Reviewer's report

Title: DCE-MRI assessment of the effect of Epstein-Barr Virus-encoded latent membrane protein-1 targeted DNAzyme on tumor vasculature in patients with nasopharyngeal carcinomas

Version: 3
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Reviewer: Heidi Lyng

Reviewer's report:

The paper describes a DCE-MRI study of 26 patients with nasopharyngeal cancer. All patients were treated with radiotherapy and randomized to adjuvant treatment targeting the Epstein-Barr Virus (EBV) – encoded LMP1 protein. Preclinical studies suggest that the adjuvant treatment can promote vascular changes in the tumor, and this hypothesis was tested here by addressing the pharmacokinetic DCE-MRI parameters Ktrans, Kep and Ve at different time points during treatment. Ktrans was found to decline at an earlier time point in the combined treatment group and the decrease was larger than in the group receiving only radiotherapy. This larger decrease seemed to be associated with a higher tumor shrinkage rate. The present study contains some novel information and is of clinical interest. Although few patients, the number is sufficient for concluding about changes in MRI-parameters during therapy. The study is hampered by the lack of histology/immunohistochemistry to confirm the proposed higher vascular effect of the combined treatment. There are some concerns related to the MR examinations and image analysis as well as other points that should be addressed before the paper can be considered for publication.

Major Compulsory Revisions:

1. The arterial input function (AIF) is a critical factor in calculation of the kinetic DCE-MRI parameters, and not easy to determine with satisfactory accuracy. AIF seemed to be measured for each patient and examination. Plots of AIF (raw data) at different examinations for a typical patient would be useful and some information about the differences in AIF across patients and across MR-examinations should be included. What kind of curve fitting was performed for the AIFs, and how good was the fitting?

2. Were problems with signal saturation in the high flow arteriers considered in the determination of AIF?

3. Were any corrections in the tracer uptake curves for differences in bolus injection start and rate applied? How was this source of error handled?

4. Data presentation in figures and tables seems not to be well founded. It would be better to use figures for all three parameters, combined in three panels to figure 1a, b and c. Data should be shown for the two treatment groups separately, as is done now for Ktrans and Kep. Table 2 and Table 3 can be omitted.
5. Figures 3, 4: Tumor contour and ROI for calculation of MR parameters must be indicated in the images. It would be useful if MR parameter and time point during therapy could be indicated in the figure, for example above (MR parameter) and at one side (time point). Figure legends can be shortened, since the same parameters are shown for all time points.

6. More focus should be on tumor shrinkage in relationship to MR parameter. Were there any relationships between the change in tumor volume and change in MR parameter? This could be of interest to show in a figure.

Minor Essential Revisions:

1. Randomization seemed not to be perfect (14 vs 10), explain why.

2. Methods, in statistical analysis (page 9) it is stated that all data are expressed as mean +/- standard deviation, but confidence intervals are used in the figures, correct this.

3. Results, page 10: include p-values for the Ktrans-data, like for the other MR-parameters.

Discretionary Revisions

1. Would it be better to have the second MR examination earlier during radiotherapy, to achieve vascular information and thereby enable change in treatment at the earliest possible time point in cases of no effect? Comment on the choice of time point for MR.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interest