Measurements of Spontaneous R2* Fluctuations for Acute Hypoxia Detection in Head and Neck Cancer

Rafal Panek[1], Liam Welsh[1], Maria A. Schmidt[1], Kate L. Newbold[1], Kee Wong[1], Angela M. Riddell[1], Dow-Mu Koh[1], Alex Dunlop[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: Oxygen status influences the response of tumours to both radiotherapy and chemotherapy and is particularly relevant in treatment of head and neck squamous cell carcinomas (HNSCC)[1-3]. It is known that the tumour microenvironment is highly dynamic[4] with subpopulations of cancer cells exposed to changing levels of oxygen content, associated with high radioresistance[5-6]. In this study we test the feasibility of measuring spontaneous fluctuations in the transverse relaxation rate, R_2*, to identify regions with intermittent blood and plasma flow[7], and hence oscillating oxygen delivery, in patients with advanced HNSCC.

Materials and Methods:

Imaging: Six patients with stage III and IV HNSCC were scanned twice (24-72h apart) prior to treatment. MRI was performed at 3T (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) using a 20 channel head and neck coil, with Ethics Committee approval and informed consent. For R_2*, a gradient echo sequence with 6 echo times (temporal resolution: 30s, FA = 24°, TE = 4.92\+4.92\29.52 ms, TR = 250 ms, FOV = 240 x 240 mm^2, 3 slices, voxel size: 0.9x0.9x2.5 mm^3) was used to scan continuously for 1h. Subsequently dynamic contrast enhanced (DCE) MRI was performed using a transaxial 3D FFE sequence (FA=3/18°, TE/TR=2.46/4.56 ms, FOV = 256x198 mm^2, 24 slices, 1.5x1.5x2.5 mm^3 voxel, temporal resolution: 2.9 s) during which gadolinium contrast was injected as a bolus (0.2 mg/kg, Dotarem®, Guerbet, France). *Signal processing:* R_2* maps were calculated offline for each time point using custom-written MATLAB software (MathWorks, Natick, MA), and signal intensity decay was fitted on a voxelwise basis to a mono-exponential model using a least-squares fit method. Non-rigid motion correction (sum-of-squared-differences[8]) was applied to TE=4.6 ms images and calculated deformation matrices were applied to corresponding R_2* maps. Corrected time series (R_2*(t)) were analysed for every ROI voxel to test for the presence of non-random fluctuations. The following processing steps, previously described by Baudelet *et al.*[7] in a preclinical setting, were performed: i) linear trend subtraction, ii) calculation of windowed autocovariance functions, iii) calculation of power spectral density, iv) chi-square test of power coefficients (frequency range: 0-0.005 Hz) to test if fluctuations were different from the Gaussian noise (α=0.01). Significant non-Gaussian R_2* fluctuations were spatially mapped using binary maps and total numbers of fluctuating voxels was determined. DCE pharmacokinetic modelling was performed using MRIW[9] using the extended Kety model[10].

Results: A total of 6 primary sites and 6 lymph nodes were imaged and used in the study. Median R_2* values were 53s^{-1} and 43s^{-1} for primaries and nodes, respectively. An example of a patient R_2* map is shown in ***Figure 1A***. Primary sites were significantly affected by patient motion, while nodes were fairly stationary (***Figure 2***). A rare incidental global motion (i.e. swallowing) affecting gross image signal intensity was infrequently observed and could not be compensated for. Significant R_2* fluctuations were detected in 1 primary site and 3 lymph nodes in 2/6 patients (min 3% of total ROI voxels fluctuating), with the number of fluctuating voxels varying between 3 and 18% (***Table 1***). Examples of a significant R_2*(t) fluctuation time course, an autocorrelation function and a power spectrum are shown in ***Figure 3***. The median value of K^{trans} calculated for tumour ROIs was 0.113min^{-1} for primary and 0.178min^{-1} for nodal sites. A rim-enhancing pattern was observed in 3/8 nodes. Examples of fluctuation maps with corresponding R_2* and K^{trans} maps for a nodal ROI are shown in ***Figure. 1***.

