MR quantification of abnormal stromal enhancement in the periphery of invasive breast tumors

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Introduction: Local breast cancer recurrences remain a significant problem following lumpectomy and radiation despite modern imaging techniques and pathologic assessment. Cancer cells have conventionally been viewed as the primary culprit in malignancy, and therefore also represent the primary target for therapies. However, histologically normal breast tissue adjacent to invasive breast cancers has also been shown to harbor genetic abnormalities[1], reflective of a permissive microenvironment that supports malignant growth[2].

MRI is a recognized modality for detection and characterization of invasive breast carcinomas[3, 4]. In dynamic contrast-enhanced MRIs, properties of tissue microvasculature and overall vascularity can be quantified using kinetics of contrast enhancement or signal enhancement ratio (SER, defined as ratio of early enhancement to late enhancement[5]). It has been shown that areas with high SER values were significantly correlated with high tumor vascularity[6], and that mean SER in nearby non-cancerous breast stroma was significantly associated with disease free survival[7].

Currently, no universally accepted methods exist to determine the optimal extent of histologically normal breast tissue to excise surgically or treat with radiation therapy. Although, a relationship between normal tissue enhancement and recurrence has been previously revealed[7], spatial resolution of enhancement with respect to proximity of the tumor within the non-cancerous stroma has not been shown. Therefore, in this project, we hypothesized that abnormalities in vasculature exist within the histologically normal appearing periphery of breast tumors that can be detected by measuring changes in enhancement intensity.

Materials and Methods: We performed a retrospective secondary analysis of 27 pre-treatment breast cancer patients presenting with invasive tumors of 3cm or less. The 27 patients were women between 14 and 85 years (average 54). Dynamic contrast-enhanced MRI was obtained at 3 time-points: pre-contrast administration, 2.5 min., and 7.5 min. post-contrast. All exams were performed on a 1.5T Signa system (General Electric Medical Systems, Milwaukee, WI, USA) using a bilateral phased array breast coil. Gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) was injected at a dose of 0.1mmol/kg of body weight, and a high resolution fat suppressed T1-weighted 3D fast gradient echo sequence was used. The MR exam parameters were 20 cm field of view, 2 mm slice thickness and 256x192 acquisition matrix. The resulting in-plane resolution was approximately 0.78x0.78mm and 60 slices were acquired in the sagittal orientation.

An automated, user-independent program was used to segment breast tissue from all other structures (adipose tissue, bones, etc.)[8]. Invasive tumor regions were identified using an SER threshold of 70%[7], and a tumor proximity map was generated giving the 3-dimensional center-to-center distance of each normal breast tissue voxel to the nearest tumor voxel[9]. In the normal stroma surrounding the tumor, a percent enhancement (PE) map was calculated using the signal intensity change between the pre-contrast and first post-contrast images, where a positive PE indicates an increase in signal intensity. The proximity and PE maps were then combined to measure breast tissue enhancement at various distances around the selected tumor.

Results: PE levels in normal breast tissue situated within 2cm of the tumor region were significantly higher than at all more distant regions. For all 27 patients, the least squares mean PE from the random effects model of all voxels at 1cm increments for 6cm is shown in Figure 1. For instance, the first dataset at (0.5,17.8) indicates that all normal breast tissue voxels that were >0cm and ≤1cm away from an invasive tumor voxel had a least squares mean PE of 17.8, etc. The numerical values for the six data points in Figure 1 are shown in Table 1, along with their corresponding p-values. Pairwise comparisons with Turkey's adjusted p-values indicated that the mean PE at 0-1cm is significantly higher than all other distant levels (p=<0.0001). Pairwise comparisons also indicated that the mean PE at 1-2cm is significantly higher than 5-6cm (p=0.006). No other pairwise comparisons were statistically significant.

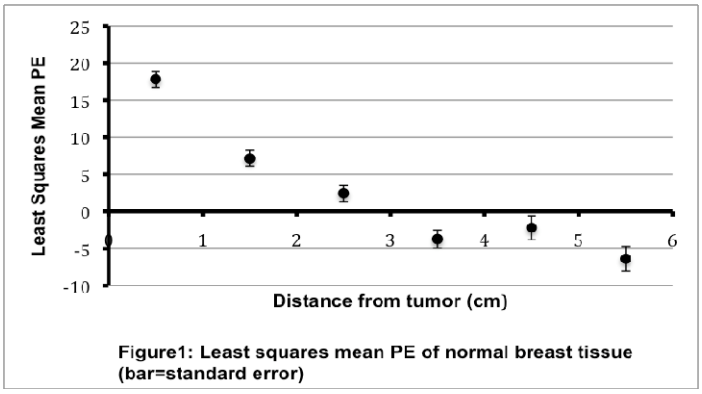

Figure1: Least squares mean PE of normal breast tissue (bar=standard error)

Distance from nearest tumor	LS Mean PE	p-value
0-1cm	17.8203	<0.0001
1-2cm	7.1458	0.0013
2-3cm	2.4433	0.2742
3-4cm	-3.7177	0.1254
4-5cm	-2.1876	0.5008
5-6cm	-6.3805	0.0626

Table 1

Conclusion: Here, we show that the normal-appearing breast stroma within 0 to 2cm of a primary tumor exhibits higher enhancement levels than stroma located far from the tumor. Although partial voluming effects might account for an artificial increase in enhancement in voxels less than 2mm from the tumor, it does not account for the increase past 1cm. These results suggest that tissue surrounding the tumor region may contain vasculature abnormalities or tumor-related angiogenesis. These findings could potentially help refine surgery and radiation therapy for breast cancer.

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