K-means clustering of DCE-MRI pharmacokinetic parameters for prediction of chemotherapeutic response of bladder cancer

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Introduction

While chemotherapy can reduce the burden of bladder cancer in patients who are responsive to the treatment, it can cause an unnecessary delay of the definitive cystectomy of resistant tumors. A previous study (1) showed that 3T DCE-MRI could reveal the difference between responders and non-responders in the microvascular change from baseline to post-chemotherapy via pharmacokinetic parameters. This study is aimed at evaluating the capability of k-means clustering of DCE-MRI pharmacokinetic parameters in predicting chemotherapeutic response of bladder cancer at mid-cycle MRI.

Materials and Methods

Subjects: 24 patients (22 males and 2 females; age range: 38-86) with cystoscopic confirmation of invasive (stage T2 or higher) bladder cancer have been included in the study. All patients had a baseline MRI before cisplatin-based chemotherapy and a mid-cycle MRI after two cycles of treatment. Patients were sent to cystectomy after their last MRI. Pathological examination of surgical bladder specimens was used as reference standard.

MRI exams: All patients were scanned on a 3T MRI system (Achieva, Philips Healthcare, Cleveland, Ohio) with 2-channel multi-transmit and using a multi-channel (32 or 16-channel) phased-array surface coil. High resolution T2-weighted (T2w) MRI was performed with a Turbo spin echo sequence. DCE-MRI was performed with a 3D-spoiled gradient echo sequence with a single dose (0.2 mmol per kilogram body weight) of Gd-based contrast agent (Magnevist, Bayer) administered at a constant flow rate of 0.5 ml/s.

Data Analysis: T2w MR images were used to measure the change in tumor volume from baseline to post-chemotherapy MRI. DCE-MRI data was processed using an IDL (Exelis VIS)-based software environment applying a modified Brix's linear two-compartment pharmacokinetic model (2) to calculate voxel-based pharmacokinetic parameters: Amp, the amplitude of signal enhancement; and k_{ep}, the exchange rate of the contrast agent between EES and the plasma space. K-means clustering (3) of voxel-based Amp and k_{ep} was performed on all cases to determine three clusters that are characterized by their centroids (centers of cluster). For each tumor, volume fraction of each cluster was subsequently calculated, and the change of cluster volume fraction from baseline to mid-cycle was determined and correlated with the tumor responsiveness to chemotherapy.

Statistical Analysis: The difference in the change of cluster volume fraction was evaluated by t-test. P<0.025 was considered statistically significant for bi-parametric analysis.

Results

11 were pathologically confirmed to have a bladder tumor of stage T1 or lower, and 8 showed a significant (greater than 70%) volume reduction at their last MRI. These 19 cases were defined as responders. The other 5 cases had a bladder malignancy of stage T2 or higher and a stable (less than 40%) or progression volume and were defined as non-responders.

Three centroids (kep, Amp) were determined by k-means clustering: (0.40 min^{-1}, 1.51 a.u.), (0.48 min^{-1}, 3.20 a.u.) and (3.55 min^{-1}, 2.04 a.u.). The signal enhancement characteristics of cluster 1 (low k_{ep} and low Amp), cluster 2 (low k_{ep} and high Amp), and cluster 3 with a steep slope (high k_{ep} and medium Amp) are illustrated in Figure 1. At mid-cycle MRI, volume fraction of cluster 2 of 18 responders increased while that of all non-responders decreased; volume fraction of cluster 1 of 14 responders decreased while that of all non-responders increased; and volume fraction of cluster 3 of 15 responders decreased while that of 3 non-responders increased (Figures 2, 3 and 4). These differences in the change of cluster volume fraction between responders and non-responders were all found to be significant (P<0.001 for cluster 1, P<0.001 for, and P<0.01 for cluster 3).

Discussions

K-means clustering classified bladder tumors in three clusters that were different in microvascular properties and in the microvascular change after chemotherapy. The changes in the volume fraction of the three clusters from baseline to mid-cycle MRIs trended in the opposite directions and were significantly different between responders and non-responders.

Conclusions

While the pure measurement of tumor volume on MR images is not reliable, this more complex quantitative analysis of pharmacokinetic parameters has shown its robustness in revealing the complex change of microcirculation at mid-cycle MRI to enable early prediction of chemotherapeutic response of bladder cancer. These promising findings are being applied to an ongoing prospective assessment.

References

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2. Yang X, Magn Reson Med. 2008, 59(6):1448-56.
3. Anderson EK et al, Acta Oncol. 2010, 50:859-65.

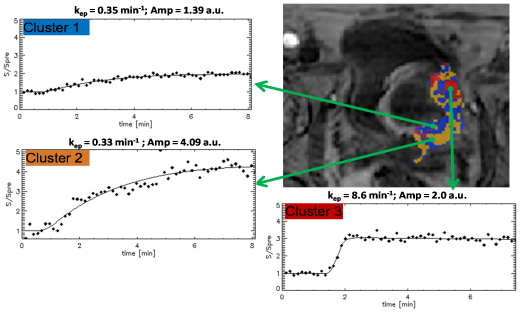

Figure 1: Signal enhancement curves of clusters.

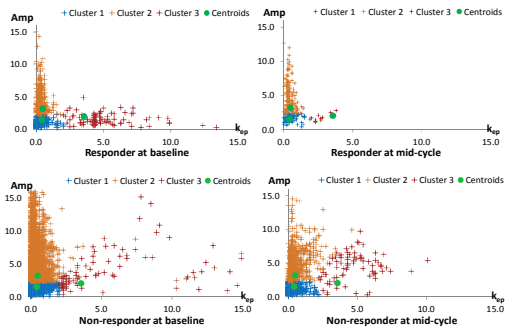

Figure 2: Cluster plot of k_{ep} and Amp for the whole tumoral volume of a responder vs. a non-responder.

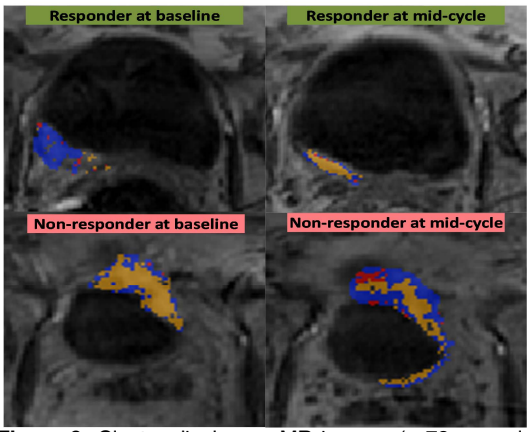

Figure 3: Cluster display on MR images (a 72-year old male (upper row) and a 54-year old male (lower row)).

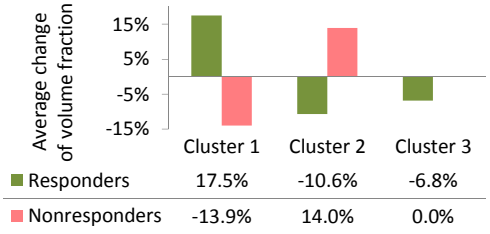

Figure 4: Cluster volume fraction change of responders vs. non-responders from baseline to mid-cycle.