Spatial Distribution of Hot Spots in Benign and Malignant Breast Tumors

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INTRODUCTION

Breast cancer was one of the most commonly diagnosed types of cancer among women in 2010 and its prevalence is expected to increase in 2011 (Jemal 2010). Breast cancer is a cancer that originates in the tissues of the breast manifested by the presence of a breast tumor, where the tumor is generally categorized as either benign or malignant. Since the effects and treatments differ for benign and malignant tumors, accuracy of the diagnostic method used to distinguish between the two is important. Dynamic contrast enhanced-MRI (DCE-MRI) is one of the widely used modalities to diagnose breast tumors. The radiologist visually examines the morphology in an enhanced region and, based on their knowledge and experience, diagnoses the patient (Liu 2011). Current research, however, has been directed to explore and develop quantitative methods to provide an objective means of diagnosis.

A recent study by Fang Liu (2011) evaluated the diagnostic performance of the time-to-peak ($T_{peak}$) parameter in DCE-MRI. The specific measure was termed as the $T_{peak}$ hot spot volume, referring to the volume of tumor tissue where the $T_{peak}$ values were less than a set threshold value (Liu 2011). The diagnostic performance of the $T_{peak}$ hot spot volume was found to be optimal at a threshold of approximately 3 minutes and from observing the total hot spot volume in the tumor, it was easy to differentiate between fibroadenoma, the most common type of benign breast tumor, and malignant tumors (Liu 2011). On the other hand, the $T_{peak}$ hot spot volume did not perform as effectively in discriminating between non-fibroadenoma and malignant tumors (Liu 2011).

The intent of this study was to further evaluate the diagnostic performance of the $T_{peak}$ hot spot volume by examining and comparing the spatial distribution of hot spots between non-fibroadenoma and malignant tumors. It was hypothesized that, in a defined outer perimeter, malignant tumors would have a greater hot spot volume than non-fibroadenoma tumors.
THEORY

Malignant vs. Benign

Breast tumors are broadly classified as either malignant or benign. Malignant and benign tumors differ in numerous properties but in general, malignant tumors refer to tumors that can metastasize (invade and form secondary tumors in other parts of the body) whereas benign tumors cannot. The most common type of breast benign tumor is known as fibroadenoma and usually appears as a discrete, rounded, firm nodule in the breast (Weinstein 1999). Studies have found that fibroadenomas exhibit a lower vessel density than malignant tumors (Weinstein 1999). This corresponds to the concept that malignant tumors undergo angiogenesis (growth of new vessels) and accordingly, tend to be ‘leaky’ (poor vessel formation) (Jackson 2010). Figure 1 contrasts malignant and benign tumors with respect to their structure.

![Figure 1. 3D representations of a malignant tumor (left) and benign tumor (right) (Liu 2011).](image)

Hot Spots

Hot spots refer to areas within the tumor where the contrast agent (utilized in DCE-MRI) is taken up at a set threshold (Liu 2011). The threshold is based on the time duration from the contrast agent injection to the maximal MRI signal for a given voxel (i.e. $T_{peak}$), where the optimal threshold was found to be around 3 minutes (Liu 2011). The outer hot spot volume represents the amount of hot spot in a given perimeter of the tumor. The perimeter was defined as a function of
the tumor size and expressed as an ‘outer ring’ 25% the size of the tumor volume. Since hot spot volume is a function of tumor size, the outer hot spot volume was expressed as a fraction of the total tumor volume. This was done to normalize and account for the various tumor sizes.

**Image and Data Analysis**

MATLAB is a high-level computing program used for endless applications, such as data visualization, data analysis, and numeric computation. Image data was acquired as 3D matrices for the tumors and hot spots. A mask matrix is a binary matrix characterized by having values of only 0s and 1s, where any value greater than 0 becomes a 1. By multiplying a tumor mask matrix with a hot spot mask matrix, the number of overlapping 1s can be calculated (i.e. amount of hot spot). The erode function in MATLAB shrinks the perimeter of the binary matrix by a set number of voxels.

Linear interpolation is performed to extract new data points from a given set of known points. When the probability distribution is graphed, skewness is a measure of the asymmetry of a set of data points. Positive skew indicates a distribution with relatively low values while negative skew indicates a distribution with relatively few high values. A Mann-Whitney test is used to verify if two independent samples of observations have equally large values. It is a non-parametric test that uses a ranking system, unconcerned with the underlying distributions of the groups, which tests the probability of a value from one sample being larger than a value from the other. If p<0.05, then the results are considered significantly different.

**METHODS**

Image data for 36 patients (16 non-fibroadenoma and 20 malignant) was randomly selected from the study done by Fang (2011). The data was analyzed in MATLAB to compute the outer hot
spot volume expressed as a fraction of the total tumor volume. The hot spot threshold was set to 3 minutes and the outer perimeter was arbitrarily defined as 25% of the total tumor volume. The following figures display a slice from a malignant tumor (in the transverse plane) outlining the basic process of the algorithm used:

Figure 2. Tumor mask matrix before (left) and after (right) one erosion

Figure 3. Hot spot mask matrix (left) (threshold of 3 minutes) and remaining hot spot matrix (right) in eroded tumor mask matrix

This process was repeated until the tumors were fully eroded. After the hot spot data was obtained, linear interpolation was performed to determine the outer hot spot volume in each
tumor. A Mann-Whitney test was run to compare the fractional outer hot spot volumes between the non-fibroadenoma and malignant tumors. A Mann-Whitney test was also run to compare the outer hot spot volume with the total tumor volume in both non-fibroadenoma and malignant tumors. The specific algorithm written can be found in the appendix and a more detailed description of the acquisition procedure can be found in Fang’s “The Time-to-peak Hot Spot Volume as an Indicator of Lesion Malignancy in Breast Dynamic Contrast Enhanced-MRI” (2011).

