Glioblastoma stem-like cells spotted by MRI

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Material & Methods

- 16 patients with glioblastoma (mean age 64 +/- 12, 11 males)
- MRI session:
  - 3D T1-weighted after 15 ml injection of Gadolinium contrast
  - FLAIR (TI/TR/TE=2400/8000/335ms)
  - Turbo-spin echo T2w
  - Diffusion-weighted
    - single shot EPI
    - TR/TE=10s,55ms
    - bvalue=1000s/mm^2, 15 directions (+1 b=0)
    - matrix=112x112x60, voxel size = 2×2×2 mm^3
  - Perfusion
    - spin-echo EPI
    - TR/TE=1700/50ms, FA=75°
    - matrix =128×128x22, voxel size=1.75x1.75x5mm^3
  - Spectroscopy
    - 2D PRESS covering the tumor
    - matrix=8x8x4, voxel size=1x1x1cm^3
- Biopsy
  - Intra-operative tissue extraction in two Hyper-Flair regions based on the spectroscopy (Cho/NAA>2 and Cho/NAA<2)
  - After biopsy extraction, GSC were (1) counted in a cytometer and (2) cultivated for up to 3 months until the formation of neurospheres could be observed
- Statistics
  - Pearson correlation coefficient
  - Independent component analysis from ADC and rCBV in the entire hyper-FLAIR

Introduction

- *Rational.* Glioblastoma (GBM) is the most aggressive and resistant type of brain tumor. With current gold standard treatment (i.e. surgical resection followed by radio- chemo-therapy), the median overall survival is only 14 months **[1]**. In 90% of patients, the recurrence occurs close to the original tumor location and in the volume targeted by radiotherapy **[2]**, suggesting the **presence of chemo- and radio-resistant cells in the peritumoral region**. A subpopulation of GBM cells with **stem-like** behavior (GSC) were found to be **particularly aggressive and radio-resistant**, and thus are good candidates for explaining the recurrences **[3]**.
- *Previous work.* Apparent diffusion coefficient (**ADC**), obtained from diffusion MRI, has been shown to provide **early signs of glioblastoma recurrence [4]**. Particularly elevated cerebral blood volume (**CBV**), measured with perfusion MRI was shown to **differentiate recurrent tumor from pseudo-progression** with high sensitivity and specificity (90%) **[5]**. Multimodal MRI, where diffusion and perfusion metrics are combined, improves the prediction of recurrence **[6]**. From these results, we can argue that diffusion and perfusion MRI are sensitive to environments where tumorous cells survive after radio- and chemotherapy.
- *Objective.* In this work, we propose to use **biopsies from the peritumoral region** of GBM patients in order to characterize the **MR signature of the preferred locations of stem-like cells**.
- *Results.* This study show that **GSC are more numerous or more aggressive in sites with high risk of recurrence** (low ADC and high rCBV).
- *Impact.* This is the first study that tries to relate MR signature and GSC *in vivo*. Being able to localize GSC would allow to target these radio-resistant cells using surgery or radio-surgery and prevent relapse.

