Rainer J. Klement, PhD
Department of Radiation Oncology
Leopoldina Hospital
Schweinfurt, Germany

Nicolaus Andratschke, PhD
Matthias Guckenberger, MD
Department of Radiation Oncology
University Hospital Zurich
University of Zurich
Zurich, Switzerland

https://doi.org/10.1016/j.ijrobp.2018.02.012

References

1. Ohri N, Tomé WA, Méndez Romero A, et al. Local control after stereotactic body radiation therapy for liver tumors. *Int J Radiat Oncol Biol Phys* 2021;110:188-195.
2. Ohri N, Jackson A, Mendez Romero A, et al. Local control following stereotactic body radiotherapy for liver tumors: A preliminary report of the AAPM Working Group for SBRT. *Int J Radiat Oncol Biol Phys* 2014;90:S52.
3. Klement RJ. Radiobiological parameters of liver and lung metastases derived from tumor control data of 3719 metastases. *Radiother Oncol* 2017;123:218-226.
4. Guckenberger M, Klement RJ, Allgäuer M, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. *Radiother Oncol* 2013;109:13-20.
5. Shuryak I, Carlson DJ, Brown JM, et al. High-dose and fractionation effects in stereotactic radiation therapy: Analysis of tumor control data from 2965 patients. *Radiother Oncol* 2015;115:327-334.
6. Klement RJ, Guckenberger M, Alheid H, et al. Stereotactic body radiotherapy for oligo-metastatic liver disease—influence of pre-treatment chemotherapy and histology on local tumor control. *Radiother Oncol* 2017;123:227-233.
7. Cameron E. On the estimation of confidence intervals for binomial population proportions in astronomy: The simplicity and superiority of the Bayesian approach. *Publ Astron Soc Aust* 2011;28:128-139.

In Reply to Klement et al

To the Editor: We would like to thank to Klement et al for their interest[1] in our recent analysis of local control rates after stereotactic body radiation therapy (SBRT) for liver tumors[2] and are grateful for their thoughtful comments regarding this work. We would like to address their points in order, as follows.

First, we acknowledge that there was a long gap from when we conducted our systematic review until our analysis was published. This is an unfortunate consequence of working in a multinational and multidisciplinary working group, with the intent of publishing multiple manuscripts in a coordinated fashion. We look forward to updating our analysis in the near future.

Conflict of interest: none.

Second, we are aware of the debate regarding the validity of the linear-quadratic model for comparing biologically effective doses (BEDs) of SBRT schedules. In the in vitro setting, we have found that alternate models are better suited to characterize dose−response curves.[3] However, the linear-quadratic model seems to be effective in predicting clinical outcomes after SBRT.[4] In the range of fraction sizes included in our analysis, BEDs calculated using a "standard" α/β value of 10 Gy are highly correlated with BEDs calculated using the highest suggested α/β value of 28 Gy (linear regression $R^2 = 0.99$). Our conclusions would therefore not be changed by using a higher α/β value.

Third, we congratulate the German Society of Radiation Oncology for compiling and analyzing a large multi-institutional dataset of patients treated with SBRT for liver metastases. Using patient-level data, this group has already demonstrated that tumor size, histology, and treatment technique influence tumor control rates after SBRT.[5] As we acknowledge in our article, these and other important factors cannot be assessed using available study-level data.

Last, we agree that a BED cutoff of 100 Gy may not be clinically relevant for all tumor types, and tumor control probability curves are likely sigmoidal in shape and do not follow a step function. As mentioned in our publication, we explored BED cutoffs ranging from 60 to 180 Gy and still found no evidence that higher BEDs were associated with improved tumor control after SBRT for primary liver tumors. This could be related to factors such as tumor size and prior liver-directed therapy that could not be incorporated into our analysis using study-level data. The Bayesian logistic dose−response model presented by Klement et al yields predicted control rates of at least 85% across the entire range of BEDs used to treat primary liver tumors, which is consistent with our finding that there was no statistically significant association between BED and tumor control probability in the currently published data.

Nitin Ohri, MD
Wolfgang A. Tomé, PhD
Department of Radiation Oncology
Montefiore Medical Center and Albert Einstein College of Medicine
Bronx, New York

Alejandra Méndez Romero, MD
Department of Radiation Oncology
Erasmus MC Cancer Institute
Rotterdam, The Netherlands

Moyed Miften, PhD
Department of Radiation Oncology
University of Colorado School of Medicine
Aurora, Colorado

Randall K. Ten Haken, PhD
Department of Radiation Oncology
University of Michigan
Ann Arbor, Michigan

Laura Dawson, MD
Department of Radiation Oncology
Princess Margaret Hospital
Toronto, Ontario, Canada

Jimm Grimm, PhD
Department of Radiation Oncology and
Molecular Radiation Sciences
Johns Hopkins University
Baltimore, Maryland

Ellen Yorke, PhD
Andrew Jackson, PhD
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

https://doi.org/10.1016/j.ijrobp.2018.02.013

References

1. Klement RJ, Andratschke N, Guckenberger M. In regard to Ohri et al. *Int J Radiat Oncol Biol Phys* 2021;110:249-250.
2. Ohri N, Tomé WA, Méndez Romero A, et al. Local control after stereotactic body radiation therapy for liver tumors. *Int J Radiat Oncol Biol Phys* 2021;110:188-195.
3. Ohri N, Dicker AP, Lawrence YR. Can drugs enhance hypofractionated radiotherapy? A novel method of modeling radiosensitization using in vitro data. *Int J Radiat Oncol Biol Phys* 2012;83:385-393.
4. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: Updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94.
5. Klement R, Guckenberger M, Alheid H, et al. Stereotactic body radiotherapy for oligo-metastatic liver disease—influence of pretreatment chemotherapy and histology on local tumor control. *Radiother Oncol* 2017;123:227-233.

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,[1] 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 aland others.[2] 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.[3,4]

3. Song et al[1] 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 × 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.[5]

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.[6] In fact, all the published clinical data to date support the simple LQ model with no additional terms,[7-10] strongly suggesting that any additional biologic effects are not the primary biologic mechanisms responsible for the impressive results of SBRT. Song et al[1] 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.

J. Martin Brown, PhD, FASTRO
Department of Neurology
Stanford University School of Medicine
Stanford, California

David J. Carlson, PhD
Department of Radiation Oncology
University of Pennsylvania
Philadelphia, Pennsylvania

https://doi.org/10.1016/j.ijrobp.2020.06.075