Prognostic imaging markers in patients with GBM: comparison between functional versus mean KPS analysis

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INTRODUCTION:

Patients diagnosed with glioblastoma multiforme (GBM), the most common primary brain tumor, generally have a very poor prognosis [1]. Temozolomide chemotherapy combined with radiotherapy yields the best survival rate and is considered the standard of care by the National Cancer Institute [2]. Treatment assessment in GBM is difficult as early imaging changes cannot be easily differentiated from tumor progression (i.e. pseudo early progression). The incidence of pseudo early progression after chemoradiation is approximately 15-30% [3]. Early measures of response may permit both an individualized adaptation of radiation delivery, and serve as prognostic markers of treatment outcomes. DCE imaging is a non-invasive imaging technique which can assess early changes in the tumor microvasculature. It could be a useful tool to differentiate early progression from pseudo early progression as increased contrast enhancement may be associated with the radiation effect on the vasculature leading to increase of permeability changes [4]. The purpose of this study was to compare a voxel-by-voxel based functional KPS analysis versus mean KPS measurements and evaluate their usefulness as early prognostic imaging biomarkers to distinguish early progression from pseudo progression in GBM.

MATERIALS AND METHODS:

29 patients (12 females, 17 males, aged 42-68 years) with Grade IV GBM were treated with 3D conformal radiation therapy (RT) (over 6 weeks) and concurrent temozolomide chemotherapy following surgical resection. All MR imaging was performed on a 1.5 T clinical MRI system (GE HealthCare, Milwaukee, WI) equipped with an 8-channel head coil. Each patient underwent MRI at 3 different time points: baseline (post surgery but prior to RT), during RT, and one month after the completion of RT. At each time point, MRI included T2-weighted FLAIR, diffusion-weighted imaging, 3D dynamic contrast-enhanced (DCE) MRI and post-contrast T1-weighted imaging. DCE-MRI was performed using the following parameters: 3D GRE, TR = 5.9ms, TE = 1.5ms, FA = 35°, FOV = 240mm, 128 × 128 matrix, slice thickness = 5mm, temporal resolution = 9s. Total acquisition time was 4:48 min for a collection of 31 volumes. Contrast media (Gd-DTPA, 0.1mmol/kg) was injected as a bolus immediately after the second DCE-MRI volume. DCE-MRI data for each time point were spatially co-registered to baseline using the FMRIB Linear Image Registration Tool (FLIRT) [5]. Data were processed further using in-house software (MR Analyst version 1.4, University of Toronto, Toronto, Canada) implemented in MATLAB. For each patient, a rectangular region of interest (ROI) was placed around the enhanced tumor area on the last volume of the DCE MRI data for the time point displaying the largest tumor area. These ROIs were then copied to all other time points to yield a consistent ROI volume throughout all time points. Voxel-by-voxel coefficients of permeability estimates (KPS) were derived for all ROIs using a 2-compartment pharmacokinetic model as described previously [6]. KPS for all tumor volumes were computed using two different approaches: functional KPS and mean KPS. Functional KPS computation was based on a voxel-by-voxel comparison of KPS between baseline and each follow-up time points (during RT and post RT). Individual KPS values were then stratified into three categories based on the change in KPS between baseline and each follow-up time-point. A functional KPS graph was generated for each patient with three different colors: red, for a significant increase; blue for a significant decrease; and, green for no significant change. Mean KPS was calculated for each tumor volume in each patient at each time point (baseline, during RT, post RT). According to clinical outcome, patients were divided into three groups: early progressors (EP), pseudo early progressors (Pseudo EP), and stable disease. Functional KPS fractions (red, blue, green) for all clinical groups as well as mean KPS for all clinical groups were compared using a one-way ANOVA and a Student's t-test. A p-value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were computed for predicting clinical outcome from KPS.

RESULTS:

25 out of 29 patients were included in the analysis. 4 cases were excluded due to absence of DCE MRI data. 13 patients were diagnosed with stable disease, 8 with early progression (EP), and 4 with pseudo progression (Pseudo EP). Functional KPS analysis revealed no significant differences for the different clinical groups during and post RT (see Fig.1A-C). Analysis of mean KPS showed a significant decrease of KPS over time for patients with stable disease, significant increase of KPS from baseline to post RT for EPs, and significant increase of KPS during RT and post RT for Pseudo EPs (see Fig.2A). Comparison of mean KPS between EP and Pseudo EP showed that KPS is significantly higher for Pseudo EPs than for EPs during RT (see Fig.2B). ROC analysis for discriminating EPs from Pseudo EPs based on mean KPS changes during RT showed good accuracy (83.3%).

DISCUSSION:

This study suggests that only mean KPS measurements seem to discriminate early progression from pseudo early progression. Lack of statistical significance for functional KPS is possibly a result of the small fraction of Pseudo EPs in our study, and due to a high variability of KPS values in this group. A larger number of patients is needed to investigate this further.

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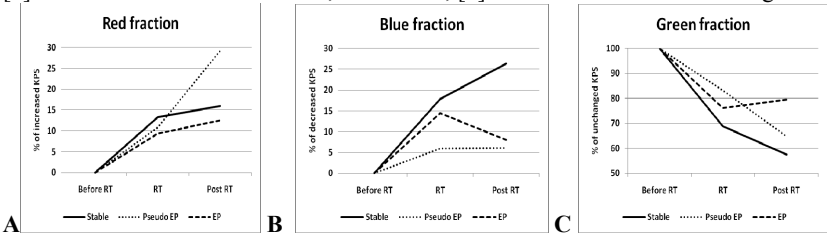

Fig.1 Changes in baseline values for functional KPS during and after RT for the different clinical groups: early progression (EP), stable disease, and pseudo early progression (Pseudo EP). The red fraction (A) shows an average percent of significantly ($p<0.05$) increased KPS values, the blue fraction (B) shows an average percent of significantly ($p<0.05$) decreased KPS values, and the green fraction (C) shows an average percent of unchanged KPS values.

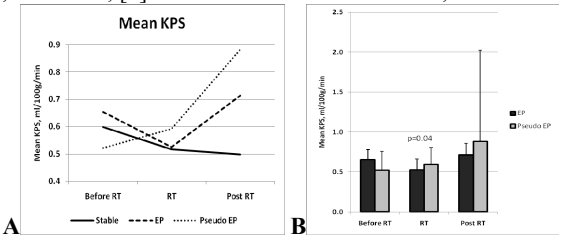

Fig.2 Mean KPS value changes over time for EP, Pseudo EP, and Stable disease (A).
Mean KPS comparison between EP and Pseudo EP at different time points. Pseudo EP has significantly higher KPS ($p<0.05$) than EP during RT (B).