Reviewer’s report

Title: Sub-lethal radiation enhances anti-tumor immunotherapy in a transgenic mouse model of pancreatic cancer

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Reviewer: Dr Arthur Hurwitz

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after discretionary revisions

This is a well-written, well-controlled and interesting report. Using their RIP-TAg model, Cao et al demonstrate that despite the ineffectiveness of single treatment with sub-lethal irradiation or adoptive transfer of tumor antigen-specific CD4+ T cells, there is synergy with the combinatorial therapy. This is evident in reduced tumor incidence and size, as well as prolonged survival. The authors also demonstrate that the combination therapy induces more infiltration of CD4+, CD8+, and CD11c+ cells. There is ample discussion of the significance of these findings in light of previously-published reports as well as therapeutic potential. The following concerns are noted:

1. There is no indication of how the authors determine tumor incidence-size, histology, blood Glc?

2. There is mention in the text that "In the regression trial?activated splenocytes alone?" do not reduce tumor burden. However, the methods do not indicate pre-activation-this should be clarified as this is different from the figure legends.

3. The immunohistochemistry studies would benefit from quantification of the infiltrates. Also, in Fig 3, it is not clear from which group these sections were derived.

4. The authors mention that CD34 staining does not indicate any alteration in vessel structure, but they do not mention vessel density.

5. There is insufficient consideration of the changes of infiltrates in terms of CD8 cells and CD11c cells. The authors should discuss the change in CD11c+ cells after irradiation (alone) as well as the infiltration of CD8 cells in terms of potential specificity. Similarly, the authors should consider/mention the effect of transfer of normal, non-transgenic splenocytes. Finally, all of the infiltrates are presumably considered of donor origin, so what is the activation profile of CD4+ T cells after transfer?

Minor points:
How many mice per group are used in the survival study?
Find a better way to say ?significant lifespan extension??e.g., prolongs survival?
What is the frequency of TcR transgenic T cells in the splenocytes? Why was a Mann-Whitney test used? Does this consider standard deviation as in some cases, the error bars suggest lack of significance?

**Competing interests:**

None declared.