Morphologic MRI Features of Brain Glioblastoma: Predictive Statistical Model for Heterogeneity and Spread

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Abstract

Brain Glioblastomas (GBM) have poor prognosis. The anatomic changes with time is not predictable. In this project we are working to statistically model the shape and intensity fluctuations that may offer additional insight into the direction or extent of spread of cancer cellularity. If the cancer growth model can be correlated with the tissue signal heterogeneity then radiation planning may be more effective. Based on a group of patient GBM features post imaging analysis are being performed with key morphologic feature extraction. This work compares geometrical features of GBM for several patients utilizing intensity fluctuations from MR imaging with contrast, morphology of abnormal perfusion in various lesions and heterogeneity within lesions as reflected in statistical changes with serial GBM treatment.

Background

Interestingly, tumor recurrence after radiation and chemotherapy are accompanied by a growth of more aggressive MES subtype of cells that are enriched by the positive expression of CD133 (CD133+), have the capacity to self-renew and recapitulate heterogeneity in the tumor.

Additionally, some GBMs are relatively radioresistant and patients have worse outcomes after radiation treatment. GBM tissues have shown genetic diversity within regions of individual tumors.

CD133- cells can convert to the CD133+ cells adding more complexity to the hierarchy in GBM. Such observations lead to the concept that mature transformed cells within and perhaps outside a GBM can reprogram to a stem-like state, that is not only can maintain a pool of self-renewing and proliferating cells but also can differentiate to become various cell lineages found in GBM.

However, there is no work relating the cell heterogeneity with the MRI signal in and around GBM. Our work analyzes MR results on GBM to review any under utilzed, existing imaging data that could add insights to GBM biology.

Listed below are variables that influence MRI signal in a cancerous tissue:

GBM MRI Signal = function of tissue magnetic susceptibility, tissue hydrogen atom density, tissue magnetic relaxations in magnetic energy exchange (T1, T2) in terms of chemical bonding and MRI contrast medium in GBM capillaries.

Methods

Hypothesis: *The heterogeneity that exist at the cellular level per GBM biology dominates in contribution to the sample MRI noise as compared to all other image generating noise sources like MRI hardware or spurious noise entering into the image pixel from surrounding tissues.*

MR data collection: *Using a retrospective IRB 12 GBM patients (age range 53-72) were analyzed and MRI signal intensity and sample standard deviations (SD) were compared (Fig 1). The signals were normalized using a common tissue standard to compare the signal and noise SD characteristics at two different field strengths (3T and 1.5T) used in these subjects.*

Relevant questions that are being reviewed as part of the hypothesis:

Q1. ***Does the cell plasticity (de-diferentiation) provide a ste-cell like behavior in GBM that lead to Tumor heterogeneity?***
The review (Ref 1) suggests yes it does, that mature transformed cells within and perhaps outside a GBM can reprogram to a stem-like state, that is not only can maintain a pool of self-renewing and proliferating cells but also can differentiate to become various cell lineages found in GBM.

Q2. ***Do we know the mechanisms of GBM radioresistance and how to improve the outcomes of patients with this deadly disease?***
The answer is not adequately, however there are attempts to understand it and develop “radiosensitizers” to enable radiation therapy more effective (Ref 2).

Q3. ***Is there a sex-bias for GBM, can sex hormones give any explanation?***
Men are more likely to develop GBM compare to women. This difference could be as high as 60%. In addition, women respond to standard therapy better than men . A blog (Ref 3) posted in National Cancer Inst on Jan 30, 2019 suggests that the effects of sex hormones might not be able to explain the sex differences in brain cancer.

Q4. ***Why GBM only occur in adult brain?***
The reason why adult is more likely to develop GBM could be due to two specific clusters of DNA methylation (H3F3A and DPGFRA), (Ref 4).

Q5. ***Where are these radioresistant cells coming from, healthy area or necrosis area?***
It is often true that the necrosis area seems to become cancer growing area. Rapidly growing tumors are frequently deprived of oxygen and nutrient and therefore results in necrotic cell death at the core region of tumors (Ref 5).

