Pattern Analysis and Magnetic Resonance Imaging in the study of Tumor Angiogenesis

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Introduction

Various image techniques are available to monitor tumor angiogenesis including magnetic resonance imaging (MRI), which allows investigating angiogenesis-related parameters such as tumor blood volume (TBV) and blood flow (TBF), the average vessel diameter in a voxel (vessel size index, VSI) and vascular permeability noninvasively in vivo. As tumor tissue is highly heterogeneous comprising areas with different degree of vascularization, analysis procedure such as pattern analysis, which accounts for shape and texture of the structures to be analyzed is promising. Shape analysis is related to the geometry of the object (tumour) and allows the extraction of shape descriptors as volume, surface area and compactness. The texture analysis is related to the contents of the object and in particular to its texture by means of a set of estimators comprising fractal dimension (FD) and lacunarity (L). While FD allows the quantification of the vessel structure across the scales, L quantitatively assesses the three-dimensional size (mass) and distribution of local structures, e.g. non-perfused areas, in the tumor [1,2].

In this study we applied principles of pattern analysis to quantitatively assess angiogenesis/vascularity in a murine subcutaneous tumor model.

Material and Methods

Ten balb/c nude mice were injected subcutaneously with 10^6 C51 cells (colon carcinoma). A first group (N=5) was treated with dimethyloxalylglycine (DMOG), a compound that has been reported to stabilize the vessel network. A second group (N=5) was treated with NaCl. MR experiments assessing TBV, TBF, VSI and permeability were performed before and after 6 days of treatment.

Data were analyzed with the standard method based on histogram analysis, and subsequently with pattern analysis technique by a homemade C++ code. The 3D shape estimators (volume, surface area and compactness) and the texture descriptors (fractal analysis and lacunarity) were evaluated over the MRI readouts. Fractal dimension was computed by means of a Box Counting algorithm [3] according to eq.1, where N(R) is the number of boxes needed to cover the image and r is the dimension of the box. Lacunarity was computed by Box Gliding algorithm [4] according to eq.2 where r is the dimension of the box, M is the mass inside the box and Q(M,r) the mass distribution probability function. L is defined as the ratio between the 2nd moment over the square of the 1st moment of the distribution Q(M,r),

$$FD = \lim_{r \to 0} \frac{\log N(r)}{\log (r)} \qquad (eq.\ 1)$$

$$L(r) = \frac{\sum_M M^2 Q(M,r)}{\left[\sum_M M^1 Q(M,r)\right]^2} \qquad (eq.\ 2)$$

Results

Fig.1 shows quantitative TBV maps of C51 tumor bearing mice treated with wither DMOG or vehicle (saline). No significant differences were found between treated and non treated animals regarding TBV, VSI or permeability readouts **averaged** over the whole tumor volume as illustrated in Fig.2 for TBV. In contrast **pattern analysis** showed significant differences (p<5%) in the spatial distribution of TBV (fractal dimension) and of non-perfused regions (lacunarity) at day 12 (Fig.3,4). As expected, these differences are not present prior to treatment (day 6).

Conclusion

In view of the heterogeneity of tumors, standard analysis relying on values averaged of the whole tumor volume is insensitive in picking up differences among treatment groups. Pattern analysis, on the other hand, is particularly sensitive to changes in tissue texture (fractal dimension and lacunarity) and thus suitable to quantify the parameters related to angiogenesis and vascularity otherwise difficult to estimate.

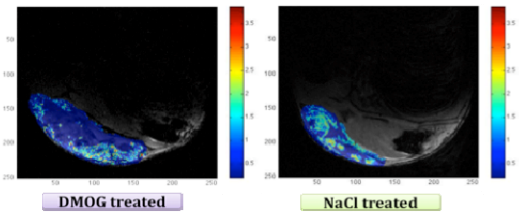

Fig.1 TBV maps at day 12 a DMOG-treated and a NaCl-treated mouse.

References

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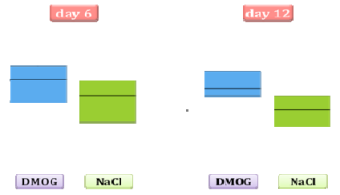

Fig.2 Average TBV box-plot at day 6 and 12 of DMOG and NaCl groups. The two groups are not significantly different (p>>5%)

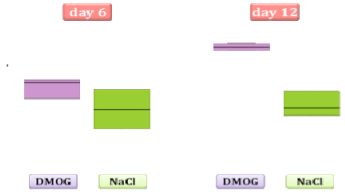

Fig.3 *Fractal dim.* box-plot at day 6 and 12 of DMOG and NaCl groups. The two groups are significant different (p<5%) at day 12

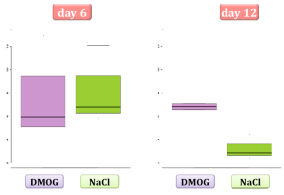

Fig.4 Lacunarity box-plot at day 6 and 12 of DMOG and NaCl groups. The two groups are significant different (p<5%) at day 12