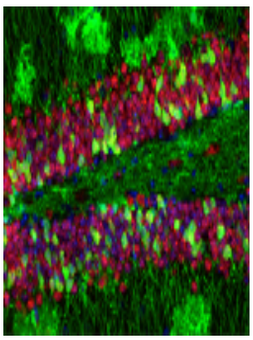

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Subventricular zone-associated glioblastoma: A call for translational research to guide clinical decision making

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Title: Subventricular zone–associated glioblastoma: A call for translational research to guide clinical decision making

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ABSTRACT

Glioblastoma (GBM) is both the most common and the most devastating primary cancer of the central nervous system, with an expected overall survival in most patients of about 14 months. Despite extensive research, outcomes for GBM have been largely unchanged since the introduction of temozolomide in 2005. We believe that in order to achieve a breakthrough in therapeutic management, we must begin to identify subtypes of GBM, and tailor treatment to best target a particular tumor's vulnerabilities. Our group has recently produced an examination of the clinical outcomes of radiation therapy directed at

tumors that contact the subventricular zone (SVZ), the 3-5 mm lateral border of the lateral ventricles that contains the largest collection of neural stem cells in the adult brain. We find that SVZ-associated tumors have worse progression free and overall survival than tumors that do not contact the SVZ, and that they exhibit unique recurrence and migration patterns. However, with minimal basic science research into SVZ-associated GBM, it is currently impossible to determine if the clinicobehavioral uniqueness of this group of tumors represents a true disease subtype from a genetic perspective. We believe that further translational research into SVZ-associated GBM is needed to establish a therapeutic profile.

MANUSCRIPT

Historical studies of glioblastoma (GBM) established the disease as following a fairly predictable natural history, whereby regardless of the type of systemic or local therapy tumors would recur within 3 cm of the original site almost 90% of the time. For years, this recurrence pattern focused attention on local control, and on delivering effective therapies to the volume of gross tumor. A combination of tri-modality using surgical resection, followed by adjuvant focal radiotherapy and temozolomide (TMZ) as established by Stupp et al demonstrated a median survival of approximately 14 months.[1] However, since the introduction of TMZ in 2005, survival for this devastating disease has plateaued.

Today the standard of care for GBM treatment involves maximal safe surgical resection, post-operative radiotherapy delivered to the surgical cavity, and TMZ delivered both during and after radiotherapy. Alterations to both the dose and treatment volume for radiation, as well as to dose and duration of TMZ have not significantly improved treatment outcomes for patients, nor as it altered the traditional paradigm of progression at the initial site of disease.[2] The addition of bevacizumab, a recombinant humanized monoclonal antibody against vascular endothelial growth factor-A (VEGF-A), while initially exciting in early clinical trials,[3,4] has been unable to improve overall survival in phase III randomized controlled trials.[5,6] As a result, the treating physician continues to approach GBM as a monolithic disease with limited tools for treatment. To achieve the next leap forward in GBM therapy, perhaps it is time to develop more nuanced treatment strategies that take advantage of more nuanced tumor biology.

Recent studies have made clear that glioblastoma is by no means a homogenous disease, with various tumor-specific factors having an impact on recurrence and survival. We know, for example, that hypermethylation of the O6-methylguanine-DNA-methyltransferase (MGMT) promoter region, a mutation present in as few as 30-40% of patients, confers a survival benefit in GBM patients receiving TMZ and radiotherapy,

with patients in the Stupp trial demonstrating a 24 month median survival.[1,7] Additionally, a non-telomerase mechanism for maintaining cellular replicative potential known as alternative lengthening of telomeres (ALT) is present in a minority of GBM patients and is known to improve survival.[8] A variety of other markers, such as IDH-1, 1p19q, EGFR, p53, ATRX and TERT to mention a few can also be prognostic and predictive. However, we believe that further subclassification of tumor presentation might be warranted. As an example of such subclassification and as extensively explored in our recent review article, physical association of the tumor with the subventricular zone (SVZ) at initial diagnosis predisposes a patient to worse progression-free and overall survival. However, a personalized treatment approach based on these factors has yet to be widely implemented.[9]

The subventricular zone is generally defined as the 3-5 mm lateral border of the lateral ventricles, and serves as the largest nidus of neural stem cells in the adult mammalian brain. Between 50% and 60% of GBM tumors contact this region, which in one study resulted in a 6-month reduction in median overall survival (16 months in SVZ-associated tumors versus 22 months in non-SVZ-associated tumors).[10] Another study found that SVZ involvement was more common in short-term survivors (defined as those surviving less than 12 months after diagnosis) than in long-term survivors (those surviving more than 36 months).[11] Several other studies of various designs have observed that SVZ involvement at diagnosis independently and significantly reduces both time to progression and overall survival in patients with GBM.[12,13] Furthermore, association with the SVZ at initial diagnosis predisposes patients to developing recurrence distant from the initial tumor volume, an observation at odds with the traditional understanding of recurrent GBM behavior.[14]

