Reviewer's report

Title: Radioactive 125I seeds inhibit cell growth and epithelial-mesenchymal transition in human glioblastoma multiforme via a ROS-mediated signaling pathway

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Reviewer: William Omar Contreras Lopez

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Major Compulsory Revisions

The authors revealed 125I seed irradiation as a more effective intervention to kill Glioblastoma multiforme (GBM) cells than conventional gamma radiation. They tested cell survival and migration properties in in vitro and in vivo assays. The performed experiments are from adequate quality and with supported with appropriate controls. The overall story of radiation sensitivity in gliomas is not novel and the seed irradiation is only exciting from a technical standpoint of view. Furthermore the paper has a few more pitfalls though:

1. It has been previously demonstrated that Stereotactic Brachytherapy (SBT) with I125 represents a safe, minimally invasive, and highly effective local treatment option for pediatric patients with inoperable LGG WHO grades I and II as well as metastatic and meningiomas (Ostertag 1989; Voges J, et al. 1990). It has been use few times in GBM because it’s diffuse and not clean borders characteristics, which doesn’t allow a conformational radiotherapy doses, compromising other structures in vicinity and the difficulty to cover all tumor area besides the risk of complications such as radionecrosis. It has been demonstrate that SBT with I-125 is a minimally invasive, safe, and effective local treatment when applied as monotherapy or in combination with microneurosurgery for circumscribed cerebral LGGs smaller than 40 to 50 mm in diameter located in functional and anatomically complex brain territories such as midline, brain stem, and/or eloquent cortical areas (Ruge ML 2011). At present it is suggest the management of patients with brain stem glioma by stereotactic biopsy and implantation of I125 seeds for interstitial radiosurgery in a single step procedure as an alternative to external radiation therapy (Lopez WO 2013).

2. The paper wrote by Yunhong Tian et al. states that radioactive 125I seeds are more effective than X-ray irradiation in inhibiting GBM cell growth. Moreover, EMT was effectively inhibited by 125I seed irradiation. Such concept may bring additional information of the feature of GBM which currently is resistance to treatment; however the experiments realized to bring such conclusion seem to be insufficient. According to the methods what is the primary target of the 125I seed irradiation? They show that apoptosis is more induced, cell survival is less but don’t show any profound underlying mechanism (i.e. DNA repair enzyme activation), that would be very interesting.
3. The authors speculate “EMT is modulated” testing this with altered motile behavior of the cells. They used e-Cadherin and Vimentin as markers, however all GBM express Vimentin and it is well know that E-Cadherin is only rarely expressed in glial tumors and in fact there are reports even saying it is a negative prognostic marker in GBMs (Lewis Tuffin et al., PlosONE 2011). It is also known that the E-to N-Cadherin switch is not a hallmark event in EMT-like process in GBMs (Kahlert et al., Cancer Letters, 2013). It worth to mention that U251 and U87 do not express e-Cadherin in Gliomas. I would suggest testing ZEB1 and SNAI1 as core factors of EMT to test if there is any regulation in mesenchymal transformation after radiation. If the authors talk about EMT in GBMs they miss to cite the pioneer paper of EMT in gliomas from Kahlert et. al (Cancer Letters 2012). Did they see WNT- pathway modulation? In fact it is strange that after conventional radiation EMT is accumulated (as tested by Vimentin expression) and after 125I seed irradiation it goes down. This is intriguing would that seed radiation more effectively kills the EMT-like GBM cells. Those cells are thought to be very resistant to conventional radiation (Mahabir et al., Neuro-Oncology 2014) and the author’s seed-technology would be from highest clinical interest. The paper should focus on that and proof with further adequate experiments.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'