Supplementary material for Kallehauge JF, et al. Tracer kinetic model selection for dynamic contrast-enhanced magnetic resonance imaging of locally advanced cervical cancer. Acta Oncol 2014;53:1064–72.

Supplementary Appendix

The two parameter TM was defined as:

$$C_{\text{tissue}}(t) = C_p(t) \otimes K^{\text{trans}} e^{-\frac{K^{\text{trans}}}{v_e} t}$$

where C_{tissue} and C_p is the contrast agent concentration in the tissue and the plasma of a feeding artery, respectively. $\otimes$ is the convolution operator, K^{trans} (min^{-1}) is the volume transfer constant and v_e is the extravascular-extracellular space (EES) per unit volume of tissue ($0 \leq v_e \leq 1$).

The three parameter ETM was defined as:

$$C_{\text{tissue}}(t) = C_p(t) \otimes (K^{\text{trans}} e^{-\frac{K^{\text{trans}}}{v_e} t} + v_p \delta(t))$$

The additional parameters were the plasma volume per unit tissue v_p ($0 \leq v_p \leq 1$) and the delta function (δ).

The three parameter C-TU is defined as:

$$C_{\text{tissue}}(t) = C_p(t) \otimes \left((1-E) e^{-t \left(\frac{PS+F_p}{v_p} \right)} + E \right)$$

where E is the extraction fraction ($E = PS/(PS + F_p)$), F_p is the flow (min^{-1}) and PS is the permeability surface area product. F_p and PS were constrained to positive values.

The four parameters 2CXM was defined as:

$$C_{\text{tissue}}(t) = C_p(t) \otimes F_p \left(\frac{(T\sigma_+ - 1)\sigma_- e^{-t\sigma_-} + (1 - T\sigma_-)\sigma_+ e^{-t\sigma_+}}{\sigma_+ - \sigma_-} \right)$$

F_p , v_e , v_p and PS can be derived from the above equation through solving the following quadratic equation:

$$\sigma_{\pm} = \frac{(T - T_e) \pm \sqrt{(T + T_e)^2 - 4T_e T_c}}{2T_e T_c}$$

where $T = \frac{v_p + v_e}{F_p}$, $T_e = \frac{v_e}{PS}$ and $T_c = \frac{v_p}{F_p}$ as shown by Sourbron et al. [21].

Overfitting of the 2CXM was established when $\sigma_- = 0$, $\sigma_+ = 0$, $\sigma_- = \sigma_+$, $A = 0$ or $A = 1$ where

$$A = \frac{(T\sigma_+ - 1)\sigma_-}{\sigma_+ - \sigma_-}$$

We consider the optimal model as the model with the smallest possible number of parameters for adequate representation of the data. Therefore, for each voxel Akaike information criterion (AIC) was calculated and corrected for small sample sizes (AICc) [28]:

$$AICc_m = n \cdot \ln \left(\frac{SS}{K} \right) + 2K + \frac{2K(K+1)}{n-K-1}$$

where n is the number of data points, K is the number of free parameters and SS is the sum-squared difference between fit and the data. The first term takes the goodness of fit into account, the second adds a penalty term for every additional parameter, and the third is the correction for small sample sizes, which is advocated in cases where the ratio $n/K < 40$ [28]. Based on the AICc values, for each voxel, the optimal model was chosen by selecting the minimum AICc ($AICc_{\text{min}}$). To assess the relative likelihood of a model, we calculated the AICc differences between models, Δ_m , as:

$$\Delta_m = AICc_m - AICc_{\text{min}}$$

with $AICc_m$ being the AICc value of candidate model m . For each model out of the set of R candidate models the Akaike weight, w_m , was calculated from Δ_m :

$$W_m = \frac{\exp(-\Delta_m / 2)}{\sum_{r=1}^R \exp(-\Delta_r / 2)}$$

The values of w_m represent the weight of evidence in favour of a certain model compared with the other candidate models.

Supplementary Figure 1. Relative uncertainty for the different parameter maps for each tracer kinetic model in one transversal slice of a patient.

Supplementary Figure 2. Central transverse tumour slices of $AICc_{\min}$ maps in 10 patients comparing TM, ETM and C-TU only.

	TM	ETM	C-TU	2CXM
K^{trans}/F_p	0.39	0.39	0.40	0.41
v_e	0.39	0.39	-	0.06
v_p	-	0.00	0.37	0.33
PS	-	-	0.01	0.08
AICc	-684.1	-682.0	-683.6	-682.2
w_m	0.39	0.14	0.32	0.15

	TM	ETM	C-TU	2CXM
K^{trans}/F_p	0.96	0.72	0.99	2.08
v_e	0.38	0.35	-	0.34
v_p	-	0.05	0.37	0.00
PS	-	-	0.01	1.10
AICc	-605.8	-718.2	-607.9	-716.1
w_m	0.00	0.75	0.00	0.25

	TM	ETM	C-TU	2CXM
K^{trans}/F_p	0.51	0.48	0.59	0.60
v_e	0.31	0.30	-	0.23
v_p	-	0.01	0.26	0.25
PS	-	-	0.03	0.04
AICc	-645.8	-647.6	-690.1	-688.2
w_m	0.00	0.00	0.72	0.28

	TM	ETM	C-TU	2CXM
K^{trans}/F_p	0.68	0.54	0.80	1.01
v_e	0.36	0.33	-	0.20
v_p	-	0.03	0.29	0.18
PS	-	-	0.03	0.30
AICc	-587.5	-618.6	-632.2	-645.0
w_m	0.00	0.00	0.00	1.00

Supplementary Figure 3. Example curves that represent the particular conditions under which the TM, ETM, C-TU and the 2CXM perform best.

Supplementary Figure 4. Data density plots with correlations between model parameters from C-TU and 2CXM.