Reproducibility and Sensitivity of T_2* Measured in Patients with Squamous Cell Carcinoma of the Head and Neck at 3T

Rafal Panek[1], Liam Welsh[1], Maria A. Schmidt[1], Alex Dunlop[1], Kate L. Newbold[1], Kee Wong[1], Angela M. Riddell[1], Dow-Mu Koh[1], Dualta Mcquaid[1], Shreerang A. Bhide[1], Kevin J. Harrington[2], Christopher M. Nutting[2], Georgina Hopkinson[3], Cheryl Richardson[3], Simon P. Robinson[4], and Martin O. Leach[1]

[1]*Royal Marsden NHS FT and Institute of Cancer Research, Sutton, Surrey, United Kingdom,* [2]*Royal Marsden NHS FT and Institute of Cancer Research, London, United Kingdom,* [3]*Royal Marsden NHS FT, London, United Kingdom,* [4]*Institute of Cancer Research, Sutton, Surrey, United Kingdom*

Introduction: The transverse relaxation time T_2* (ms) of the vascular space depends on blood oxygenation (Y), haematocrit (Hct) and field strength (B_0)[1-2], and is being increasingly used to identify well oxygenated and hypoxic tissue regions in both preclinical and clinical settings[3-6]. For quantitative studies, it is important to consider additional influences on macroscopic magnetic field homogeneity, affecting measurement reproducibility, spin relaxation in the extravascular space and vessel size[4,7]. In this study, the reproducibility of T_2* was calculated, and blood oxygen saturation dependence of tissue relaxation times simulated, for patients with squamous cell carcinoma of the head and neck (SCCHN) at 3T.

Materials and Methods:

Reproducibility: MR images acquired in two scanning sessions (24-72h apart) prior to treatment in six patients with stage III and IV SCCHN were used in the study. Written informed consent was obtained for this research, which was approved by the institutional review board and research ethics committee. MRI was performed at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) using a 20 channel head and neck coil, and a gradient echo sequence with 6 echo times (FA = 24°, TE = 4.92\+4.92\29.52 ms, TR = 350 ms, FOV = 240 x 240 mm^2, 7–24 slices, 2.5 mm slice thickness). T_2* maps were calculated offline using custom-written MATLAB software (MathWorks, Natick, MA), and signal intensity decay was fitted on a pixel-by-pixel basis to a monoexponential model using a least-squares fit method. Volumes of interest (VOI) including primary and nodal tumour sites were manually delineated by an experienced radiologist (AR) using the radiotherapy planning station Pinnacle (Philips Healthcare). Median T_2* was calculated for each VOI. A Shapiro-Wilk test was used to assess normality of the sample distribution. Bland-Altman analysis[8] was used to plot the median T_2* difference between two scans against the mean value of T_2* for both visits. The coefficient of variation and threshold of reproducibility (RPC, α = 0.05) were calculated.

Simulation of blood oxygenation dependence on T_2:* A quadratic model with a linear term[1-2] was used to describe the blood transverse relaxation rate R_2* (=1/T_2*) as a function of oxygenation: $R_2^*=A^*+B^*(1-Y)+C^*(1-Y)^2$, where A*,B* and C* are empirically derived coefficients dependent on B_0 and Hct. In our simulations, a tissue hematocrit (H_{tiss}) was used taking into account: a) blood volume fraction typical for SCCHN (BV=5 ml/100g[9]) and b) a vascular factor (f_{vas}=0.85) to account for Hct differences between large vessels and capillary network[6-7]: H_{tiss}=Hct*BV*f_{vas}. A set of A*-C* coefficients measured at 3T[2] was extrapolated for the H_{tiss} and used to plot the dependence of blood oxygen saturation on T_2* values in SCCHN, together with corresponding 95% levels of agreement (RPC). Relative rather than absolute T_2* values were used to recognise the effect of tissue specific extravascular spin relaxation ($T_2^*{}_{Y=0}$=0).

