Peer Review File

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**Review Comment**

This is a very well written manuscript with a very complete review of existing studies regarding hypofractionation mainly for elderly patients. The review is complete, unbiased, and fair.

**Comment 1:** The only consideration is the definition of palliative being contracted than standard fractionation, in other words hypofractionated regimens. Although a fair consideration, some may argue that the hypofractionated doses used are not palliative doses as they are slightly higher than given for brain metastases (37.5 Gy in 15, 30 Gy in 10, and 20 Gy in 5). I suggest that the authors discuss further as it may confuse the readers.

**Reply 1:** I agree, it can get confusing and that is why we defined what we are considering as palliative radiations. The concept of radical/definitive vs palliative radiation can be blurred in GBM/HGG pts as they are seldom cured. A standard course of treatment still provides the best though suboptimal outcomes for the better prognosis patients. In patients with shorter expected survival, radiation with standard fractionation is unlikely to benefit them and a hypofractionated course of radiation delivering a much lower BED yields similar survival. So the concept of palliative radiation for a patient is based on the estimated poor survival of the patient and as a result, a less intensive and better tolerated course of radiation (hypofractionated) delivering a less than radical dose to such a patient is regarded as palliative radiation. In fact, one can argue that even radiation with standard fractionation is palliative in such a patient with poor prognosis but will do more harm as it is worse tolerated, and the patient will be spending a bigger proportion of his/ her remaining time getting treatment. Hence, the Table 9 can serve as an important guide to decide treatment plan.

I have further modified the aim in Intro to say that we will be discussing upfront hypofractionation for patients with poor prognosis. Subsequent paragraphs highlight the poor outcomes in this patient populations. This encourages the use of hypofractionated radiation that results in improvement in survival while at the same time not resulting in a decrease in patient's QOL.

I acknowledge that palliative is not solely defined by using a hypofractionated regimen and have added that in discussion. One cannot help but notice the lack of granularity within our current repertoire of how we describe treatment intent: curative versus palliative. In medical oncology, there are other terms including life prolonging therapy, which may be more akin to how we approach GBM treatment. As many of us may believe we are prolonging survival but not necessarily curing patients, we are selecting a radiation dose/fractionation that is tailored to expected life expectancy. Our review essentially focuses on the evidence behind alternate dose/fractionation schemes for patients with poorer life expectancy/performance status.

**Comment 2:** There are some minor errors, including “patents” in line 236 and reference “(Reynold 2012)” on line 317 that I caught.

The recommendations provided by Table 9 are backed up by the studies discussed. This table is certainly the strength of this manuscript as it provides guidance to the readers how they recommend employing hypofractionated RT and temozolomide.
**Reply 2:** Thank you for pointing those out. They are fixed.