Non-enhancing pixels: a specific additional DCE-MRI kinetic parameter for assessing antivascular effects of anti-angiogenic and vascular disruptive agents

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Introduction: When assessing tumour response to therapy using DCE-MRI, it is usual practice to exclude non-enhancing (NE) pixels because they are non-vascularised tissues and anatomically represent cystic degeneration, necrosis, regions of dense calcification or ossification. This method of analysis has been used extensively to assess the antiangiogenic effects of a variety of therapies including chemotherapy, hormones and vascular disruptive agents (VDAs) and antiangiogenic agents[1]. However, it is our experience that the VDA Combretastatin (CA4P) and the antiangiogenic agent Bevacizumab cause a profound vascular shutdown that results in increased numbers of NE pixels. In order to evaluate systematically whether NE pixels should be included /excluded when evaluating the antivascular effect of therapies, we compared DCE-MRI data from 2 patient groups: (1) primary breast cancer receiving neoadjuvant chemotherapy (NAC)[2], (2) a phase I study cohort where CA4P was given with Bevacizumab[3].

Methods: 20 patients from the breast cohort were imaged before and after 2 cycles of NAC using a multislice DCE-MRI protocol. 11 patients had two baseline measurements for reproducibility calculations. The CA4P-Bevacizumab study evaluated 18 patients with advanced solid malignancies. DCE-MRI measurements were made before (x2 for assessing reproducibility), after the first CA4P (d1), before the second CA4P (d6), after the second CA4P (d7) and finally 6 days after the second CA4P but with Bevacizumab (d13). Analyses of both datasets were identical. Tumour ROIs were drawn on all slices. Data were analysed using the Tofts model utilizing a modified Fritz-Hansen arterial input function with MRIW software[4-6]. Outputted pixels were associated with model fitting codes, permitting the identification of NE pixels. Median values for transfer constant (K^{trans}) were calculated twice per dataset, once with all NE pixels removed and then with the NE pixels retained.

For both study cohorts, responders were those with K^{trans} reductions greater than the negative individual reproducibility value (-r %). Non-responders had either no change or an increase in K^{trans} values. The effects of removing/retaining NE pixels on DCE-MRI test performance in the breast cancer cohort were evaluated by assessing the number of patients correctly categorised by final pathological (path) response, with additional ROC analysis used to evaluate group test performance. In the CA4P-Bevacizumab cohort, there is no independent standard for benefit, therefore only cross comparisons were made of individual and group changes at each treatment time point.

Results: K^{trans} reproducibility (r) for the breast cohort was ±45% without NE pixels and ±47% with NE pixels. Using these cut-off values, test performance was similar for the 2 methods of analysis (table). Only one additional responder was correctly classified with NE pixels retained (a tumour that underwent cystic degeneration). K^{trans} reproducibility (r) for the CA4P-Bevacizumab cohort was ±31.2% without NE pixels and ±31.4% with NE. In the CA4P-Bevacizumab cohort, greater numbers of individuals and substantially greater group reductions in K^{trans} are noted when NE pixels are retained.

	Data without NE pixels		**Data with NE pixels retained**	
Breast (n=20)	Individuals correctly predicted	Group change (%)	Individuals correctly predicted	Group change (%)
• Path non-responders (n=7)	7	+2.93	7	+3.60
• Path responders (n=13)	6	-41.50*	7	-46.10*
ROC (Area under curve)	0.85 (95% CI: 0.67-1.0)		0.87 (95% CI: 0.7-1.0)	
CA4P+Avastin (n=18)	No of patients with K^{trans} reduction greater than -r%	Group change (%)	No of patients with K^{trans} reduction greater than -r%	Group change (%)
• d1 - CA4P – 1st dose (n=18)	2	+1.8	6	-13.8*
• d6 - (n=16)	1	+4.7	1	+1.8
• d7 - CA4P 2nd dose (n=16)	4	-9.4*	6	-20.8*
• d13 - CA4P 2nd dose + Bevacizumab (n=17)	8	-27.7*	12	-39.7*

*Statistically significant group change ($p<0.05$)

Discussion: For the breast cohort (where antivascular effects are secondary to cytokine withdrawal after primary cytotoxic tumour cell kill), there were no significant differences between the 2 analysis methods, implying that the development of cystic degeneration/necrosis/avascularity is not a dominant effect of NAC. However, for the CA4P-Bevacizumab cohort (where the primary target of therapy is the tumour vasculature) it is only when NE pixels are retained that there is a convincing demonstration of the failure of tumour vasculature to recover when CA4P is given with Bevacizumab (thus corroborating preclinical data[7]). When the results of both studies are taken together, it can be concluded that increasing numbers of NE pixels is a specific measure of effectiveness of drugs that target directly the tumour microvasculature and NE pixels should be retained during DCE-MRI analyses.

References:

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