The reason for these worse outcomes is not eminently clear. However, SVZ-associated tumors may represent a distinct sub-group of GBM worthy of more extensive characterization. One group has observed that SVZ-associated tumors are more likely to be multi-focal at diagnosis, leading them to hypothesize that these tumors may originate from the malignant transformation of neural stem cells.[13] This hypothesis raises both an

interesting opportunity and challenge in treating patients with this subtype of GBM. Surgery and focal radiation, the current local therapies available to patients with GBM, have been directed at the site of the gross initial tumor. If SVZ-associated tumors arise from stem cells scattered throughout the SVZ, these treatment techniques would necessarily miss more distant sites of microscopic disease, and thus allow the SVZ to serve as a nidus for GBM tumor cell repopulation and recurrence. As a result, expansion of local therapies to include treatment to this region could have an impact on patient outcomes.

Our review of published retrospective reports that expanded radiation treatment fields to include the SVZ, however, revealed a split in the literature. Of the 9 studies available for analysis, six reported improved outcomes in either progression-free survival (PFS) or overall survival (OS), while three reported either worse or no significant change in PFS or OS. Furthermore, the dose levels at which significant associations became apparent were variable, ranging from less than 40 Gy to more than 60 Gy.[15] Variability within and across the retrospective studies could help explain differences in observed outcomes, and several prospective studies are underway to better evaluate the effect of expanded radiation fields on SVZ-associated tumors.

However, larger volume irradiation is not without risk. With significant neurocognitive deficits known to be associated with whole-brain irradiation,[16] some decrease in neurocognitive function would be expected if the current focal radiation fields were to expand to include the SVZ. Furthermore, stem cells are notoriously difficult to treat with radiation, and higher doses may be required to achieve desired therapeutic effect.

One group has observed that SVZ-associated tumors demonstrate a unique tangential and multi-polar migration pattern that differs from the "ventricle-directed" migration pattern of tumor growth observed in those tumors not geographically associated with the SVZ.[17] The kinetic differences in SVZ-associated tumor growth may be reflective of differences in the expression of genes impacting tumor motility. Furthermore, neural stem cells and GBM cells share similar cellular markers such as CD133 and nestin, as well as similar

migratory capacities, observations which have led some to conclude that neural stem cells are intricately involved in GBM tumorigenesis. More research at the cellular and genetic level of SVZ-associated tumors specifically is needed to help clinicians identify those patients who might benefit the most from extended volume focal radiation.

A translational approach to GBM research with the goal of better understanding the characteristics of SVZ-associated tumors is vital to determine if these tumors should be treated differently than other types of GBM. For example, glioma stem cells have been isolated that utilize alternative lengthening of telomeres (ALTs), a telomerase-independent, recombination-mediated replication of telomeric DNA.[18,19] Although we know that the presence or absence of ALTs are prognostic for survival in GBM patients,[8] no research has been done to explore their association with the SVZ. Should there prove to be an association, these variant solutions to proliferation arrest and the problem of replicative senescence may help explain the different recurrence patterns seen with SVZ-associated tumors. Additionally, if disease recurrence proves to be due to repopulation within the SVZ and subsequent distant migration to the initial primary site, therapies directed at blunting the migratory capacity of cancer cells could be effective. Indeed, some groups have demonstrated that neural stem cell migration is dopamine-receptor (DR) dependent,[20,21,22] a discovery reflected in prostate cancer research where neurotransmitter stimuli have been found to influence tumor aggressiveness.[23] To explore how this observation could be applied to GBM behavior, U87 cell lines and GBM murine models have been treated with DR2/DR3 blocking medications such as first generation anti-psychotics and have demonstrated reduced tumor burden as compared to controls.[24,25]

The heterogeneity of GBM at the cellular level, even within a single tumor, has been well established in some cases. For example, karyotypic analysis within a single glioma has revealed differences between regions of the tumor, and variable expression of differentiation markers across these same regions has also been observed.[26] Whether similar variability can be extended to help distinguish between SVZ-associated and non-SVZ-associated tumors has not been established.

However, clinical observations at the macro level such as those described above and in our review do seem to support the notion that physical association with the SVZ reflects a unique tumor subtype that requires a different approach from the traditional established therapies. Whether RT alone or combination of RT with targeted agents or other ablative options, the arena for exploration remains quite an open avenue of research pursuit. What remains is to discover the biologic reasons for these clinical-behavioral observations, and to use this knowledge to guide clinical decision-making.

Conflict of Interest: None

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