Results

► This figure shows the MR spectroscopy (MRS) overlaid on the contrast-enhanced T1. MRS was used to determine the two sites of biopsy. Arrows indicate the sites of biopsy with Cho/NAA>2.
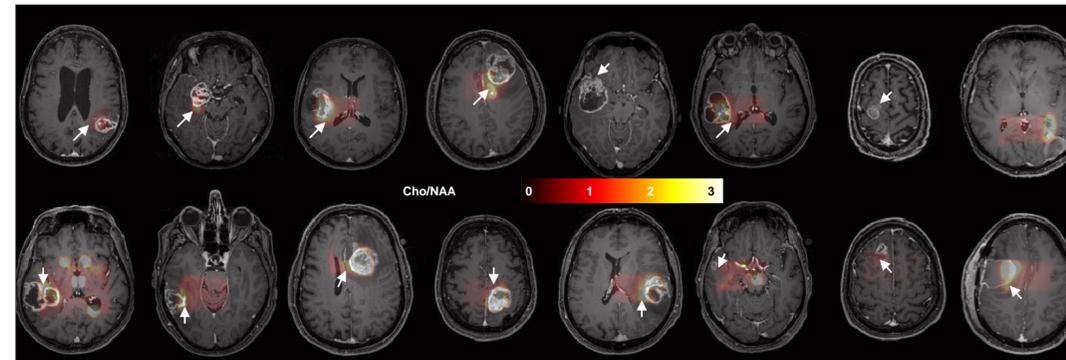
► This figure shows the relative cerebral blood volume (rCBV) overlaid on the contrast-enhanced T1.
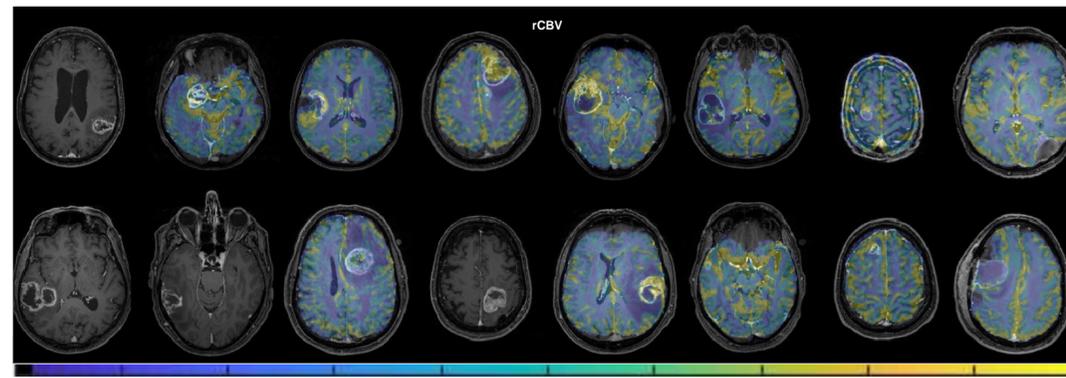
► This figure shows the apparent diffusion coefficient (ADC) overlaid on the contrast-enhanced T1.
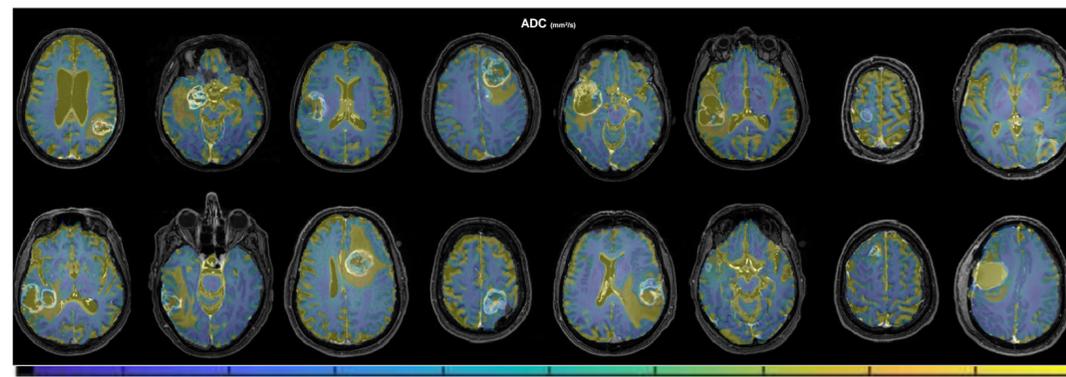
▼ These plots show the correlation between the MR signature and GSC. It appears that ADC is a good predictor of the time to grow GSC neurospheres (aggressiveness) and rCBV is a good predictor for the proportion of GSC. Other correlations were not significant.
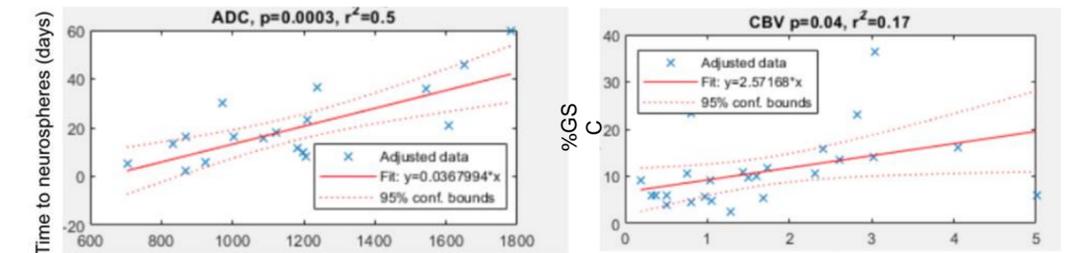
▼ These plots show the correlation between the independent components analysis (ICA) and GSC. Finding the independent components with ADC and rCBV improves the prediction for the proportion of GSC (r2=0.27 instead of 0.17 with rCBV only).
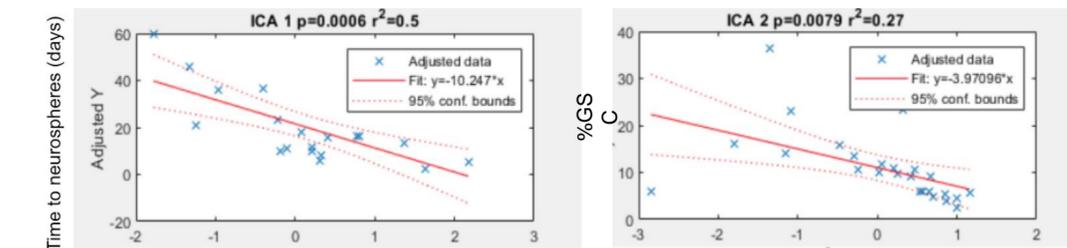
References

[1] Park et al. 2010
[2] Loeffler et al. 1990
[3] Cheng et al. 2010
[4] P.D. Chang et al., AJR. American journal of roentgenology, 2017, 208, 57
[5] McKinney 2010
[6] Cha et al. 2014

Conclusion

This study support the idea that **GSC are responsible of glioblastoma recurrence**. This study also confirm that peritumoral sites with low ADC or high rCBV should be preferably removed at surgery since radiotherapy is particularly inefficient on GSC cells

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