrast

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Table 1
Tumors' characteristics and measured parameters. NAWM: normal appearing white matter.

	Gender and age	MR lesion	C+ glial tumor			C− glial tumor	
			Global R1 (s^{-1})	Lipids R1 (s^{-1})	R2* (s^{-1})	Global R1 (s^{-1})	Lipids R1 (s^{-1})
1	M, 64	Infiltrative intra-axial right fronto-parietal non-enhancing lesion bearing focal enhancing area with central necrosis.	1.383 ± 0.075	4.371 ± 0.871	7.979 ± 6.750	1.386 ± 0.088	4.743 ± 0.613
2	M, 41	Intra-axial left frontal enhancing and partially necrotic lesion.	1.354 ± 0.090	4.227 ± 0.901	18.390 ± 23.130	–	–
3	M, 68	Intra-axial right frontal enhancing and partially necrotic lesion infiltrating the knee of the corpus callosum and with peritumoral oedema.	1.446 ± 0.112	4.792 ± 0.698	15.050 ± 15.480	–	–
4	M, 65	Intra-axial right fronto-parietal enhancing and partially necrotic lesion with peritumoral oedema.	1.405 ± 0.068	3.802 ± 1.159	17.170 ± 14.980	–	–
5	F, 79	Intra-axial left temporo-parietal enhancing and partially necrotic lesion with peritumoral oedema.	1.406 ± 0.330	3.944 ± 0.854	20.480 ± 17.350	–	–
6	F, 73	Intra-axial right parieto-occipital infiltrative enhancing lesion.	1.630 ± 0.322	5.026 ± 0.968	13.790 ± 10.600	–	–
7	F, 34	Non-enhancing infiltrative right hemi-pontine lesion.	–	–	–	1.538 ± 0.136	3.552 ± 0.786
8	F, 28	Non-enhancing well defined left superior frontal lesion.	–	–	–	1.294 ± 0.101	3.859 ± 1.223
9	M, 72	Intra-axial right parietal enhancing lesion with peritumoral oedema.	1.485 ± 0.077	3.975 ± 0.781	19.040 ± 38.410	–	–
10	M, 48	Intra-axial left temporal enhancing lesion.	0.784 ± 0.173	4.090 ± 0.979	24.330 ± 38.210	–	–
11	M, 68	Intra-axial left temporal enhancing lesion.	1.393 ± 0.124	3.676 ± 0.726	48.610 ± 23.500	–	–
12	F, 47	Intra-axial left temporal polar non-enhancing lesion.	–	–	–	1.522 ± 0.307	4.768 ± 0.784
13	F, 41	Intra-axial vermian enhancing tumor.	1.589 ± 0.217	3.734 ± 2.827	28.150 ± 13.230	–	–
14	M, 44	Callosal enhancing and partially necrotic lesion infiltrating the right frontal lobe and with peritumoral oedema.	1.339 ± 0.136	4.346 ± 0.670	13.930 ± 12.180	–	–
15	F, 26	Intra-axial left mesial temporal non-enhancing lesion.	–	–	–	1.395 ± 0.211	3.745 ± 0.954
16	M, 64	Intra-axial left temporal enhancing and partially necrotic lesion with peritumoral oedema.	1.378 ± 0.072	3.494 ± 1.003	18.010 ± 11.910	–	–
17	F, 50	Intra-axial left temporal polar non-enhancing lesion.	–	–	–	1.531 ± 0.104	4.332 ± 0.980
18	M, 70	Intra-axial right fronto-temporal enhancing and partially necrotic lesion with non-necrotic callosal extension.	1.562 ± 0.199 1.524 ± 0.120	4.969 ± 1.286 4.829 ± 1.105	8.399 ± 9.286 23.300 ± 12.710	–	–
19	M, 41	Intra-axial right temporal lateral non-enhancing lesion.	–	–	–	1.638 ± 0.112	5.173 ± 1.000
20	M, 85	Intra-axial right temporal enhancing lesion with associated oedema.	1.438 ± 0.058	4.437 ± 0.924	39.830 ± 23.670	–	–
21	F, 53	Intra-axial interparietal cortico-subcortical non-enhancing lesion.	–	–	–	1.483 ± 0.103	4.712 ± 0.436
22	M, 37	Left hemispheric gliomatosis cerebri.	–	–	–	1.449 ± 0.097 1.381 ± 0.088	4.663 ± 0.546 4.526 ± 0.358
23	F, 42	Intra-axial left temporo-parietal enhancing and partially necrotic lesion with peritumoral oedema.	1.361 ± 0.122	4.216 ± 0.885	26.880 ± 30.460	–	–
24	M, 65	Intra-axial left temporal enhancing and partially necrotic lesion with peritumoral oedema.	1.390 ± 0.057	3.585 ± 0.734	44.240 ± 32.650	–	–
25	M, 52	Gliomatosis cerebri bi-frontal, limbic and left insular.	1.358 ± 0.129	4.795 ± 0.945	59.740 ± 92.240	1.514 ± 0.080	4.734 ± 0.571
Mean values for the group of patients			1.401 ± 0.177	4.239 ± 0.492	24.850 ± 14.330	1.466 ± 0.097	4.437 ± 0.507

agent [30,31] since changes in tissue oxygen concentrations have been demonstrated to induce closely related changes in R1 relaxation rate (where R1 = 1/T1) of water [30–34]. These R1 changes are sensitive not only to tissue water content but also to blood flow modifications [28,32]. The T1-weighted MR contrast, known as TOLD (tissue oxygen level dependent), showed to be more closely related to tumor growth delay after single high dose irradiation than BOLD [31]. Our group recently described another MR technique able to estimate the variations in tissue oxygenation by monitoring changes in R1 relaxation rate of the lipids rather than those of water [35], based on higher solubility of oxygen in lipids than in water [36,37]. The concept was acronymized MOBILE, for mapping of oxygen by imaging lipids relaxation enhancement [37]. The measurement of lipids T1 is based on a saturation pulse of the water signal, and the application of a rapid inversion-recovery sequence centered on the lipid frequency [37] (Supplementary Figs. 1–4). A close relationship between lipids R1 and pO_2 values was demonstrated on