Editorial

The Subventricular Zone Neural Progenitor Cell Hypothesis in Glioblastoma: Epiphany, Trojan Horse, or Cheshire Fact?

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In the current issue of this journal are 2 reports concerning a provocative and controversial theory on the genesis and treatment of glioblastoma multiforme (GBM).

First, Lee and colleagues (1) report a pooled analysis at 2 institutions that included 173 GBM patients treated with intensity modulated radiation therapy (IMRT) and temozolomide (TMZ) showing that progression-free survival (PFS) was improved by an ipsilateral subventricular zone (SVZ) dose above 59.4 Gy. Next, in a largely concordant fashion, Chen and colleagues (2) evaluate 116 patients with GBM treated by IMRT and TMZ and observe that among the 41 patients undergoing gross total resection, SVZ dose above 40 Gy correlated with improved PFS and overall survival (OS). The putative mechanism for this benefit involves an effect upon neural progenitor cells (NPCs) residing in the SVZ.

We all agree that current management strategies for high-grade primary brain tumors are unsatisfactory, to say the least. GBM, along with unresectable pancreatic cancer and anaplastic thyroid cancer, remains among the nastiest scourges we face in all of oncology. We applaud any new insight that sets us on a path toward meaningful clinical benefits beyond the limited success we currently achieve. Nevertheless, as with any propitious proposition that promises prosperous progress, we must ask ourselves: is it real, is it a trap, or is it just an illusion?

Eureka! We Found It!

Legend has it that Archimedes got very excited when he suddenly conceived the intellectual insight about how to measure the volume of an object by the water it displaces and immediately jumped out of his bath in his birthday suit and ran around town to share the news. Ordinances in most municipalities prevent that particular form of public celebration, but maybe we should consider at least some level of curbed enthusiasm about the SVZ-NPC-GBM axis connection. After all, there is some good science and logic behind the notion of eradicating the GBM by choking off a possible root cause of the problem.

The published investigations that provide credibility for the findings of Chen et al and Lee et al establish the following: (1) The adult human SVZ constitutes the largest area of neurogenesis and houses the greatest concentration of NPCs (3); (2) NPCs contribute to GBM initiation, promotion, and recurrence as their oncogenic activation in rodents increases cellular proliferation, survival, and migration and ultimately the development of infiltrating gliomas (4, 5); and (3) NPCs can be particularly radioresistant because of preferential activation of the DNA damage checkpoint and DNA repair responses (6). Thus, it is logical to conclude that the SVZ contains a significant proportion of NPCs that can migrate to gliomas, support recalcitrant tumor behavior, and exhibit marked resistance to standard glioma treatment.

It also follows that aggressive therapy directed at the SVZ might enhance glioma control, prolonging patient PFS and OS. Indeed, 2 prior small retrospective studies have suggested that higher radiation doses to the SVZ in adults with high-grade gliomas might enhance patient survival (7, 8).

Therefore, it makes sense to eradicate NPCs in the SVZ to improve PFS and OS for GBM. Q.E.D.

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Beware Malware?

In today’s cyber parlance, the image of a wooden horse filled with Greek soldiers sneaking into Troy morphs into a program downloaded from the internet that is supposed to enhance your laptop’s processing speed or remove viruses but in reality deletes files and steals your identity. You only learn of the infiltration when your credit card is rejected at a fancy restaurant and suddenly that last bite of Baked Alaska tastes like a jalapeno soufflé. The Trojan Horse metaphor is applied here to ask whether a strategy that might at first glance be appealing (who would argue against improving PFS and OS for patients with GBM?) might in other ways be deleterious.

The pediatric brain tumor literature is replete with reports that radiation therapy is associated with the development of long-term neurocognitive impairment. Of direct relevance to our current discussion are data suggesting that NPCs residing in regions such as the SVZ and hippocampus are, in fact, exquisitely radiosensitive (9) and that injury to NPCs contributes to neurocognitive complications (10, 11). Several studies have linked radiation dose to specific brain regions, notably the hippocampus, to the development of neurocognitive deficits in children who received cranial radiation (12-14). Preclinical evidence with clinical histopathologic correlation lends strong support to the association between NPC injury and cognitive sequelae after brain radiation therapy (15).

