Reviewer's report

Title: Prognostic implication of intratumoral metabolic heterogeneity in invasive ductal breast cancer patients

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Reviewer: Dacian Bonta

Reviewer's report:

I am grateful to the authors for their submission. This article relates the tumor metabolic heterogeneity, as imaged by PET/CT, with the clinical behavior of these tumors. The statistical tool used are appropriate and the results obtained are reasonable under the circumstances described by the authors. Related to the submission, I have a number of concerns:

Major compulsory revisions:

• The derivative of the threshold function is not well defined in the abstract, or in the body of the paper. I urge the authors to reformulate it, precisely indicating what its component quantities mean, and what its units of measurements are. Also TLG is reported without units. Units should be clearly indicated. Also, because the function is defined as negative leads to the situation where lower values reflect more heterogeneity. (Discretionary revision: Would authors consider modifying the function to reflect the absolute change in volume with changing in glycolysis threshold? This way, values would be positive, and higher values would reflect higher tumor heterogeneity.)

• It is not clear to me how the 40% and the 80% values were reached. Could the authors present a detailed explanation?

• Due to limited PET resolution, PET would only be able to identify variations at a macroscopic scale. Therefore microscopic variability in tumor metabolism cannot be supported as an explanation/motivation for the findings. Authors need to focus on mechanisms of tumor heterogeneity that explain findings at the spatial scale of their observations.

• Second, macroscopic areas of tumor necrosis will increase the observed tumor metabolic heterogeneity. Necrotic tumors are biologically more aggressive. Do authors consider the possibility of the signal they identified simply reflecting necrosis in the tumor?

Minor concern:

Throughout the paper, authors report their quantities using 4 significant digits. 2 would suffice, in my opinion.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

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

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