Results

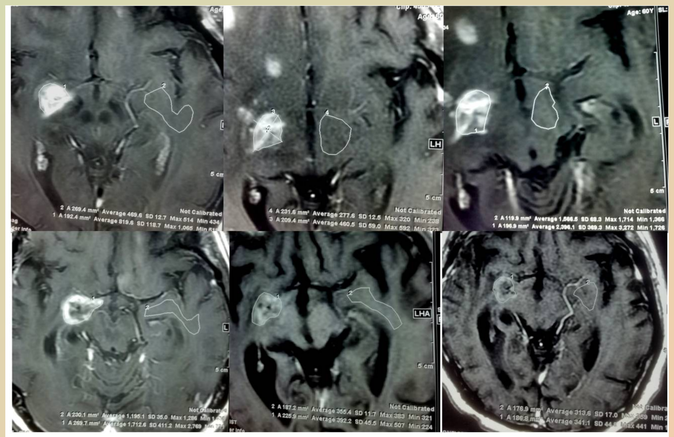

Figure 1. A 60y/M with GBM went through six consecutive MRIs as shown between AUG 20xx and MAR 20xx approx 3 weeks after Radiation+Chemotherapy

The ROI based SI and SD are shown in Ipsi-and-contralateral aspects and are plotted in **Figure 2.**

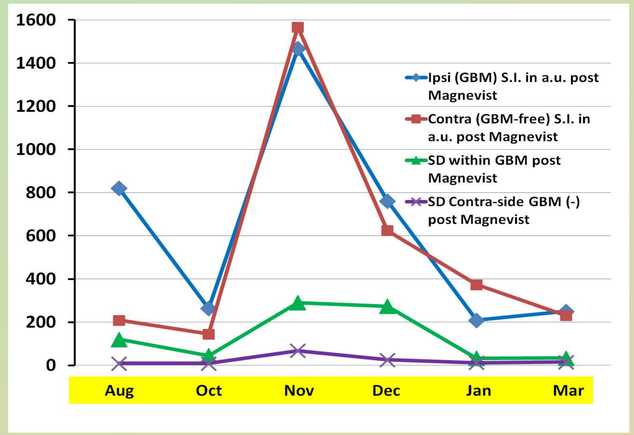

Figure 2. The ROI based MRI signal intensity (SI) and noise or standard deviation (SD) from Figure 1 in Ipsi-and- contralateral aspects are plotted **.** Notice the ipsi and contra sides are clearly different only for SD estimates while SI are the same in tumor and healthy sides.

Discussions and Conclusion

The MRI signal intensity (SI) in Ipsi and Contra ROIs are both following similar patterns during the 8-month diagnostics duration while the SD in the contra(normal) side stayed low and SD in ipsi (same as tumor) side remained high.

Hence the SD within the GBM is a better marker for cancer spread and May reflect the increased heterogeeneity present from time to time perhaps when GBM stem cells proliferate. The correlation of SD increase and stem cell-like behavior needs to be done but is almost impossible since biopsy correlation in severely ill patients from brain is risky.

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References

1. Dinorah Friedmann-Morvinski, Glioblastoma Heterogeneity and Cancer Cell Plasticity. *Critical ReviewsTM in Oncogenesis.* 19(5):327-336 (2014).
2. Yousuf Ali et al. Radioresistance in Glioblastoma and the Development of Radiosensitizers. *Cancers.* 2020, 12:2511.
3. https://www.cancer.gov/news-events/cancer-currents-blog/2019/glioblastoma-treatment-response-differs-by-sex
4. Tamimi AF In: *Glioblastoma*. Steven De Vleeschouwer (Editor), Chap 8, Codon Publications, Brisbane, Australia. 2017.
5. Su Yeon Lee et al. Regulation of Tumor Progression by Programmed Necrosis", *Oxidative Medicine and Cellular Longevity*, vol. 2018, Article ID 3537471, 28 pages, 2018.