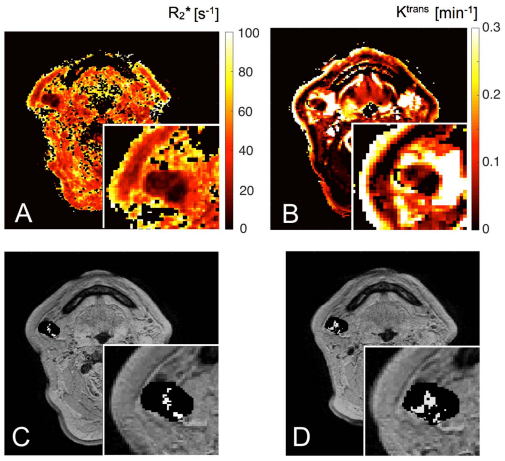

Figure 1. *MRI parametric maps for a stage IV HNSCC patient with a zoomed nodal ROI region. Transverse relaxation rate R_2* **(A)**, K^{trans} **(B)** and binary maps (**C:** MR1, **D:** MR2) showing spatial distribution of spontaneous non-Gaussian R_2* fluctuations (white voxels) for a nodal ROI (Patient No 5, N2 in Table1).*

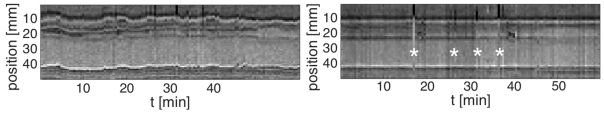

Figure 2. *A time trace of nodal projection (50mm long A/P profile positioned at the centre of the node visible in Figure 1) without (left) and with motion correction (right). Pronounced global motion (i.e. swallowing) is marker with a star.*

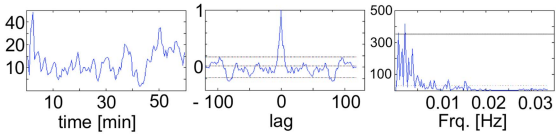

Figure 3. *Examples of a significant R_2*(t) [ms] fluctuation time course, an autocorrelation function and a power spectrum with chi-*

	MR1						MR2					
	P		N1		N2		P		N1		N2	
No	%	ROI	%	ROI	%	ROI	%	ROI	%	ROI	%	ROI
1	2	511	5	97	2	104	6	480	7	98	2	131
2	0	410	0	429	NA	NA	0	415	0	429	NA	NA
3	0	374	N	NA	NA	NA	0	361	N	NA	NA	NA
4	2	891	N	NA	NA	NA	1	829	N	NA	NA	NA
5	0	640	15	278	8	348	2	696	8	303	18	390
6	0	843	0	329	NA	NA	0	769	0	448	NA	NA

Table 1 *Nodal (N1,N2) and primary sites (P) (grey background : fluctuating voxels > 3%).*

Discussion: Primary tumours may be significantly affected by internal motion that was difficult to compensate for. Non-random fluctuations were detected in parts of lymph nodes with low K^{trans} and R_2* values, often in the vicinity, but not in the centre, of necrotic nodal cores. This suggests the presence of fluctuating blood oxygen levels, which could be caused by an insufficient or intermittent blood delivery as a result of aberrant vasculature.

References: [1]Janssen HL *et al.* Int. J. Rad. Onc. Biol. Phys. 2002;54:1537-49, [2]Brizel DM et al. Radiother Oncol 1999;53:113–117; [3]Vaupel P. Berlin: Springer 2009:273-290; [4]Lunt SJ *et al*, Clin Exp Met 2009;26:19-34; [5]Chaplin *et al*, IJROBP 1986;12:1279-1282. [6]Dewhirst *et al*, Nat. Rev. Cancer 2008;8:425-437; [7]Baudelet C. et al. Phys. Med. Biol. 2004;49:3389-411, [8]Myronenko A IEEE Trans. Med. Im. 2011;29:1882-1891, [9]D' Arcy J.A. et al. Radiographics. 2006 Apr;26(2):621–32 [10]Tofts P.S. et al J. Magn. Reson. Imaging. 1999;10 (3):223–232.

Acknowledgements: This work was supported by CRUK Programme Grants. We also acknowledge the support of CRUK and EPSRC to the Cancer Imaging Centre in association with MRC & Dept of Health and NHS funding to the NIHR Biomedicine Research Centre and the Clinical Research Facility in Imaging.