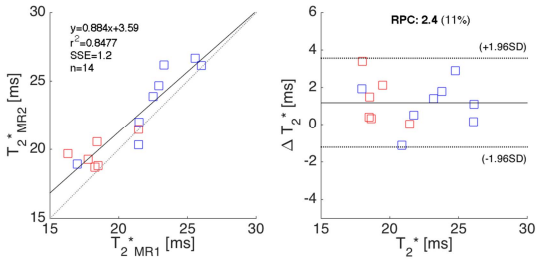

Figure 1. A) Scatter plot of the relation between test and retest ($T_2^*{}_{MR1}$: MR1, $T_2^*{}_{MR2}$: MR2) of median T_2* values in patients with SCCHN (red squares: primary sites, blue squares: involved lymph nodes, solid line: linear trend, dotted line: identity). B) Bland–Altman plot showing median T_2* difference between two scans against the mean value of T_2* for both visits. Mean difference (solid line) and 95% limits of agreement (reproducibility values for an individual, dotted lines) are also shown.

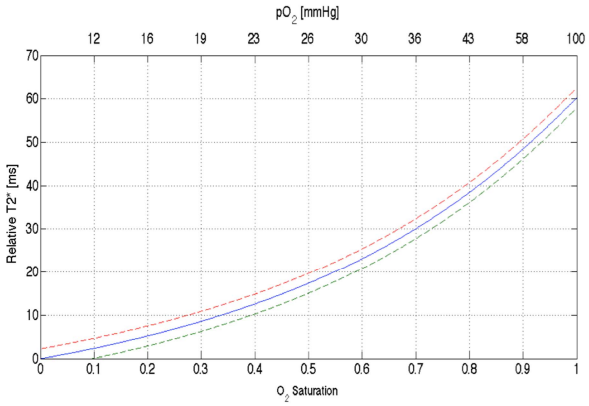

Fig. 2. Simulated relative transverse relaxation time constant T_2* plotted as a function of blood O_2 saturation (blood volume fraction: 5 ml/100g, hematocrit: 0.43, micro-capillary vascular factor 0.85, field strength: 3T. Dashed line shows repeatability coefficient limits (α = 0.05). Oxygen partial pressure was calculated using Hill's equation (human blood, coefficient for blood oxygen binding: 2.26, temperature: 37 °C, pH: 7.4).

Results: *Reproducibility:* 6 primary and 8 nodal tumour sites were delineated and analysed in the study. The distribution of median differences (ΔT_2*) between the two MR examinations did not differ from normal (p=0.97), with the mean value of 21.4 ms (σ = 3 ms). The scatter plot of the relation between test and retest of T_2* values is shown in the Figure 1A. Bland – Altman plot showing median T_2* difference between the two scans (MR2 – MR1) against the mean value of T_2* for both visits is shown in Figure 1B. The coefficient of variation and reproducibility coefficient were 5.5 and 11% respectively. *Simulations:* The calculated average SCCHN tissue hematocrit level H_{tiss} was 0.018. Extrapolated A*, B* and C* coefficients were 12.42, 19.58 and 17.5 respectively. Simulated relative transverse relaxation time constant T_2* plotted as a function of blood O_2 saturation in SCCHN is shown in Figure 2.

Discussion: The reproducibility coefficient of median T_2* value can be used to estimate the size of change that would be needed to be significant in an individual measurement in patients with SCCHN. The simulation of tissue T_2* shows that the sensitivity of the method increases as a function of blood oxygenation, and is sufficient for the majority of reported oxygen tensions in SCCHN (pO_2 range 0–70 mmHg, with a median between 10 and 20 mmHg[10-11]), with the exception of anoxic and severely hypoxic tumour regions (Y<0.1) where sensitivity is lower than measurement reproducibility. The simulations suggest that both baseline T_2* values and blood volumes should be taken into account when employing changes in T_2* for assessing tissue oxygenation. This is important in the context of studies where T_2* changes are associated with modulated blood oxygenation as a result of an acute intervention like blood transfusion, vascular disruptive therapy or hyperoxic gas challenge.

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