

Radiotherapy to volumes defined by metabolic imaging in gliomas: time to abandon monstrous margins?

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Abstract: The survival in patients with high grade gliomas (HGG) remains poor even after the adoption post-operative radiotherapy (RT) to magnetic resonance imaging (MRI) based volumes. Despite delivery of ‘standardized’ doses of radiation, recurrence is the norm, rather than the exception. Recurrences occur both within, and outside of the volume of irradiation, leading us to two questions—firstly concerning the adequacy of the dose of radiation used, and secondly about the current methods of treatment volume delineation. The emergence of newer radiopharmaceuticals for use in positron emission tomography (PET) have kindled the hope of more precise volume localizations for post-operative RT, and it is likely that these new radiopharmaceuticals can help us define accurate areas at highest risk of recurrence and thus allow us to use increased doses of radiation with confidence.

Keywords: Metabolic imaging; radiopharmaceuticals; glioblastoma; high grade glioma (HGG); radiotherapy (RT)

Submitted Dec 17, 2015. Accepted for publication Jan 15, 2016.

doi: 10.3978/j.issn.2305-5839.2016.01.19

View this article at: <http://dx.doi.org/10.3978/j.issn.2305-5839.2016.01.19>

The current standard for target delineation in radiotherapy (RT) planning for high grade gliomas (HGG) involves the use of magnetic resonance imaging (MRI) defined volumes. While the T2-weighted MRI is used to define target volumes, areas enhancing on gadolinium contrast on T1-weighted imaging are considered for additional boost. But the current guidelines require the addition of margins so as to derive clinical target volume (CTV) and planning treatment volumes (PTV) (1,2). A clinician using advanced image-guided RT can actually omit PTV in the modern era since the brain happens to be a fixed organ within a frame (skull) which can be effectively immobilized. But, conventional logic assumes that it is rather risky to reduce CTV margins, since these are added with an intention to cover radiologically invisible microscopic disease. Despite the addition of CTV, recurrence in HGG after RT is a norm rather than the exception. While overall outcomes remain dismal with failures occurring in and out of the target volumes, that too despite the adoption of MRI based treatment volume delineation, it is a matter of surprise that the same old guidelines continue to be used with the same old ‘conventional dosing’ (54–60 Gy in conventional fractionation) (3,4).

Pattern of failure analyses yields excruciating impressions—with failures occurring not only outside and within the target volumes, but also within the ‘boost’ volumes. This leads us to field two questions:

- (I) Is the currently used method of volume delineation correct?
- (II) Is the currently used dose adequate?

Difficult questions need bold answers. Answering the first question, it is possible that the MRI based volume delineation may at times be inadequate (with many ‘non-central failures occurring’) and at times be an ‘overkill’ (in that the addition of CTV margins can enlarge irradiated volumes leading to dosing of crucial amounts of brain tissue). Answering the second question, the currently used dose of 54–60 Gy to post-operative target volumes is clearly inadequate, given that recurrence is more often a rule rather than the exception (4).

While it is technically very feasible in this era to provide dose escalation safely via the utilization of stereotactic methods, the greater issue seems to be that of selecting the appropriate target for irradiation. The gadolinium contrast enhancing areas are already shown to not always

be representative of the area at risk for recurrence, given that newer metabolic imaging such as positron emission tomography (PET) using ^{11}C -methionine have shown loci of disease in and out of the MRI defined volumes (5,6).

Unlike ^{18}F -fluorodeoxyglucose (FDG), the commonest radiopharmaceutical used for PET scans currently) which has a poor tumor:brain accumulation ratio, ^{11}C -methionine has a high specificity to accumulate within malignant cells, and their use can enable:

- (I) Greater confidence in terms of tumor coverage;
- (II) Greater sparing of normal tissue by reduced volume of irradiation;
- (III) Dose escalation to small foci of hyper-avidities.

In addition to the use of ^{11}C -methionine, additional newer PET radiopharmaceuticals also hold good prospects—such as radiolabelled peptides, choline derivatives, amino-acids and nitroimidazoles, all of which have their own characteristics (7–9). Magnetic resonance spectroscopy (MRS) can also be a complementary method of precisely defining areas appropriate for irradiation (10).

The α/β ratio of brain tumor cells is likely to be very low, especially for those dormant cells which lead to recurrence months after completion of irradiation. Given that cells with low α/β ratio respond better to high fraction sizes, it may be very naive of us to assume that conventional fractionation at 1.8–2 Gy per fraction would be adequate (4). Thus, integration of two high-dose fractions delivered stereotactically, one before & one after the conventional course of RT could be radio biologically superior. Given the current availability of very precise image-guided delivery systems, this is an avenue which is not only worthy of evaluation, but unfortunately underused.

As such, the outcomes with the currently used standards of care, i.e., MRI defined volumes and conventional dose-fractionations, are very poor. Experimenting with the integration of high-dose fractions to complement conventional fractionation is unlikely to worsen the already worse outcomes, and at the best may yield path-changing benefits. And higher doses can be used only for small precise targets, not to the volumes utilizing colossal margins upon the already large MRI defined volumes. For the purpose of defining precise targets it is necessary for us to expedite the adoption of metabolic imaging with MRS and newer radiopharmaceuticals for imaging.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Susheela SP, Revannasiddaiah S. Radiotherapy to volumes defined by metabolic imaging in gliomas: time to abandon monstrous margins? *Ann Transl Med* 2016;4(3):55. doi: 10.3978/j.issn.2305-5839.2016.01.19