Reviewer's report

Title: Preclinical evaluation of Gd-DTPA and gadomelitol as contrast agents in DCE-MRI of cervical carcinoma interstitial fluid pressure

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Reviewer: Elizabeth A. Repasky

Reviewer's report:

This manuscript addresses a very important issue faced by clinicians when planning treatment of patients with cervical cancer. It has been well documented from earlier clinical studies from two different groups that patients having high tumor interstitial fluid pressure (IFP) at the time diagnosis of cervical cancer have a very poor prognosis as compared to those with lower IFP. Further, patients with tumors that are also hypoxic have a worse prognosis. It is thus clear that knowledge of the tumor status with respect to IFP and hypoxia would be of enormous help in treatment planning. However, it is not clear exactly how this particular manuscript further helps others in the field as only a single cell line is examined here, that appears to give different data from a previous study in which only a single cell line was examined. I believe that the authors need to more clearly justify the basis for this study over previous excellent work and to better indicate limitations of this study.

Minor essential revisions:

1) The researchers have used Gd-DTPA (small size) and Gadomelitol (medium size) MR contrast agents and their conclusion is that Gadomelitol is a superior contrasts agent. This group has in a previous publication have shown that gadomelitol is a useful as a MR contrast agent for tumor IFP (reference 21 in this manuscript). Reports from other groups have also shown the distinct advantages to using larger sized MR contrast agents for DCE-MRI. Gadolinium covalently linked to human serum albumin being one of those agents. The small sized Gd-DTPA is not a contrast agent of choice for DCE-MRI since the efflux rates for small sized molecules are high especially in tumors with high IFP. Thus the results do not appear to be novel. Can the authors please clarify these points in their study.

2. In their earlier report on A-07 melanoma model, this group did not find any correlation between Ktrans and IFP, and a positive correlation between Vb and IFP. In this paper they report positive correlation of both parameters with IFP and it is not clear to this reviewer why apparently different results are obtained. The authors have suggested that the differences could be because of the presence of connective tissue surrounding microvessels in CK-160 tumors. This brings up the problem of only having data using a single cell line in the current study, and also in the previous study. A more comprehensive analysis would be very helpful to the field as each cell line is likely to result in different results. The authors should
certainly comment on this deficit.

3). The authors report that IFP in the CK-160 human cervical carcinoma xenografts are in the range 5 to 45 mmHg. This range of tumor IFPs have been reported in clinical studies by other groups, however those reports are for tumors from individual patients. Thus, this wide range of IFPs seems unexpected given the more likely homogeneous nature of cell line derived tumors. Can the authors comment on this heterogeneity?

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I have no competing interests.