Reviewer's report

Title: Dynamic [18F]-Fluoromisonidazole PET Predicts Radiation Treatment Outcome in Head-and-Neck Cancer

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Reviewer: Rodney Hicks

Reviewer's report:

General
The authors of this manuscript are members of an institution that has made significant contributions in the field of hypoxia imaging using PET and are well credentialed to perform and report such a study. Given the growing recognition of the importance of hypoxia to therapeutic outcomes and therefore, prognosis in various malignancies, particularly including head and neck cancer, this paper is timely and provides useful information on which to base further studies.

The focus of the current paper is both technical and clinical, in that it seeks to validate a model of a hypoxia tracer kinetics studied by dynamic PET by demonstrating its ability to predict failure of local control. Accordingly, it is presumed by the authors that this failure reflects the presence of tumoral hypoxia. Based on previous literature from their own group and others, this presumption is not unreasonable but is somewhat simplistic since many other factors likely also contribute to local disease control. The paper appears to overlap in content, and presumably also in primary patient data, with an earlier report from this institution by Eschmann et al., which is referenced. However, it focuses only on a subgroup of patients with head and neck cancer. There is however, significantly more technical content in the current paper and further development of concepts raised by in previous paper.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Although, overall the paper is well written and the data are presented clearly overall, there is inconsistency in the number of patients referred to in various sections of the manuscript. The abstract and the initial comment in the methods section indicate that 16 patients were included in the analysis. All but one of these patients appears to have received chemotherapy concurrently with radiotherapy. However, in the FMISO data acquisition method section, only 15 patients are detailed. It is assumed that either one patient did not have dynamic imaging or else was the patient subsequently identified as not being able to be evaluated for therapeutic response in the results section was omitted here also. The remainder of the data presented relate to the 15 patients in whom eventual response could be assessed. It is unclear whether 15/16 or 15/15 patients received chemotherapy. Therefore, I think that it would be best to amend the abstract and methods to include only the 15 patients who underwent FMISO and could be evaluated for therapeutic outcome.

2. While the data presented suggest that the perfusion information provided by the early dynamic phase of the study improves the ability to predict patient outcome, the abstract conclusion that FMISO PET scans “need to be acquired dynamically and analysed by a kinetic model” overstates the strength of these data. I would recommend changing this to: “may benefit from dynamic acquisition and analysis by a kinetic model”. This is particularly the case since information regarding tissue perfusion could also be obtained by other techniques including dynamic contrast CT or MRI that may be more practical than using PET. A similar issue relates to the final conclusion in the paper. It is not true that “PET scans can only be interpreted with respect to hypoxia if a kinetic analysis is performed”. Several groups have demonstrated that useful prognostic data can be
obtained from the delayed imaging data alone. It may be that prediction of outcome cannot be reliably done without incorporating information also about tissue perfusion but this likely reflects factors other than hypoxia. For example, higher perfusion may deliver chemotherapy more efficiently rather than necessarily allowing better re-oxygenation as the authors postulate and suggest that they have further data to support.

3. The final issue relates to the tumour retention potential (TRP) wherein the authors suggest that this is an important parameter since it deals with low signal from necrotic regions of the tumour. Based on comparison of FDG and FMISO, there is no difficulty identifying necrotic regions of tumours. If one assumes that such necrotic regions are bordered by hypoxic cells, the ability to identify the presence and extent of hypoxia should not be compromised in the context of delayed static imaging. The authors should provide more justification for use of the TRP.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests