Location of Glioblastoma and its Significance in Response to Treatment

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Abstract
Recent years have seen progression in the understanding of the pathogenesis, epigenetic and genetic changes in glioblastoma (GB). These characterizations have focused mainly on the prognostic significance and potential targets for therapeutic intervention. However, other traits of these highly malignant tumors have also been discovered as biproducts or as primary areas of research. Both surgery and radiation are less effective in periventricular glioblastoma, perhaps owing to this area being the niche for pluripotent stem cells in glioblastoma. Surgery carries less of a survival benefit in deep seated glioblastoma, in part because gross total resection of these tumors is uncommonly reached. All treatment modalities are less efficacious for multifocal glioblastoma. There is not enough data in the literature about the prognosis and treatment of specific single lobe supratentorial glioblastoma.

Introduction
Recent years have seen progression in the understanding of the pathogenesis, epigenetic and genetic changes in glioblastoma (GB) [1-13]. These characterizations have focused mainly on the prognostic significance and potential targets for therapeutic intervention. However, other traits of these highly malignant tumors have also been discovered as biproducts or as primary areas of research. Among these is differential localization in the central nervous system (CNS), and its significance in prognosis, in pathogenetic pathways and in amenability to different therapies.

Sensitivity of Differently Located Tumors to Treatment Modalities
Periventricular glioblastoma
Perhaps the most commonly explored location of GB is the periventricular zone (PVZ). GB in the PVZ has been shown to have significantly better migration and invasion capacities compared to cortical GB, related to down-regulation of the RND-1 [14]. Tumors in this area have been shown to be more likely to employ the MAPK/TSC/mTOR pathway, also bringing about a more aggressive phenotype [15]. Finally, and perhaps most importantly, PVZ glioblastoma have also been shown to contain niches, in which glioblastoma stem cells are in direct contact with the endothel of blood vessels [16-19]. Ventricular and periventricular zone GBs have been shown to have unique molecular and genetic alterations. These alterations have also been shown to translate into poorer survival for these tumors. This is true even when controlled for extent of resection (EOR) and complication rate, suggesting a truly biologically unfavorable tumor, rather than a difference in resectability [20-26].

Radiation treatment is more cumbersome in the periventricular and subventricular zones. It has been shown that radiation doses over 54Gy do not improve, and may potentially worsen prognosis when given to GB in the periventricular zone [27]. Whether this represents increased sensitivity of the area to radiation treatment or saturation of the sensitivity of GB in this area to radiation (related to their stem cell potential, discussed earlier), is unclear.

Basal ganglia and thalamus glioblastoma
Deep seated glioblastoma – tumors in the basal ganglia, insula and thalamus, have been shown to carry a worse prognosis as compared to glioblastoma in other locations [22,28,29]. However, extent of resection, a known predictor of outcome in glioblastoma, has also been shown to be significantly lower in deep seated glioblastomas [30-33]. It is unclear whether the worse prognosis is merely a representation of the lesser extent of resection or an actual survival difference. There has been no direct assessment of
the efficacy of radiation for treatment of deep seated glioblastoma compared to GB in other locations.

**Multifocal glioblastoma**

There is some evidence to show that multifocal glioblastoma are not only variable in location, but that the different tumors in the same patient may, in fact, carry different pathways [34,35]. However, the monoclonal origin of the different tumors in the same patient has also been shown. [36,37]. Molecular and intracellular pathways are not the focus of this review, but the potential variability of origin of multifocal glioblastoma will certainly be the focus of further research. Multifocal glioblastomas carry a poorer prognosis, as compared to focal or lobar glioblastoma [38,39]. As described earlier for deep seated glioblastoma, this may, in fact, be representative of a treatment bias, as the majority of multifocal glioblastomas will undergo biopsy rather than meaningful resection. Significant resection is a well-documented prognostic factor in glioblastoma [35].

Radiation is less effective for multifocal tumors, and in many centers is reluctantly used, due to the cognitive effects, which have been shown to be worse in treatment for multifocal disease. In many of these cases, in fact, Temozolomide is given as single treatment. Withdrawal of radiation may also contribute to the poor prognosis associated with multifocal glioblastoma [40,41]. As second line treatment, Bevacizumab is commonly given, but is also less efficacious in these tumors compared to focal glioblastoma [42,43].

**Glioblastoma in single supratentorial lobes**

There is information in the literature regarding glioblastoma in specific lobes, including insights of lobe-specific presentation, lobectomy vs. resection and insular involvement [44-47]. However, there is no direct comparison of the outcomes of surgery, or other treatment modalities for glioblastoma in different lobes.

Even the relative incidence of glioblastoma in different lobes is unknown, and it is unclear whether this incidence correlates to the volume of the different lobes or not.

**Conclusion**

Both surgery and radiation are less effective in periventricular glioblastoma, perhaps owing to this area being the niche for pluripotent stem cells in glioblastoma. Surgery carries less of a survival benefit in deep seated glioblastoma, in part because gross total resection of these tumors is uncommonly reached. All treatment modalities are less efficacious for multifocal glioblastoma. There is not enough data in the literature about the prognosis and treatment of specific single lobe supratentorial glioblastoma.

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**Conflict of Interest**

No conflict of interest.

**References**


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