Author's response to reviews

Title: Kinetic Analysis Dynamic [18F]-Fluoromisonidazole PET Correlates with Radiation Treatment Outcome in Head-and-Neck Cancer

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Response to reviewer comments

First we would like to thank both reviewers for fast, helpful and constructive comments.

Comments by Dr. Nordsmark:

General
The title has been rephrased with more emphasis on the modelling approach.

Major Compulsory Revisions
We concur with the argument, that the number of patients is not high enough to perform reliable Kaplan-Meier outcome analysis. As suggested, figures 2 and 3 were omitted. The respective parts in the text have been changed accordingly.

Measurement of pre-treatment tumor volume was added to subsection "Data Acquisition" as follows: For the delineation of the tumor volume relevant in the context of this study, the FDG PET image data was used. The tumor volume was defined as the volume including all voxels with at least 40% of the maximum intensity. This delineation technique was combined with a 12 mm margin (3 PET voxels). The tumor volume variable V used in the current study refers to the described FDG PET volume. It is determined as $V = n \cdot v$, where $n$ is the number of tumor voxels. $v$ represents the volume of a single voxel, in our case $v = (0.4 \cdot 0.425) \text{ cm}^3 = 0.068 \text{ cm}^3$.

Additional CT imaging data was available for RT treatment planning. The method subsection "Patients" was amended in the following way: For each patient, additional computed tomography (CT) image data was available. These CT scans, on which delineation of target volumes and organs at risk was performed, were used for RT treatment planning.

Discretionary Revisions
Formulation has been changed to “even though”.

Comments by Dr. Hicks:

Major Compulsory Revisions
1. The initial number of patients involved into this study was 16. But one patient died seven months after the end of therapy of a therapy related laryngeal oedema without evidence of local failure. In this case, it was not possible to determine reliably the response to therapy. Therefore, this patient has not been taken into account for the statistical analysis and the number of patients taken into account there was set to 15.

We agree, that this situation is confusing for the reader. Therefore, we amended the abstract and methods in a way, that the group of patients in the study has a size of $n = 15$.

2. As the study presented here contains only a low number of patients, we agree, that the conclusion drawn in the abstract and in the conclusion section is overstated. The respective passages in the text have been rephrased according to your suggestions. Abstract: The presented study established, that Fmiso PET scans may benefit from dynamic acquisition and analysis by a kinetic model. Conclusion:
The interpretation of Fmiso PET examinations with respect to hypoxia benefits greatly from a kinetic analysis.

3. Fmiso PET data does not allow to extract separate information about the number of hypoxic cells in a tissue area and their grade of tracer uptake. One can only assess the 'concentration' of hypoxia specific uptake, which is termed the Tracer Retention Potential (TRP = # of hypoxic cells times hypoxicity).

Another aspect of Fmiso PET imaging is related to the problem that necrotic areas contain only a low amount of viable cells, so that necrotic areas themselves are essentially "invisible". Thus, on a static Fmiso image alone, voxels containing necrotic areas appear to have relatively low SUV. While it appears possible to identify the presence of wholly necrotic voxels by a combination of static FDG and Fmiso images, it appears somewhat optimistic to assume it would be possible to quantify the "extent" of hypoxia without further ad-hoc assumptions about the spatial distribution of the necrotic patches. Since these patches can range from 100µm to few mm in diameter, partial volume effects etc. cause an ambivalence in static images. The greater information content of dynamic images seems to be more suitable to quantify the tracer retention potential in front of a high background of unbound tracer as in the case of voxels containing necrotic patches, and other regions with a low density of hypoxic cells.

In order to reach a better formulation concerning the definition of TRP and the question of dealing with necrotic areas, the respective text passages have been amended.