Tumor Volume Reduction and Perfusion Changes in Breast Cancer evaluated with Dynamic Contrast Enhanced MRI.

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Purpose:

Angiogenesis and perfusion play a vital role in tumor growth[1]. Hence, anti-angiogenic therapy is a growing area of cancer therapy research. DCE-MRI has been employed as a means by which the effect of these treatments can be monitored non-invasively over time in vivo. Tumors however are morphologically dynamic, changing in size, shape, and spatial distribution over time. These changes may be due to growth, spontaneous necrosis, or the effect of chemotherapy, but they make the comparison of perfusion over long intervals of time difficult. The difficulty lies in which portions of the imaged tissue to include at each point in time. In the present study we obtained DCE-MRI data from breast cancer patients in a trial of anti-angiogenic therapy. We develop an analysis based on comparing only those tissues where observable contrast enhancement occurred during the DCE-MRI acquisition. This permitted the simultaneous evaluation of tumor volume and perfusion in response to therapy. We evaluated the relationship between changes in tumor volume and a semi-quantitative measure of perfusion. The objectives were to: 1) articulate and apply an approach to the problem of changing tumor morphology in longitudinal DCE-MRI studies, 2) apply this approach to a study of the different effects of two chemotheraputic strategies, and to 3) determine whether our tissue selection criteria resulted in perfusion measurements whose changes were correlated with positive theraputic effect.

Material and Methods:

All subjects received two 8-week cycles consisting of docetaxel 35 mg/m2 IV infusion weekly for six weeks with a two-week break. Subjects were divided into two groups, (Group 1: N=9, Age: 45.5±5.6 years, Group 2: N=8, Age: 43.5±8.8 years). Group 2 also received concurrent therapy with bevacizumab 10 mg/kg IV infusion every 2 weeks without break. DCE-MRI was repeated three times for each subject: once just prior to the start of each treatment cycle, and once at the end of cycle 2. Subjects were scanned using a 1.5T Magnetom Symphony (Siemens Medical Systems, Erlangen, Germany) outfitted with a bilateral breast-imaging coil. The diseased areas were identified using T1 and T2 weighted sequences from Siemens' standard breast examination protocol. All subsequent imaging employed T1-weighted 2d FLASH acquisitions (TR/TE: 43/4 msec, slices=5, thickness=8mm, gap=2mm, matrix=128x128). FOV varied between 300mm-350mm between subjects but was kept constant within each subject. This sequence was used to estimate pre-contrast T1-maps using a variable flip angle approach[2] with paired acquisitions at flip angles of 10° and 50°. Five-point averaging for increased SNR was used to improve the accuracy of the estimates. The dynamic MR acquisitions used single averaging for increased temporal resolution and were comprised of a series of 180 acquisitions repeated at 4.8 sec intervals. After three acquisitions, an intravenous dose of Gadolinium-DTPA (Magnevist: 0.1mg/kg body weight) was administered over 30sec using a power injector (Spectris, Medrad). Dose administration was limited to nearest ml. Thus dose was kept constant across sessions unless the proportional change in the subjects weight justified a proportional change of at least 1ml without rounding. The dynamic contrast enhanced images were evaluated as follows. The three pre-injection images were averaged, and then subtracted from the entire image set on a voxel-by-voxel basis, resulting in a time sequence of images showing the raw image enhancement. At approximately 70 sec post injection, the fast enhancing voxels of the tumor tissue were clearly visible. A user-selected threshold was applied that maximally separated fast-enhancing tumor voxels from background. The desired voxels were further segregated using a computer algorithm that permitted the user to drawn a closed boundary outside of all voxels that were excluded regardless of the results of the thresholding step. This approach allowed straightforward ROI delineation in difficult cases of diffuse infiltrating tumors, or those with spatially complicated distributions of necrotic and viable tissue. Tumor volume was defined as the number of voxels×individual voxel volume. For the selected tissue, gadolinium concentration was calculated based on the relative voxel values with respect to pre-contrast baseline, the estimated pre-contrast T1, in-house measures of the contrast agent relaxivity α_1=3.58 $sec^{-1} \bullet mmol^{-1}$, using the FLASH equation [3]. Mean concentration vs. time curves were plotted for each study for each patient. From these, the area under the curve for the initial 90 secs after the arrival of the contrast agent (IAUC) was calculated and taken as an analog of tumor perfusion [4]. Changes in tumor volume and perfusion with respect to pretreatment baseline were assessed using repeated measures ANOVA with simple planned comparisons (baseline as reference) with treatment subgroup as a fixed factor. Percent changes in tumor volume at the end of each cycle were correlated with baseline IAUC, and percent change in IAUC after cycles 1 and 2 (Pearson product moment correlation coefficients). Null hypothesis rejection criteria was defined as $p<0.05$.

Results:

Mean tumor volumes, and IAUC at each stage within each treatment group are given in Table 1. Across subjects, tumor volume was statistically significant reduced with respect to baseline after cycle 1 (F=8.9, p=0.01). Volume was also reduced after cycle 2 but this was not statistically significant. There was a statistically significantly greater reduction in volume after cycle 1 in the group receiving both docetaxel & bevacizumab compared to docetaxel alone (F=5.38, p=0.036). IAUC was also reduced across all subjects after each cycle, but the changes were not statistically significant at $p<.0.05$. The percent change in IAUC and the percent change in tumor volume were modestly correlated (r=0.48, p=0.029, 1-tailed). No other statistically significant correlations were observed.

Table 1

Treatment Group	Tumor Variable	Baseline	Post Cycle 1	Post Cycle 2
Docetaxel	**Volume**	**27.6 ± 6**	**25.0 ± 22**	**17.1 ± 25**
	IAUC	**13.4 ± 3.5**	**10.9 ± 6.9**	**9.3 ± 7.8**
Docetaxel & Bevacizumab	**Volume**	**56.9 ± 42**	**14.6 ± 11.4**	**17.6 ± 35.4**
	IAUC	**15.3 ± 10.9**	**11.0 ± 9.8**	**10.6 ± 6.5**

Discussion:

We assumed that active cancer would always exhibit a much larger signal increase from Gd-DTPA due to the presence of dense, proliferating neovasculature with permeabilities much greater larger than established capillary networks. Under these assumptions we conclude that our tissue segmentation approach provided a more valid comparison of tumor size and perfusion over time. Applying these measures we were able to differentiate between treatment strategies on volume, but not perfusion. This opposed our a priori belief that perfusion would track changes in tumor size. In our study cohort, large changes in tumor size and perfusion were observed, and adjunct antiangiogenic therapy produced the larger changes. Thus, the finding that these changes were only modestly correlated with each other was unexpected. It suggests observed reductions in average tumor perfusion over time may be the result of tumor size reductions that induce the inclusion of tissue that is not diseased.

References:

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