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## Linear Quadratics, Vascular Damage, Immunomodulatory Effects, and Other Radiobiological Hypotheses in Radiosurgery: a Conversation

### In Regard to Song et al



*To the Editor:* We read with interest the recent article by Song et al,<sup>1</sup> which proposes that the clinical effectiveness of stereotactic body radiation therapy (SBRT) is the result of indirect cell death caused by vascular damage arising from high single doses (>10 Gy) of radiation. We have several comments.

1. Vascular damage and reduced blood flow are not restricted to high single doses; they also occur after the

accumulated damage of fractionated irradiation, as demonstrated earlier by Song et al and others.<sup>2</sup> Thus, if indirect cell death occurs with high single doses, it also occurs with conventional fractionated irradiation; therefore, it is unlikely to be the primary mechanism underlying the enhanced efficacy of SBRT.

2. There are also publications that show no evidence for indirect cell death after high single doses to experimental tumors.<sup>3,4</sup>
3. Song et al<sup>1</sup> suggest that it would take doses that are too high to achieve the expected 8 logs of cell killing needed for tumor control. However, with their data of approximately 2.5 logs of cell kill by 20 Gy, the SBRT regimen of  $3 \times 20$  Gy would produce 7.5 logs of cell kill, and thus within the needed range of cell killing for tumor control.
4. The effective doses delivered with SBRT are huge, with biologically effective doses 2 to 3 times those of conventional fractionation. It seems self-evident that such doses would increase tumor control rates over those of conventional radiation therapy.
5. There is strong evidence in mouse models that tumor cells, rather than endothelial cells, are the critical targets of single-dose radiation therapy.<sup>5</sup>
6. The high local control rates of SBRT, at least for early-stage non-small cell lung cancer and brain metastases, are well predicted by the linear quadratic (LQ) model of cell killing, particularly if the known range of sensitivities of individual tumor cells is applied.<sup>6</sup> In fact, all the published clinical data to date support the simple LQ model with no additional terms,<sup>7-10</sup> strongly suggesting that any additional biologic effects are not the primary biologic mechanisms responsible for the impressive results of SBRT. Song et al<sup>1</sup> suggest that this agreement of the clinical data with the LQ model might be a coincidence. We think it more plausible that there is little or no additional cell kill at high doses over and above that which is predicted by the LQ model and conventional radiobiology.

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## In Reply to Brown and Carlson



*To the Editor:* We would like to thank Brown and Carlson for their comments<sup>1</sup> on our article. What follows are our responses to each of their comments.

1. Numerous reports show improved vascular function during conventionally fractionated radiation therapy.<sup>2</sup> The deterioration of tumor vasculature toward the end of or after fractionated radiation therapy might not be the cause of tumor cell death but a result of shrinkage of tumor mass.<sup>3</sup>
2. The number of surviving clonogenic cells in each tumor is determined from the number of tumor cells recovered and their plating efficiency in vitro. In the referenced studies,<sup>4,5</sup> the authors experienced considerable difficulties in determining the recoverable cell numbers, probably because the methods they used were crude, as

they stated. Nevertheless, the authors<sup>4,5</sup> observed that the cell death in tumors estimated from the tumor growth delay was 10-fold greater than that obtained by in vivo—in vitro excision assay; they concluded that indirect cell death occurred because of nutrient deficiency when tumors were left in situ after high-dose irradiation.

3. The cell survival decreased only by 1.5 logs, not 2.5 logs, when determined immediately after 20 Gy irradiation, and it decreased further to 2.5 logs in 2 days owing to additional and indirect cell death. If cell death is due only to direct effect, then  $3 \times 20$  Gy would produce only 4.5 logs, not 7.5 logs, of cell death.
4. Calculations of the biological equivalent doses are based on the assumption that the linear quadratic (LQ) model accurately predicts cell death by high dose per fraction irradiation. The high biological equivalent doses for stereotactic body radiation therapy and stereotactic radio-surgery may be due to the inherent flaw in the LQ model.<sup>6</sup>
5. The newly formed tumor vessels are composed not only of endothelial cells but also tumor cells, transdifferentiated mesenchymal progenitors, and myeloid cells. Furthermore, the vasculogenic mimicry and mosaic blood vessels composed of tumor cells are frequently found features in growing tumors.<sup>7,8</sup> Increasing the radiosensitivity of tumor cells would inevitably increase the radioresponse of tumor vascular networks.
6. The cell survival curve calculated with the LQ model continuously bends downward with increasing radiation dose, thereby leading to overestimation of cell killing at high radiation doses. Despite such an inherent flaw, the LQ model may appear to work for some clinical cases, because there is additional cell death at high-dose per fraction irradiation.<sup>6</sup>

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