Reviewer’s report

Title: The use of superparamagnetic iron oxide-polymer composite microcapsules for magnetic resonance-guided high-intensity focused ultrasound cancer surgery

Version: 4 Date: 24 September 2014

Reviewer: Bryan Smith

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The article by Sun et. al. seems to be much improved.

Major Compulsory Revisions

A few comments on the author’s responses.

1. The previous comment “This should be further addressed in the discussion, as perhaps the signal observed by the authors is due entirely to the smallest say 5-10% of particles in the distribution.” was meant only to suggest that the smaller particles in the distribution might be contributing to the signal observed – we don’t know whether it is 5-10% or 10-20% as the authors have now written, but the point was to include in the discussion the possibility that the signal was due to the lower end of the distribution tail.

2. 9. Figure 6. The very small size of the error bars seems quite impressive. However, what do they represent? S.E.M., S.D., …? This must be included in the caption.

Furthermore, while the previous Figure has now been quantified, why did the authors not perform statistical analyses on it to show statistical significance between groups and between time-points?

The error bars in the Figure 6 represent standard deviation (SD). This has been included in the caption. In addition, we want to observe the MR signal intensity (SI) changes to demonstrate the MR enhanced effect of the PLGA-coated Fe3O4 microcapsules. Therefore, we measured the MR SI of the targeted tissue in liver and performed statistical analyses on these data between groups and between time-points.

Where is this statistical analysis on Fig. 6? I don’t see any reference to comparisons between time-points, etc. Please include it.

3.

15. “H-L Liu et. al used focused ultrasound to destroy the blood-brain barrier to allow the magnetic particles to entering the brain parenchyma and then used the
magnetic nanoparticles to target and monitor the delivery of macromolecular chemotherapeutic agents into the CNS under MRI guidance. But, the magnetic nanoparticles did not enhance HIFU therapy.

The authors believe that more accurate image guidance remains an unmet need for some tumors. In this study, the functional superparamagnetic microcapsules were intravenously injected and enabled enhanced MR imaging of the liver tumor prior to HIFU ablation. This effect was beneficial for guiding effective HIFU therapy and, more importantly, enhanced the HIFU cancer ablation efficiency of the superparamagnetic microcapsules.”

It is still not clear that guidance was truly provided. A non-guidance control is really needed to be able to state this unequivocally. Otherwise, the authors may be over-interpreting their data.

Also, authors should cite previous work in which it has been shown that temperature can be enhanced with magnetic nanoparticle using HIFU (at least in vitro), e.g., Dibaji et. al., 2013, J. Nanotechnol. Eng. Med.

To observe the capability of PLGA-coated Fe3O4 microcapsules as the contrast agents for MR imaging, prior to MR-guided HIFU ablation, 18 rabbits were randomly divided into three groups: (i) MR-guided HIFU treatment without microcapsules, (ii) MR-guided HIFU treatment with pure PLGA microcapsules, and (iii) MR-guided HIFU treatment with PLGA-coated Fe3O4 microcapsules. T2-weighted images were acquired before and 5 min after injection of the agents. As mentioned in Figure 5a1,2, 5b1,2 and 5c1,2, the superparamagnetic PLGA-coated Fe3O4 microcapsules generated negative contrast enhancement in the T2-weighted images of the liver (5c2) compared to other two groups.

Furthermore, we measured the MR SI of both the normal liver parenchyma and the liver tumor before and after injection of agents. As a result, the SI significantly decreased in the normal liver parenchyma after administration of the PLGA-coated Fe3O4 microcapsules (P<0.05, Figure 6A), but the SI decreased to a significantly lesser degree in the liver tumor tissue (P<0.05, Figure 6B). These results demonstrate that the PLGA-coated Fe3O4 microcapsules could provide an accurate localization of the tumor in liver compared to the other two groups without such agent. In addition, we have cited previous work carried out by Dibaji et. al in the manuscript.

Understood what the authors have done. The issue is that it is not clear that MR-guidance is required (or helpful) without doing a control group that lacks MR-guidance.

17.

“1. The Figure 4 caption should be more explanatory of the figure.

Figure 4 caption has been reedited

For instance, what do the different colors stand for in the fig? This should be part of the legend. It should also be made more clear what the relationship is between optical density and cell viability in the caption.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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