Reviewer’s report

Title: Diffusion weighted magnetic resonance imaging (DW-MRI) as a non-invasive, tissue cellularity marker to monitor cancer treatment response

Version: 0 Date: 24 Jun 2019

Reviewer: Joan M. Greve

Reviewer's report:

Review of BCAN-D-19-00623

OVERALL

This work uses DWI to assess therapeutic response following irradiation. They use two tumor models, which is excellent, and have tested two radiation doses. Although the manuscript is clear, there is no spatial localization of changes when comparing MRI to IHC and it is unclear what the contribution is that advances the field.

ABSTRACT

None.

INTRODUCTION

This sentence is confusing. Pointed out here because it is important in describing how DWI works. Deleting 'accomplished' improved clarity for me: "In more detail, DW-MRI measures the indirect value of cellularity accomplished by applying the same gradient at continuous short time intervals."

MATERIAL AND METHODS

I believe all this information is repeated just below in Tumor Model. Please consolidate into one location. "All experiments were tested in two different syngeneic tumor models with tumor placement on the lower flank of the mice. Models included a colon carcinoma cancer model using murine CT26 wildtype colon cancer cells (CRL-2638, ATCC, Virginia, USA) and a breast cancer model using murine 4T1 breast cancer cells (CRL-2539, ATCC, Virginia, USA)."

Why were the cell lines or types of tumor chosen? Are these types of tumors often treated with radiotherapy in the clinic?

For MRI data, please clarify if the whole tumor was analyzed? Or, just a single image?

The use of the MUSE cell analyzer, by its nature, precludes the ability of spatial correlation to MRI data. This is a limitation that should be mentioned in the Discussion.
Did the IHC mice undergo MRI too? If they also underwent MRI, was there any alignment or maintenance of orientation of the tumor between MRI and IHC? Or, was this, too, a global comparison? If no spatial alignment at all, please note as a limitation in the Discussion. (Please see Carano et al. Quantification of Tumor Tissue Populations by Multispectral Analysis Magnetic Resonance in Medicine 51:542-551 (2004). Although they did not register MRI and ex vivo data, they maintained some alignment to look at spatial 'correspondence'.)

RESULTS

How was reproducibility quantified? If not, please qualify with 'qualitative'. "DW-MRI scan sequence was performed with high reproducibility."

Should slides be slices in this sentence? "Optimal image quality seen in center of coil, but no eddy currents- or motion artifacts were seen in either of the slides, which is otherwise known to be an obstacle for EPI sequences."

Please include an outline of the ROI in Figure 2.

DISCUSSION

Noting the difference between precision and accuracy, I think precision is still an overstatement here. Perhaps, correlation or relationship between. "The precision of the ADC-value as an indirect measure of cellular density was investigated by comparing with ex vivo measurement of cellular density."

You mention biopsy in 2nd paragraph. Are you talking clinically here? Or, did you biopsy the mouse tumors? Please clarify. The rest of the sentence discussing challenges of biopsy-ing heterogeneous pathology is good.

FIGURE LEGENDS and FIGURES

Figure 1: Interesting that 10 Gy had greater effect? This is not seen in Annexin data or IHC data. Comments?

Figure 2: Point out some features, e.g. dark signal in controls is necrosis? Why not more effect on ADC? If necrosis, I would expect ADC to increase.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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