High plasma flow as measured using DCE-MRI and the 2CXM is associated with increased disease-free survival in patients with carcinoma of the cervix

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TARGET AUDIENCE Imaging scientists and clinicians interested in predicting cervical cancer survival using dynamic contrast enhanced (DCE) MRI.

PURPOSE To determine whether the predictive value of K^{trans} in cervical cancer is due to microvascular perfusion, permeability or both.

Patients with locally advanced cervical cancer are currently treated with concurrent chemoradiotherapy. Although 5-year overall survival rates are relatively high (60–70%), there is a need to identify prior to treatment patients who will have a poor outcome. DCE-MRI studies using the Tofts models[1-3] show that high values of pre-treatment K^{trans} is associated with increased tumour regression[1,3] and improved disease-free survival[2]. Since K^{trans} is related to both microvascular perfusion and permeability[4], it is unknown whether one or a combination of these may predict survival. Resolving this ambiguity is crucial for developing predictive tools and new treatments. In this prospective study we measure perfusion and permeability separately using the two-compartment exchange model[5] (2CXM) and present evidence that may help resolve this ambiguity.

METHODS Forty-two patients (median age 50.4 years; range 39.3–64.5 years) with locally-advanced carcinoma of the cervix were prospectively recruited between July 2005 and March 2010. Patients underwent MR examination prior to treatment, and were followed for a median of 3.1 years. Local research ethics committee approval was obtained and all patients gave written informed consent.

Imaging was performed on a 1.5 T Siemens Magnetom Avanto scanner (Siemens, Erlangen, Germany). High-resolution T_2-weighted images were acquired, covering the same FOV as subsequent T_1 mapping and dynamic scans. 3D T_1-weighted volumetric interpolated breath-hold examination (VIBE) sequences (TR/TE = 5.6/1.08 ms, NSA = 5) were used for T_1 mapping (flip angles 5°, 10°, and 35°) and dynamic imaging (flip angle 25°, temporal resolution 3.0s). A bolus of 0.1 mmol/kg Gd-DTPA was administered via power injector through an antecubital vein cannula. A radiologist (G.H., 7 years experience) defined the tumour regions of interest (ROIs). Arterial input functions were obtained by manually drawing an arterial ROI in the descending aorta. Arterial contrast agent concentration was calculated using the FLASH signal equation assuming pre-contrast T_1 of 1,480 ms for blood and hematocrit of 0.42. Voxelwise estimates of pre-contrast T_1 (secs), equilibrium longitudinal magnetisation (M_0, a.u.), plasma flow (F_p, ml min^{-1} ml^{-1}), permeability surface area product (PS, ml min^{-1} ml^{-1}), plasma volume (v_p, ml ml^{-1}), interstitial volume (v_e, ml ml^{-1}) and offset time (t_0, secs), were made by jointly fitting variable flip angle and dynamic signal models to the measured variable flip angle and dynamic data. Signal decay due to T_2^* effects was assumed negligible (TE << T_2^*), and water exchange between cellular, interstitial, and plasma spaces was assumed to approach the fast exchange limit. Model fitting was performed in IDL 8.2.2 (Exelis Visual Information Solutions, Boulder, Colorado, USA).

To reduce risk of overfitting, scalar variables F_p, PS, v_e, v_p, patient age (years), and tumour volume (defined as the product of ROI voxel count and voxel volume; mm^3) were each converted to two-level categorical variables by thresholding on the sample median of each variable. Similarly, FIGO stage was converted to categories low (stages I and II) and high (stages III and IV). Null hypotheses of no difference in survival function between the two levels of each variable were tested using Kaplan-Meier plots and univariate Cox regression. Multivariate random survival forest analysis[6] was used to assess the relative importance of each variable for predicting survival. A final multivariate Cox model was built using forward selection, entering variables into the model in decreasing order of relative importance. The model with lowest corrected Akaike information criterion was selected. Statistical analyses were performed using R version 2.15.

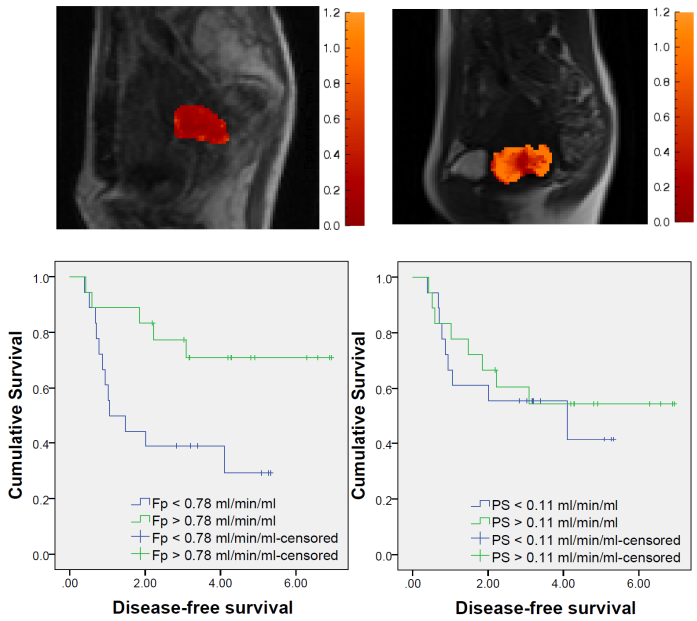

Figure 1 *Top row: Example plasma flow (F_p) maps for patients with low median F_p (0.34 ml min^{-1} ml^{-1}) and short disease-free survival (DFS) (0.34 years) (left), and high median F_p (1.0 ml min^{-1} ml^{-1}) and long DFS (3.17 years) (right). Colour bars represent the magnitude of F_p (ml min^{-1} ml^{-1}). Bottom row: Kaplan-Meier DFS curves for F_p and PS. Units for the horizontal axes are years.*

	Univariate		Multivariate		
	HR	***P*-value**	**HR**	***P*-value**	**Relative Importance**
F_p	0.29	0.022*	0.34	0.051	1.0
PS	0.79	0.63	-	-	-0.18
Volume	2.3	0.096	-	-	0.016
Age	2.8	0.054	-	-	-0.28
Stage	3.3	0.020*	2.7	0.059	0.18

Table 1 *Univariate and multivariate hazard ratios (HR) and P-values for each factor. Relative importance measurements were derived using a random survival forest analysis and estimate the predictive importance of each parameter towards disease-free survival. Large importance values indicate variables with high predictive value, whereas zero or negative importance values identify non-predictive variables.*indicates P < 0.05.*

RESULTS Kaplan-Meier disease-free survival curves are shown in Figure 1. Hazard ratios (HRs), *P*-values, and relative importance measures are shown in Table 1. F_p (HR = 0.29) and FIGO stage (HR = 3.3) were statistically significant (P < 0.05) in the univariate analyses. F_p was the most important predictive factor in the random survival forest analysis, followed by stage, but these variables were borderline significant in the final Cox regression model. Tumour volume, patient age, PS, v_p and v_e were not statistically significant in any analysis.

CONCLUSION This study, which we believe is the first to prospectively assess the prognostic value of the 2CXM in cervical cancer, suggests the predictive value of K^{trans} reported previously is attributable to perfusion (F_p) alone, rather than to permeability (PS) or a combination thereof. From the clinical parameters studied, only FIGO stage was found to be prognostic in the cohort studied. We hypothesise that high F_p reflects increased oxygen and chemotherapeutic delivery, leading to reduced perfusion-related hypoxia, increased intracellular drug concentration, and hence improved cell kill. Further work is required to test this hypothesis.

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