Reviewer's report

Title: Tumor Cells With Low Proteasome Subunit Expression Predict Overall Survival in Head and Neck Cancer Patients

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Reviewer: Douglas R. Spitz

Reviewer's report:

Overall: The authors report interesting and potentially important results identifying a low proteasome expressing population in human head and neck cancers that appear to fit the profile of cancer stem cells and appear to be radioresistant and correlate with poor treatment outcome when found in primary tumors. Once the authors have satisfactorily responded to the following specific comments this work will represent a significant contribution to the literature.

Specific Comments:

1) The authors don’t clearly explain the biochemical/biological argument behind why low proteasome expressing cells may be representative of cancer stem cells and render them resistant to radiation, relative to the rest of the cancer cells in the population that have high proteasome activity. Is it because they have low metabolic levels of reactive species that damage proteins so they turn proteins over more slowly? Some comment on this should be added.

2) In the section on x-irradiation what was the potential applied to the x-ray tube and the filtration used to generate the beam.

3) How were spheres counted in each well when they were not attached?

4) When cells were injected into animals did they form metastasis?

5) In the patients were follow analysis by FDG-PET imaging accomplished? Was there any correlation between SUV by PET imaging and CSCs or relapse?

6) Does the accumulation of the fluorescent fusion protein in cells cause toxicity?

7) Table 1 contains rather small numbers of animals/group. Which values are statistically different from other values on this table?

8) It seems like the data with the patients that underwent successful resection is different than the ones without resection? Could the authors speculate why this is true?

9) The references many times are not following a standard format and some are missing volume numbers or have unnecessary information added to the reference. This is true for references 6, 7, 9, 27, 34 and maybe others. This needs to be checked carefully and corrected.

10) Figure 3 b is an awkward presentation. Why aren’t the low, intermediate, and high proteasome expressors with N values clearly labeled on the figure? This needs to be labeled more clearly.
Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

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

Declaration of competing interests:
I have no competing interests.