Parametric Response Mapping: a voxel-based analysis of quantitative diffusion MRI changes for individualized assessment of primary breast cancer response to therapy

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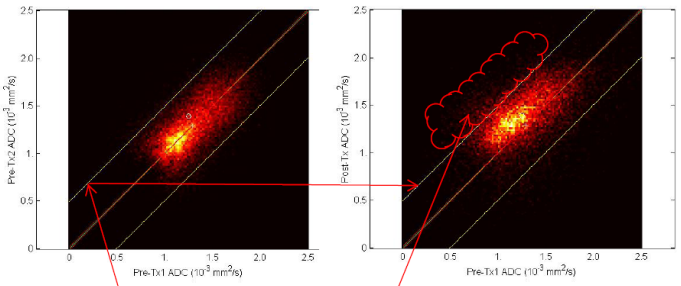
This is a double-blinded study where the blinded estimates of response to therapy have been obtained from registered, voxel-by-voxel, quantitative apparent diffusion coefficient (ADC) scans and was used to predict individual patient response to the first cycle of neoadjuvant chemotherapy. Likewise in a blinded fashion the breast oncologist independently estimated the clinical response of the patient at the end of the first adriamyacin/cyclophosphamide (AC) cycle before initiation of the second cycle of therapy involving Taxotere. The results for each patient are shown on the following Figure. Although the number of patients is very small, the results are clearly encouraging.

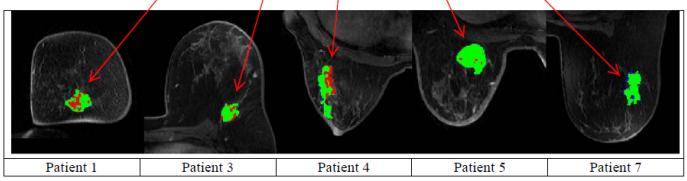
In this protocol patients with breast CA that have elected neoadjuvant chemotherapy prior to surgery receive 2 baseline exams, typically given within 15 minutes of each other where the patient is removed from the scanner and then repositioned for the second scan; for obvious reasons these scans are referred to as "coffee-break exams", and are used to observe the null change distribution since no macroscopic changes have occurred to the tumor in this interval. The initiation of the first cycle of chemotherapy (AC) is typically within one day of the coffee-break exam. Another MRI exam is obtained 8-11 days after initiation of the first cycle of therapy (this is our definition of "early").

The computed ADC scans from the coffee-break exams are registered using our warping algorithm [1] and then a voxel-by-voxel histogram (distribution) of the two ADC scans is constructed to measure the null distribution in order to account for all sources of noise in the process. An Nth percentile threshold is estimated, where here we demonstrate the successful use of both a 97.5th percentile as well as a 95th percentile. Next the same process is repeated for one of the coffee-break exams and the post-chemotherapy initiation scan pair. This distribution represents the treatment effect distribution. The Figure's top right distribution clearly reveals that ADC values have increased in several ways: first the mean has moved upwards, and secondly there are many more counts above the 97.5th percentile line derived from the null distribution.



Null distribution from coffee-break exams ← **Patient 4** → PostTx vs. PreTx, Treatment Effect distribution

PostTx re PreTx		Research Case #				
		Patient 1	Patient 3	Patient 4	Patient 5	Patient 7
Count % increase above threshold	97.5%tile null thresh	1.02	1.14	1.04	-0.23	-1.62
	95%tile null thresh	1.61	1.75	1.4	-0.33	-2.4
Clinical Outcome		cPR	cPR	cPR	cSD	cSD



For each patient the first two rows of the Table show the incremental percent increase in counts above the null's 97.5th and 95th percentile for their Treatment Effect distribution. At this stage increases above both the 97.5th and 95th percentile correlate perfectly with clinically assessed partial response (cPR), while decreases correlate perfectly with clinically assessed stable disease (cSD) for the first cycle of chemotherapy for these first 5 patients. The bottom row of images shows a single slice of each the anatomical reference breast exams overlaid with red-green-blue mask of the tumor. Here red indicates the presence of voxels whose ADC changes (postTx minus preTx) are greater than the 97.5th percentile of the null distribution (i.e. regions of cell kill and limited noise) green indicates voxels whose changes are within the 2.5th – 97.5th percentiles (regions of no significant change) and blue indicates changes that are less than the 2.5th percentile of the null (regions of continued tumor growth and limited noise). Recall that we are very early in this process of tumor change, i.e. only 8-11 days after the initiation of the first (AC) cycle of chemotherapy. Presumably these changes are initially proportional to the time interval between the pre-therapeutic and post-therapeutic scans.

Moreover for these five patients the 97.5th percentile corresponds to ADC changes whose mean is not significantly different than ±0.5 10^{-3} mm^2/s, the same threshold used for the successful differentiation of PD and SD in brain cancer patients assessed with the same general methodology in our previous publications [2-4] . In summary data obtained from the first 5 patients strongly suggests that our imaging and image processing approaches will yield a new imaging biomarker to allow accurate, early prediction of treatment response in breast cancer patients.