Survival prediction of patients with glioblastoma based on combination analysis of mammalian target of rapamycin (mTOR) - epidermal growth factor receptor (EGFR) pathway and dynamic susceptibility contrast (DSC)-MR perfusion imaging

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Target audience: Neuroradiologists, neurosurgeons, neuro-oncologists and MR physicists.

Purpose: Phosphatidyl-inositol-3 kinases (PI3Ks) constitute a family of intracellular lipid kinases that are frequently hyperactivated in glioblastoma, mammalian target of rapamycin (mTOR), a key mediator of PI3K signaling and epidermal growth factor receptor (EGFR), has emerged as a compelling molecular target in glioblastoma patients. However, the association between mTOR-EGFR pathway and hemodynamic changes in glioblastoma, and their prediction value of survival, are still unclear. The purpose of this study is to assess the association between mTOR-EGFR pathway and quantitative dynamic susceptibility contrast (DSC)-MR perfusion imaging derived indices, and evaluate their survival prediction value based on combination analysis.

Methods: 41 cases (mean age is 62.317±12.1) with new pathology confirmed glioblastomas were enrolled in this study. Mean and maximal relative blood volume (rCBV) ratio, of the enhancing tumor ($rCBV_{mean}$ and $rCBV_{max}$), maximal rCBV ratio of peri-enhancing tumor area ($rCBV_{peri\text{-}tumor}$) were measured as well as mean, maximal and minimal percentage of signal recovery (PSR) of the enhancing tumor. The analyses of Ki-67, IDH mutation, mTOR activation, and EGFR amplification were performed. The association between $rCBV_{mean}$, $rCBV_{max}$, $rCBV_{peri\text{-}tumor}$, mean PSR, maximal PSR and minimal PSR and mTOR and EGFR were assessed, the Cox regression was used to evaluate the implication of age, sex, operation method, DSC-MR PWI derived indices and genomic information on overall survival time (OS). The difference of above parameters between the patients who survived less than 12 months and more than 12 months was compared.

Results: The $rCBV_{peri\text{-}tumor}$ had significant correlation with mTOR, (*p* value was 0.016). The maximal PSR showed the trend to correlate with EGFR (*p* value was 0.054). The Cox regression analysis showed that $rCBV_{peri\text{-}tumor}$ and mTOR were the two strongest predictors of OS. There were 21 patients who survived less than 12 months after initial diagnosis, and 20 patients survived more than 12 months. There was significant difference of $rCBV_{peri\text{-}tumor}$ between these two groups (mean $rCBV_{peri\text{-}tumor}$ value was 4.42±1.82 and 2.52±1.63 separately, *p* value was 0.001), $rCBV_{peri\text{-}tumor}$ and age had larger area under the curve (AUC) than other parameters in ROC analysis, but combination of $rCBV_{peri\text{-}tumor}$ and mTOR had better predication of survival time (Figure 1, 2).

Conclusions: Molecular signature of mTOR in glioblastoma correlated with $rCBV_{peri\text{-}tumor}$, which indicated that mTOR-EGFR pathway may moderate increase of neoplastic vasculature and infiltration in the peri-enhancing tumor area. The evaluation of mTOR-EGFR pathway not only provided additional genomic information, combination of $rCBV_{peri\text{-}tumor}$ and mTOR could improve prediction of survival time in patients with glioblastoma.

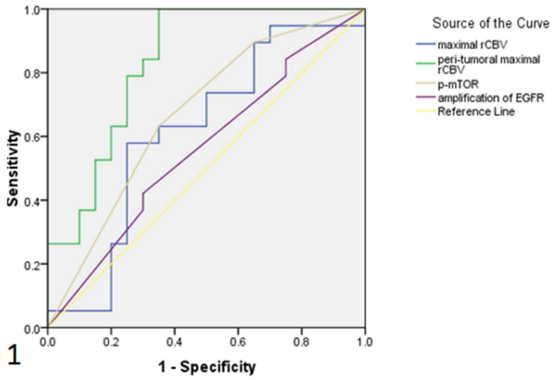

Fig 1

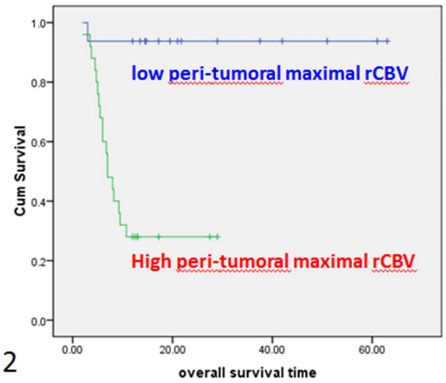

Fig 2

Figure 1: ROC curve shows $rCBV_{peri\text{-}tumor}$ has AUC in distinguishing glioblastoma patients survived less or longer than 12 months. **Figure 2:** Kaplan-Meier survival curve shows the patients with lower $rCBV_{peri\text{-}tumor}$ survive longer than the patients with higher $rCBV_{peri\text{-}tumor}$.

References:

1. Jain R et al. Radiology. 2014 Aug;272(2):484-93.
2. Jain R et al. Radiology. 2013 May;267(2):560-9.