The dose—volume effect in these structures is still unknown and needs to be defined, given the potential impact on neurogenesis. Nevertheless, the avoidance of radiation dose to NPC-containing niches holds promise as a means to reduce the significant neurocognitive sequelae experienced by pediatric survivors after cranial radiation. To be fair, we acknowledge that in adults with GBM, long-term toxicity considerations might be a lower priority than anything that lengthens OS. However, as with all new hypotheses directing new avenues for treatment, one must consider the potential costs, particularly in the most vulnerable populations, where finding the best balance between quantity and quality of life is not a straightforward task.

Chen et al (2) do offer a primum non nocere defense insofar as patients’ functional status, as assessed in a limited manner by Karnofsky Performance Scale, was not hindered by an SVZ dose above 40 Gy. Interestingly, the same group has investigated dose-painting strategies to protect against neurotoxicity by limiting dose to regions of neurogenesis in the SVZ of patients with various brain tumors, including GBM (16). Alas, it is impossible to have it both ways: we can’t simultaneously limit and escalate dose to the same regions, so something has to give.

“The Cheshire Cat vanished quite slowly, beginning with the end of the tail, and ending with the grin, which remained some time after the rest of it had gone” (Lewis Carroll, Alice in Wonderland).

The term “Cheshire fact” has been coined to represent “the datum solemnly recorded, earnestly explained, vehemently defended, and then never seen again” (17). Like the fantastic fading feline, what appears at first to be a solid truth is later understood to be only a mirage, a phantom, a trompe-l’œil. In his famous lecture on the topic, the Nobel Laureate Irving Langmuir cited examples such as Blondlot’s N rays and the Davis-Barnes effect as instances in which “there is no dishonesty involved but where people are tricked into false results ...by subjective effects, wishful thinking, or threshold interactions” (18).

We have to be careful here, because our inclination toward schadenfreude can sometimes steer us first to try to disprove any new theory that is not our own or is otherwise not palatable and to enjoy a smug sneer rather than applaud creativity and effort. For example, skeptics of the impact of nutritional intervention on cancer outcomes routinely feast on the low-hanging fruit of failed dietary intervention trials, which, in 1 case, took the actual form of low-hanging fruit: to wit, the trial that failed to show a reduced rate of breast cancer recurrence among patients randomized to increase their consumption of fruit and vegetables (19). We would bet that many of those same Doubting Thomases are quick to toast the studies showing a protective effect of red wine on the incidence of heart disease (20) …but we digress.

Back to the effect of the SVZ NPC dose on outcome in GBM and the pressing question: can this phenomenon still be just a Cheshire fact, now that 2 groups have seen it?

In fact, a correlation between ipsilateral SVZ dose and improved PFS or OS has not been uniformly observed. Although in one of the current series, Lee et al combine data from 2 institutions (1), some of these patients were included in an earlier report of 55 patients (38 with GBM, 17 with anaplastic astrocytoma), which curiously showed that higher bilateral SVZ dose—and not ipsilateral SVZ dose—correlated with improved PFS (7). A possible explanation is that irradiation of the SVZ initiates a migratory signal to the corpus callosum in response to injury, thus illustrating the importance of bilateral SVZ dose over ipsilateral SVZ dose (21). In the current series, however, the opposite finding was shown. Muddying the waters further, Gupta et al (8) observed that although higher ipsilateral SVZ dose was favorable, a higher contralateral SVZ dose was associated with worse outcome.

Maybe these observations are all true, but for reasons we don’t yet completely understand. Maybe tumors located close to the SVZ present at an earlier point, on average, in their natural history. Maybe it is actually the incidental dose to nearby thalamic substructures that delays harmful corticospinal tract dissemination in some cases. Maybe a contralateral SVZ dose sometimes stimulates migration of reparative stem cells, whereas in other cases the sheer burden of a tumor requiring irradiation covering the contralateral SVZ is simply overwhelming.

Maybe the thing we can all agree on, though, is that with our modern arsenal of sophisticated dose delivery technology, with which we can modulate the dose to substructures of the brain, we need to move beyond the simple enhancement-plus-margin target concept in the treatment of GBM and explore more nuanced approaches. Prospective studies of nonstandard target design should, of course, include neurocognitive and other quality of life metrics along the way to be sure we don’t achieve small quantitative gains for the price of large qualitative losses. Nevertheless, we have been stuck in a rut with the treatment of GBM for quite a while now, and provocative studies that generate innovative hypotheses are a welcome contribution.

References


