Which voxels should be analysed in DCE-MRI studies of anti-vascular/angiogenic compounds?

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INTRODUCTION Dynamic contrast-enhanced MR imaging (DCE-MRI) biomarkers provide estimates of microvascular flow, permeability and vascular volume[1]. One common parameter is the median or mean value of the volume transfer co-efficient (K^{trans}) computed for the whole tumour[2]. This abstract describes a problem with the way that K^{trans} is often computed in the context of studies of anti-vascular/angiogenic compounds, provides a simple geometrical explanation, and proposes a solution.

Because there is potential for confusion between median and voxel-wise K^{trans}, in this abstract we use K^{trans} to refer to the former and κ to refer to the latter. There are two ways of computing K^{trans}: by averaging the contrast agent uptake time series for all tumour voxels and then fitting a tracer kinetic model to obtain K^{trans}; or by fitting a tracer kinetic model to each tumour voxel's contrast agent uptake time series, and then averaging the resulting κ values to obtain K^{trans}. The relative merits of these methods have been described by other investigators and are not of interest here; we are concerned with how best to perform the second, voxel-wise, calculation.

Values of κ are often highest on the periphery of tumours, where angiogenesis is believed to be most active. In this abstract we refer to these as enhancing peripheral (EP) voxels. The tumour core typically has lower values of κ, associated with low angiogenic activity. When K^{trans} is computed from all tumour voxels, the contribution of the voxels most indicative of tumour angiogenesis—the EP voxels—can be attenuated by core voxels. This is apparent when recalling the definition of the sample median (the central value in the sorted sample) and by considering that the volume of the tumour core (approximately spherical) increases at a faster rate as a function of tumour diameter than does the volume of the EP region near the tumour surface (approximately a spherical shell). The degree of attenuation is likely to increase with the number of tumour voxels. One alternative is to compute K^{trans} using just the EP voxels. This abstract compares the statistical power of the two methods.

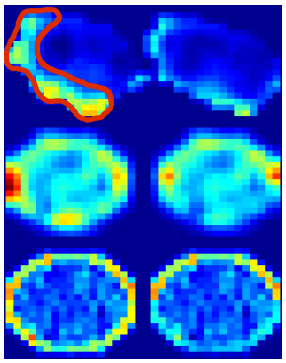

Figure 1 *Pre- and post-treatment maps of κ (left and right), showing real (top, with EP region highlighted), and small and large (middle and bottom) synthetic κ maps.*

METHOD In-house software was developed to simulate 3-D κ maps comprising three components: non-tumour, EP and core voxels. Tumours were generated to be spherical in shape (subject to the discrete nature of voxel-based images) with unit radius. Voxels within 0.8 units of the centre were considered to be core voxels and those further away (and within the sphere) were considered to be EP voxels. Core and EP voxel values were sampled from two normal distributions; each distribution was estimated from manually selected voxels from three real κ maps. Spatial correlation between neighbouring voxel values was introduced by convolution with a 3-D Gaussian kernel. We simulated heterogeneous post-treatment drug action by copying the pre-treatment tumour and reducing the values in half of the EP voxels by a factor sampled uniformly in the range 0.3 to 1 (no change). Quantitative and qualitative assessments of the realism of our model were performed: Firstly, we used *k*-means clustering[3] to estimate the number of EP voxels in a set of 21 κ maps generated from real data. We then generated volume-matched synthetic κ maps and compared the number of EP voxels in the real and synthetic data sets as functions of whole tumour volume. There was good agreement between the two, with the exception of two large real tumours, which had far fewer EP voxels (we return to this point later). Secondly, we visually inspected the synthetic κ maps to confirm that they were sufficiently realistic for this work.

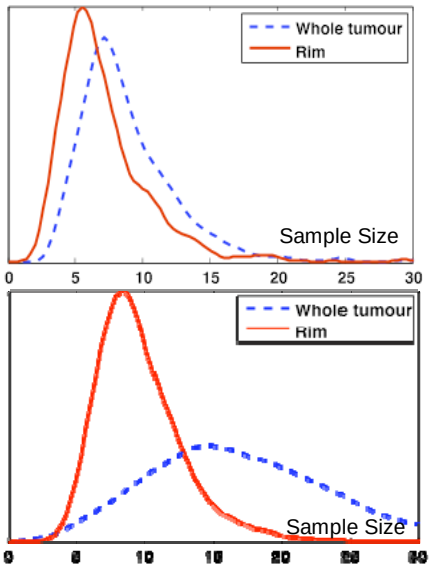

Figure 2 *Bootstrapped kernel density estimates of the distributions of required sample sizes. Top: small simulated parameter maps. Bottom: large simulated parameter maps.*

To demonstrate the problem described above, we simulated a typical phase I trial by generating 10 synthetic pre- and post-treatment κ maps. The tumours had 2000 voxels, simulating tumours of approx. 4 cm diameter (using 3×3×3 mm^3 voxels)—see Fig. 1. For each image, K^{trans} was computed using all tumour voxels, and using EP voxels only. Pair-wise differences in pre- and post-treatment K^{trans} were then computed for each synthetic tumour and each method. In a typical drug trial, one might then perform a *t* test to investigate drug action. However, we are interested in the statistical power of such tests. To investigate this, for each method we used bootstrapping[3] to estimate the distribution of the sample size that would be required to achieve a statistical power of 0.8. For each method of computing the median, 1000 bootstrap samples were taken and post hoc sample size calculations were performed on each bootstrap sample. The experiment was repeated using tumours with 8000 voxels, simulating tumours of approx. 7 cm diameter—see Fig. 1.

RESULTS Figure 2 shows bootstrapped kernel density estimates of the distributions of the required sample sizes for small and large κ maps. For small κ maps, there is little difference between the estimated distributions of required sample size for the two methods. When using the whole-tumour method in large tumours, however, K^{trans} is attenuated by the 'uninteresting' core voxel values, requiring a substantially larger sample size. For given effect and sample sizes, computing K^{trans} using all tumour voxels is more likely to lead to type II errors. This is a substantial problem if pharmaceutical go/no-go decisions depend—if only in part—on the results of DCE-MRI studies. The large real tumours had far fewer EP voxels than our synthetic tumours. In such tumours, the core voxels are likely to completely dominate estimates of median K^{trans}, resulting in underpowered tests.

CONCLUSIONS Our results provide additional evidence that investigators should use appropriate criteria to determine which voxels to include in analyses[4,5]. Computing K^{trans} from EP voxels in DCE-MRI studies of anti-vascular/angiogenic compounds may provide complementary information to the whole-tumour method, and may reduce type II errors, particularly if large tumours are included.

REFERENCES 1. *O'Connor et al.* Brit. J. Cancer 96(2):189–195, 2007. **2.** *Tofts.* J. Mag. Reson. Imag. 7:91–101, 1997. **3.** *Hastie et al.* Springer. ISBN 0-387-95284-5, 2001. **4.** *Gribbestat et al.* J. Mag. Reson. Imag. 4:477–480, 1994. **5.** *Thukral et al.* Radiology 244(3):727–735, 2007. **ACKNOWLEDGEMENTS** Financial support was provided by GlaxoSmithKline and Cancer Research UK.