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EDITORIAL

A Hypothesis: Indirect Cell Death in the Radiosurgery Era

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The smoldering debate regarding whether or not the linear quadratic model (LQ model) or any modified version thereof is applicable to high-dose single or hypofractionated radiation therapy has recently been rekindled by the remarkably high control rates observed in the modern era of stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT). Thus, we read with great interest the articles by Brown et al (1, 2) and subsequent comments by Rao et al (3). Brown et al concluded the following: (*1*) "new biology" is not needed to account for the clinical outcome of SBRT for non-small cell lung cancer (NSCLC) because the high rate of tumor control by SBRT can be explained by the high biologically effective dose (BED); (*2*) the LQ model is not perfect but remains the best available model to predict the observed findings; and (*3*) the data supporting the vascular effects of radiation are "fragmentary" (2, p 259). Rao et al (3) disagreed with the statistical methodology applied by Brown et al (1) for analyzing the relationship between the clinical results and BED.

We also disagree with applying the LQ model and BED concepts to SRS and SBRT. First, the LQ model and the modified LQ models are based on the assumption that radiation-induced cell death in tumors is due solely to DNA strand breaks. Both seminal and recent articles, however, strongly suggest that high dose/fraction (>10 Gy) radiation causes devascularization in tumors, which then induces delayed indirect tumor cell death. (4-9). A comprehensive review of this topic is beyond the scope of this forum, and readers are referred to previous reports on this subject (5-8). In brief, literature dating from 1947 (4) to the first volume of this journal in 1976 (5) and more recent studies (6-8) support the hypothesis that indirect tumor cell death from devascularization occurs after high-dose/fraction radiation, and thus it is reasonable to hypothesize that such indirect tumor cell death plays an important role in SRS and SBRT. The cellular α/β ratio in the LQ model is directly quantified by an in vitro survival curve, which simply does not account for vascular or immune responses. Therefore, we assert that applying the LQ model, which has been very useful and extensively used for conventionally fractionated radiation therapy, to high-dose/per fraction SRS and SBRT, is conceptually flawed. Second, we disagree that the literature supporting this mechanism is "fragmentary."

Our hypothesis is that indirect cell death due to vascular damage plays an important role in SRS and SBRT with high dose per fraction. This hypothesis is summarized graphically in Figure 1. The initial part of the survival curve at doses of 0 to 5 Gy (curve a) represents the death of fully oxygenated cells in tumors in which 10% of clonogenic cells are hypoxic. With the increase in radiation dose to greater than ~5 Gy, the survival curve becomes less steep,

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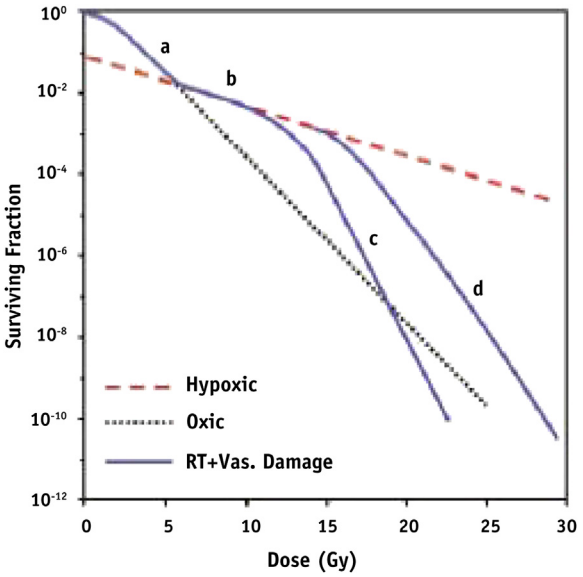

Fig. 1. Hypothetical model of cell survival by dose: 0 to 5 Gy correlates with death of well-oxygenated tumor (curve a); 6 to 10 Gy correlates with death of hypoxic tumor (curve b); doses of >10 Gy correlate with indirect delayed death of hypoxic cells by devascularization and possibly radiation-induced immune enhancement (curves c and d).

corresponding to the death of hypoxic cells (curve b). It is conceivable that as the radiation dose is increased further to ~12 Gy, indirect cell death (curve c) occurs by virtue of vascular damage. In the tumors in which vasculatures are radioresistant, indirect tumor cell death would occur starting at relatively higher doses (17 Gy) (curve d). It is of note that recent literature suggests that extensive tumor cell death accompanied by massive release of tumor-specific antigens may evoke tumor-specific immune response (10). This implies that the extensive indirect tumor cell death by SRS and SBRT may elicit significant immune reactions that may lead to further tumor cell death. Consequently, the indirect cell death, represented by curves c and d in Figure 1, may include not only the cell death caused by vascular damage but also the cell death caused by immune response resulting from the vascular damage.

