Early prediction of responses/benefits from anticancer treatment using DCE-MRI and pharmaco-kinetic modelling

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Purpose: Treatment effectiveness evaluation by size reduction is generally inaccurate [1] and delayed several months after treatment instigation (5 months in the case of our data). Many angiogenic inhibitors, which act by normalization of the capillary bed, were developed against cancer [2]. The objective of our study is to prove experimentally that it is possible to perform earlier the diagnosis of responders and non-responders, as early as 7 to 12 weeks after treatment instigation, instead of 5 months, using functional pharmaco-kinetic parameters in adjunction to the variation of lesion size.

Methods: Saturation prepared Fast Gradient Echo (FGRE) sequence was employed for the dynamic contrast studies [3], using a 3 Tesla GE Signa Vhi MRI scanner. Eighteen patients with metastatic renal cell carcinoma included in an oral angiogenesis inhibitor Phase I/II study were imaged before treatment (baseline), after one cycle and two cycles of treatment. Tumours are located in liver, lymph node, bone, kidney, lung, pleura, and adrenal. The drug was the PTK787/ZK222584 (Novartis Pharmaceuticals) [4]. Patients were separated into two groups according to their clinical evolution. Responders had a time to progression superior to five months, i.e. without any new lesion or increase in lesion's size. Five patients are considered as responders. Thirteen patients are non responders. The first examination (C1) is carried out 2 to 46 days after drug introduction. The second MRI (C2) is completed 35 to 81 days post therapy. A bicompartimental model [5] has been used to generate parametric images. Four microcirculatory parameters have been estimated: tissue perfusion (F), capillary permeability index or endothelial transfer coefficient (K^{trans}), blood volume fraction (v_p) and extracellular extracapillar fraction (v_e) assimilated to interstitial volume. Parametric images were generated for each pharmaco-kinetic parameter. The histograms of pharmaco-kinetic parameters have been processed using an unsupervised statistical classifier. At each cycle, patients have been clustered into five classes of drug effectiveness. Two parsimonious expert systems, with either one or two classification rules, have been used to perform the diagnosis of responders and non-responders.

Results: The first expert system with a single classification rule has allowed the correct classification of 94% of patients after cycle C2, while the second expert system with two classification rules has correctly classified 100% of patients. In comparison, only 44% of patients have been correctly classified using only size information. Hence, better classification scores are obtained when using not only lesion size but also pharmaco-kinetic parameters.

Discussion: Our experimental results confirm that the conventional method of diagnosis, which is based on lesion size, is insufficient to correctly perform the classification of responders and non-responders. Better classification scores have been obtained using not only lesion size but also pharmaco-kinetic parameters. Our two expert classification systems allow the prediction of responses/benefits from anticancer treatment, as early as 7 to 12 weeks after treatment instigation, instead of 5 months. The first expert classification rule does not require any learning from imaging data, unlike the second one that is based on two thresholds to discriminate late responders from non-responders. We plan to later perform a large scale evaluation in order to better estimate these parameters. If our preliminary results were confirmed by this large scale evaluation, unnecessary treatments could be stopped earlier for many non-responders without stopping treatment for responders.

References

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