Reviewer’s report

Title: A 3D-microtissue-based phenotypic high content screen of chemotherapeutic drugs that overcome tumour resistance to radiation therapy

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Reviewer: David Yu

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Major Compulsory Revisions
1. Is there a reason why the spheroids treated with 2-8 Gy are whitened in the middle? The images appear saturated or photo bleached. Brightfield images for these spheroids would be helpful to clarify the nature of these whiter areas.

2. While the authors ruled out the synergistic inhibition effect of Docetaxel and radiation based on Supplementary Figure 3B, the data provided is not clear. Analysis of sensitization (or lack of) using more rigorous statistics would be helpful.

3. While the authors claim that presence of NHDF-GFP does not affect spheroid formation of T47D-RFP and MDA-MB-361-RFP (line 203-205), it seems that MDA-MB-361-RFP may be affected. This is evident when comparing spheroid formation of these cells as shown in Figure 2A for monotypic and Supplementary Figure 5B for heterotopic 3D-MT, which resembles MDA-MB-231 phenotype to some extent. In addition, if the assays quantitation is based on area, dispersed cell growth as seen for MDA-MB-231 and MDA-MB-361 may affect the data significantly.

4. As shown in Supplementary Figure 5, NHDF-GFP fibroblasts spheroid size is not consistent from sample to sample which is inconsistent with the authors' conclusion that growth is negligible (line 214-215). For example the size of NHDF-GFP in Supplementary Figure 5A appears different between 100nM Vinblastine and 100nM Doxorubicin treated samples. Quantitation should be provided.

Minor Essential Revisions:
1. There are some inconsistencies in the terminology used in the text of the manuscript, i.e. supplementary figure and additional file are used interchangeably through out the manuscript.

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

I declare that I have no competing interests