Parameters of vascular permeability in hepatocellular carcinomas: assessment with low- and high-molecular-weight agents in the rat

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Introduction

Endothelial leakiness is one of the best documented abnormalities of tumor vessels. Dynamic contrast-enhanced magnetic resonance imaging is increasingly used for non-invasive imaging of the tumor microcirculation and for monitoring the action of antiangiogenic agents. The volume transfer constant K_{trans} has been recently recommended as a primary end-point to assess the tumor microcirculation and the effect of anti-angiogenic treatments [1]. However, K_{trans} is a lumped parameter that equals the product of the blood flow F and the extraction fraction E. Because of this formulation, K_{trans} reflects the blood flow, the endothelial permeability or both, depending on the fact that the perfusion is flow- or permeability-limited. Therefore, the purpose of the study was to reassess which perfusion parameter should be measured to estimate the vascular permeability in tumors.

Material and methods

Seven rats with chemically-induced hepatocellular carcinomas were imaged on a 1.5 T scanner (Gyroscan NT Intera T15; Philips Medical Systems, Best, The Netherlands) Dynamic MRI of the dominant tumor was performed with a fast T1-weighted spoiled gradient-echo sequence with a slice thickness of 4-mm, a TR of 6.8 ms, a TE of 2 ms, a flip angle of 45°, an effective preparation time of 290 ms, a matrix of 256 x 128, and an acquisition time per image of 1.1 s. Imaging was performed before and after injection of a low-molecular-weight contrast agent of 0.56 kDa (Gd-DOTA, gadoterate) and two high-molecular-weight contrast agents of 6.47 kDa (P792, gadomelitol) and 52 kDa (P717, carboxymethyldextran Gd-DOTA). Injections were performed first with Gd-DOTA (0.05 mmol kg^{-1}) and were repeated with P792 (0.005 mmol kg^{-1}) and P717 (0.017 mmol kg^{-1}) with 60 minutes between each examination.

Models

Signal intensity versus time curves were obtained after segmentation of regions of interest in the hepatic tumour and in the abdominal aorta. To convert the signal intensity into R1 relaxation rate which is proportional to contrast media concentration, a calibration procedure was used [2]. The data were analyzed with the compartmental model of Tofts and Kermode, with the compartmental model of Patlak in which it is assumed that the tissue voxels contain a vascular component and with the distributed parameters model of St Lawrence and Lee [3-4-5].

Results

With the three models, the volume of the extravascular extracellular space V_e accessible to the high-molecular-weight agents decreased. Similarly, the extraction fraction E and the permeability-surface area product PS decreased with the high-molecular-weight agents. In contrast, the volume transfer constant K_{trans} or the blood volume V_b did not differ significantly when low- or high-molecular-weight agents were used.

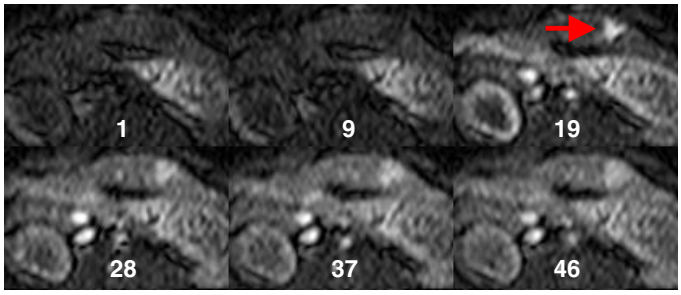
Conclusion

It is concluded that permeability differences can be better assessed by measuring the volume of extravascular extracellular space rather than the volume transfer constant. These results suggest that the volume of extravascular extracellular space accessible to high-molecular-weight agents should be used as the primary end-point to assess the permeability changes induced by antiangiogenic treatments.

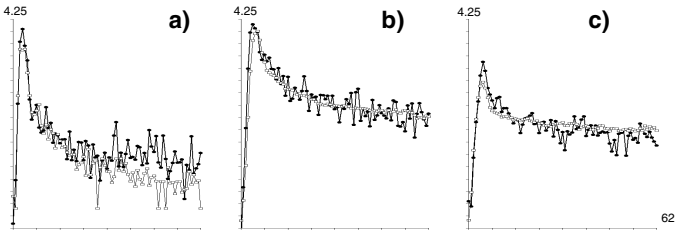
References

[1] Leach MO, et al. British J Cancer 2005; 92:1599-1610, [2] Van Beers BE, et al. Magn Reson Med 2003; 49:692-699, [3] Tofts PS, et al. J Magn Reson Imaging 1999; 10:223-232. [4] Daldrup H, et al. Pediatr Radiol 1998; 28:67-78. [5] St Lawrence KS, Lee TY. J Cereb Blood Flow Metab 1998; 18:1365-1377.

Figure: MR Sequence acquired in a rat with hepatic tumour.



Graph: R1 versus time curves measured in the hepatic tumour (black circles) and fitted by the model of St Lawrence and Lee (white square): a) Gd-DOTA b) P792, c) P717.



[3] **Tofts and Kermode** $C_t(t) = K_{trans}.C_a(t) \otimes e^{-K_{ep}t}$

[4] **Patlak** $C_t(t) = K_{trans}.C_a(t) \otimes e^{-K_{ep}t} + V_b.C_a(t)$

[5] **S[t]Lawrence and Lee** $C_t(t) = \rho.F.C_a(t) \otimes R(t)$

$$\begin{cases} R(t) = 1, & 0 \le t < T_c \\ R(t) = E.e^{-\rho\frac{EF}{V_e}(t-T_c)}, & t \ge T_c \end{cases}$$

$$PS = -F.(1-H_{ct}).\ln(1-E)$$

Model	K_{trans} ml/min/100g	E %	V_e ml/100g	V_b ml/100g	PS ml/min/100g
Gd-DOTA	506 ± 447		50 ± 26		
[3] P792	553 ± 280		31 ± 11		
P717	546 ± 255		28 ± 15		
Gd-DOTA	276 ± 188		47 ± 16	14 ± 14	
[4] P792	339 ± 170		36 ± 12	13 ± 9	
P717	437 ± 304		30 ± 14	9 ± 17	
Gd-DOTA	172 ± 154	51 ± 17	28 ± 16	36 ± 17	152 ± 199
[5] P792	123 ± 63	36 ± 7	14 ± 11	43 ± 15	56 ± 36
P717	84 ± 43	23 ± 10	10 ± 10	41 ± 9	28 ± 24
DOTA vs P792		**DOTA vs P717**		**P792 vs P717**	

Colour code for significant differences (*p<0.05 Wilcoxon signed rank test*)