To optimize the use of these powerful modalities (SRS and SBRT), much research on various biological aspects of these treatment regimens remains to be done. Some of the many intellectually provocative research questions and ideas stemming from this model include the following: (*1*) Can this model be independently confirmed, particularly in human tumors in vivo?; (*2*) Can the efficacy of SRS/SBRT be improved with hypoxic cell sensitizers and/or hypoxic cell cytotoxins?; (*3*) What is the effect of antiangiogenic and antivascular agents in conjunction with SRS/SBRT?; (*4*) Can the efficacy of SRS/SBRT be improved by immune stimulants or immune checkpoint inhibitors?; (*5*) Can SRS/SBRT produce an enhanced immune response, resulting in distant response (abscopal effect)? (10); (*6*) How will normal tissue tolerance be redefined with respect to acute and late toxicity from doses above the "devascularization threshold"?; (*7*) If the hypothetical model is applicable to normal tissue, how do we achieve a dose distribution in which the tumor is fully encompassed by the dose that exceeds the "devascularization threshold" while keeping most of the peritumoral normal tissue below this dose?; (*8*) Regarding SBRT hypofractionation, what are the optimal dose/fraction, total dose, and interval time between fractions?; (*9*) With respect to single-fraction SRS, which, if any, and to what extent, do the 5 Rs (Repair of sublethal damage, Repopulation of cells after radiation, Redistribution of cells within the cell cycle, Reoxygenation of the surviving cells, and intrinsic Radiosensitivity) explain the results seen with the single treatment, when one could argue there is no Re-anything?; (*10*) Which of these processes are most affected by fraction size?; (*11*) On the other hand, one could argue that SRS and SBRT are only rarely delivered as a continuous, single acute exposure because a dose of 20 Gy given in 20 minutes is not biologically equivalent to the same dose delivered in 2 hours. Although protracted exposure could be considered multiple fractions (thus allowing the theoretical possibility of repair of sublethal radiation damage), with newer technology, treatment times continue to decrease. Nonetheless, laboratory research and clinical trials should correlate delivery time with outcomes.; and (*12*) What will be the rate of, and predictive factors for, late injuries that are rare with conventional radiation but may become more common with SRS/SBRT, such as phrenic nerve paralysis and ventricular aneurysm? Tolerance for the doses used in SBRT depend on volume, fraction size, cumulative dose, and the nature of the specific types of normal cells exposed, not just a dose−volume histogram that presumes that the organ is homogeneous.

These issues are important, complicated, and acutely clinically relevant. Practicing radiation oncologists are now routinely confronted with related clinical dilemmas, such as the lung cancer patient with a centrally located tumor near radiosensitive tissues: which is better for the patient; 2 Gy × 30 fractions or 6 Gy × 5?

In closing, we agree that a "new biology" is not needed to model the high control rates of SBRT/SRS; however, it is not the LQ model but rather the indirect cell death by devascularization that may be the key mechanism in SRS/SBRT. As indicated above, it has been known for several decades that vascular damage by high-dose radiation results in indirect tumor cell death, and the literature supporting this phenomenon is not "fragmentary" but actually quite robust. The LQ model and the concept of BED have been critical to our understanding and safe delivery of conventional radiation therapy for decades. However, we have consistently underestimated the role of indirect cell death by devascularization and its possible role in radiation-induced immune enhancement. We, as a community, simply did not recognize the potential of this model until

advances in technology made SRS/SBRT doses clinically feasible. It is incumbent upon us to recognize it now and to direct future research as above that may pave the way to progress in patient care. If, on the other hand, we fail to recognize its potential, future research may be misdirected with loss of time, resources and possibly patient lives.

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