Can DCE-MRI predict the nature of ovarian tumors ?A correlation between DCE-MRI and angiogenesis biomarkers.

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Introduction:

The therapeutic strategy in ovarian tumors varies largely between benign, borderline and malignant tumors. The characterization of ovarian tumor, however, is difficult to assess prior to surgical intervention.

Since tumor angiogenesis has been found as a prognostic indicator in ovarian carcinoma [1], we have undertaken a study to investigate whether dynamic contrast enhanced MRI (DCE-MRI) [2] was capable to predict the nature of ovarian tumors.

Materials and methods:

Forty one epithelial ovarian tumors, proven by pathology, were included in this study (12 benign, 13 borderline and 16 malignant tumors). MRI was acquired on a Siemens Sonata MR scanner operating at 1.5T. Dynamic contrast-enhanced T1-weighted gradient-echo images were acquired through a plane including simultaneously the tumor and the uterus (TR/TE, 38/4.8; flip angle, 70°; slice thickness, 5 mm; number of slices, 3; excitation, 1; field of view, 400-300 mm; matrix 246 x 134). An image was obtained every 5 s for 120 s. A bolus of 0.1mmol/kg of DTPA-Gd was injected at 2ml/s. Regions of interest were obtained from the solid portion of the tumor and from the myometrium of the uterus to generate time intensity curves. Myometrium enhancement was studied as the reference of pelvic perfusion for each patient and compared to tumor enhancement. Enhancement curves obtained by dividing the signal intensity curves by the pre-contrast signal intensity were fitted with Kaleidagraph to the following sigmoïd function (Hills function): $E(t)= A / (1 + (B/t)^C)$, where A = enhancement amplitude, B = time of half rasing. The slope of maximal raising (D) was calculated by first derived function of hills in B point $(E'(t)=(A*B^C*t^{-(C+1)})/(1+(B/t)^C)^2)$.

After surgery, the tumors were immunohistochemically stained successively with a CD34 antibody to mark the endothelial cells of the *microvessels*, an anti-alpha1smooth muscle actin antibody (SMA) to evaluate the *pericyte coverage index*, and a VEGFR-2 antibody to evaluate the expression level of *pro-angiogenic receptors*. The microvascular density and the capillary surface index were quantified semi-automatically on anti-CD34 stained slides by using Image-J routines.

Results:

The myometrium smooth muscle has a typical enhancement curve with a much steeper rise and higher peak than skeletal muscles. Amplitude and slope of raising of the myometrium were independent from age and hormonal status or treatment of patients. As compared to the enhancement curve of the myometrium, each tumor type had a specific behavior (fig 1). There was a statistical significant faster enhancement of malignant compared to borderline and benign tumors ($p=0.04$ and $p=0.002$ respectively), and a statistical significant higher amplitude of enhancement of malignant compared to borderline and benign tumors ($p=0.03$ and $p<0.0001$ respectively) (fig 2).

Our data demonstrated a gradation of the slope of raising of the three groups of tumors: Benign tumors have a weak slope (1.9), borderline an intermediate slope (2.6) and malignant an intensive slope of enhancement (11.9). Statistically significant differences were noted between borderline and malignant ($p=0.0001$) and benign and malignant ($p<0.0001$). No statistically significant difference was observed between benign and borderline tumors.

Microvessels of malignant tumors were larger and stained significantly less SMA and greater VEGFR-2 on epithelial and endothelial cells than two other groups.

The enhancement amplitude was correlated with total capillary surface ($p=0.01$), and the slope of raising was correlated with weak pericyte coverage index ($p=0.02$) and high VEGFR-2 expression ($p=0.002$). There was no correlation with the microvessel density.

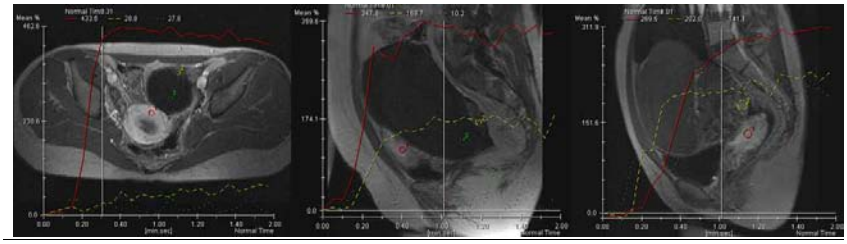

Figure 1 Typical enhancement curves from epithelial ovarian tumors (yellow curve) and myometrium (red curve): a) benign tumor, b) borderline tumor, c) malignant tumors. The curves are extracted form the ROIs visible on the images.

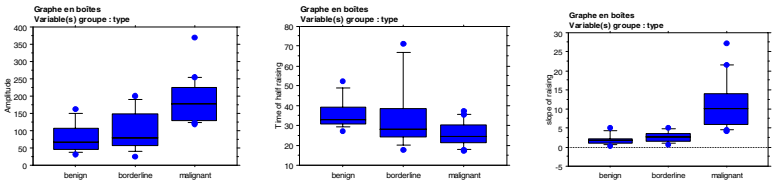

Figure 2: Plots of amplitude, time of half raising and slope of raising for ovarian tumors as a function of pathologic type. These data were obtained from fitting of the enhancement curve of 12 benign, 13 borderline and 16 malignant ovarian epithelial tumors, as indicated in the text. Each horizontal line represents the average value of the parameter, and error boxes represent the standard deviation.

Conclusion:

Taking the myometrium as an internal reference, it is possible to classify accurately the ovarian epithelial tumors between benign, borderline and malignant tumors with DCE-MRI.

The early enhancement characteristics of the ovarian tumors correlate significantly with the tumor angiogenic status as demonstrated by immunohistochemical staining. The capillary surface index is a linked to the tissue blood volume, and the pericyte coverage index and VEGFR-2 expression are linked to capillary leak.

DCE-MRI can allow a better choice of the surgical procedure in ovarian tumors, and could help in the choice of pre-surgical treatment, based on the analysis of the heamodynamic of the neo-angiogenic vascular network.

References:

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