RESULTS

![Box plot](image.png)

**Figure 4.** Distribution and medians of fractional outer hot spot volumes in non-Fibroadenoma (B) and malignant (M) tumors.

A comparison between the fractional outer hot spot volumes of non-fibroadenoma (n=16) and malignant tumors (n=20) is shown in Figure 4 as a box plot. The Mann-Whitney test resulted in
a p-value of 0.3477 (p>0.05) indicating no significant difference in the outer hot spot volumes between the two tumor groups (Figure 4). Although the range of the non-fibroadenoma group was much wider than the malignant group (reaching greater than 0.12), the fractional outer hot spot volumes for both groups seemed to be concentrated between the values of 0.02 and 0.04. It is important to note, however, the difference in skew of the two groups. The non-fibroadenoma tumors, along with its outlier (represented by a red cross), are positively skewed, whereas the malignant tumors approximately have zero skew (symmetric).

The results from the Mann-Whitney tests comparing the outer hot spot volume to the total hot spot volume in non-fibroadenoma and malignant tumors are recorded in Table 1. In both cases, the p-value was calculated to be less than 0.05 implying a significant difference between the outer hot spot volume and total hot spot volume for both groups.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fibroadenoma</td>
<td>0.0035</td>
</tr>
<tr>
<td>Malignant</td>
<td>0.000011045</td>
</tr>
</tbody>
</table>

Table 1. Mann-Whitney analysis for outer hot spot volume to total hot spot volume in non-Fibroadenoma and malignant tumors.

**DISCUSSION**

The intent of this study was to analyze the spatial distribution of hot spots in non-fibroadenoma and malignant tumors. Based on the concept that malignant tumors tend to be leaky, the hot spot volume near the surface of malignant tumors was expected to be larger than those of
non-fibroadenoma tumors. Yet, the results show that there was no significant difference in the outer hot spot volumes between non-fibroadenoma and malignant tumors. An important implication of this observation proposes that non-fibroadenoma tumors may behave similarly to malignant tumors in regards to their vasculature. The distribution and morphology of blood vessels in malignant tumors are both structurally and functionally abnormal, including certain features such as a lack of normal vessel tapering pattern, vessel tortuosity, and excessive branching (Raza 1997). These features would be expected to be found in some of the non-fibroadenoma tumors as well. The results also showed a significant difference between the outer hot spot volume and total hot spot volume in both non-fibroadenoma and malignant tumors, entailing the likelihood that most of the hot spot volume is located near the center of the tumor. This observation challenges the notion that there is a direct relationship between hot spots and leaky vessels. Alternatively, the distribution of hot spots concentrated closer to the center of the tumor suggests that the contrast agent, or blood flow, is taken up the most rapidly near the center.

There were several limitations that occurred in this study. The wide range of outer hot spot volumes in the non-fibroadenoma group occurred due to the fact that the group was composed of many other subtypes of benign tumors. These subtypes were most likely characterized by differing properties in their structure and function, resulting in an inaccurate representation of the group as a whole. While some non-fibroadenoma tumors may have behaved like malignant tumors, others may have greatly differed. Moreover, a limitation of the Mann-Whitney test was that it was meant to be applied for exactly two groups. In future studies, the Mann-Whitney test should be run between a non-fibroadenoma subgroup and malignant tumors. Further statistical analysis can be done by creating a ROC curve to evaluate the diagnostic performance of using outer hot spot volume. The effects on the outer hot spot volume with varying hot spot threshold and tumor
perimeter can also be observed. Another noteworthy area of research is to examine and understand why some benign tumors exhibit similar vasculature to malignant tumors.

**CONCLUSION**

A comparison of the spatial distribution of hot spot volume between non-fibroadenoma and malignant tumors demonstrated no significant difference. This suggests the possibility of similar vasculature between the two groups. Further evaluation of the outer hot spot volume to the total hot spot volume seemed to indicate that, for both non-fibroadenoma and malignant tumors, most of the hot spot volume was distributed closer to the center of the tumor. This observation provides a better understanding of breast tumor vasculature and future studies can be done to examine the relationship between hot spots and vessel structure.
REFERENCES


Algorithm developed to calculate outer hot spot volume.

```matlab
mask = Tumor_Mask_Matrix;
TTP(TTP>3)=0;
TTP = min(max(TTP, 0), 1);
tumor_mask=[];
hs=[];
for i = 0:1:15
    SE = strel('disk', i);
    x = imerode(mask,SE);
    hs(j) = nnz(x.*TTP);
    tumor_mask(j) = nnz(x);
    inner_percent(j) = tumor_mask(j)/nnz(mask);
    j = j+1;
end;

tumor_mask = tumor_mask';
hs = hs';
inner_percent = inner_percent';
a = hs(1:5);
b = inner_percent(1:5);
inner_hs_volume = interp1(b, a, 0.75);
outer_hs_volume = hs(1) - inner_hs_volume;

f1 = outer_hs_volume/nnz(mask);
f2 = nnz(TTP)/nnz(mask);
```