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COMMENTS

Local Control Following Stereotactic Body Radiation Therapy for Liver Tumors

In Regard to Ohri et al

We would like to comment on the article "Local control following stereotactic body radiation therapy for liver tumors" by Ohri et al,[1] in which the authors provide optimal dosing schedules based on their finding of no dose–response relation between biologically effective dose (BED) and local control for primary liver tumors, but only for liver metastases which they investigated further using a logistic tumor control probability model.

First, the article, which was submitted in November 2017, reports the same results as a "preliminary analysis" abstract from 2014[2] and did not include newer data. Since then the field of liver stereotactic body radiation therapy (SBRT) and available clinical outcome data have evolved rapidly. For example, Klement[3] was able to extract 1041 individual metastases data from studies published until October 2016 using the same method as Ohri et al, which is a 259% increase in sample size compared with their 290 data points.

Second, the authors calculated BED using the linear-quadratic model and cited 2 references from 1989 and 2006 to justify their choice of $\alpha/\beta = 10$ Gy. However, no mention was made of the recent debate about the validity of the linear-quadratic model for SBRT[4,5] or indications that α/β is probably higher than the usually assumed 10 Gy in SBRT for liver metastases.[3]

Third, the authors were not able to analyze metastasis histology and tumor size as possible factors influencing local control, and they call for improved reporting of such factors to better understand their influence. We previously conducted a detailed study of these factors in the currently largest cohort of SBRT-treated liver metastases, arguing that the worse response of colorectal metastases could likely be confounded by usual administration of pre-SBRT chemotherapy.[6]

Last, the approach to compare 2 Kaplan-Meier curves dichotomized by a BED threshold is suboptimal to determine evidence for or against a dose–response relationship. As an alternative, we compared a Bayesian logistic dose–response model with an intercept-only model assuming constant treatment effects with no dependence on biologically effective dose (Supplementary Material [available online at https://doi.org/10.1016/j.ijrobp.2018.02.012] and Fig. 1). Both models naturally account for the sample size–dependent uncertainties associated with the individual study tumor control probability estimates. The logistic regression model resulted in a substantially better fit to the primary liver tumor data as judged by the deviance information criterion, thus providing evidence for a dose-response relation.

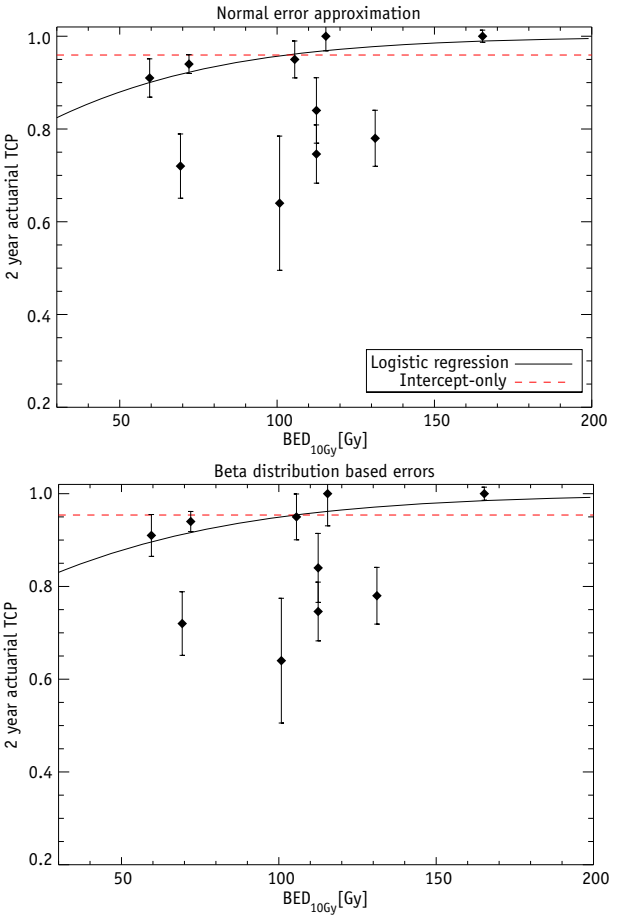

Fig. 1. Dose–response relationship of a logistic regression and a constant-intercept model fitted to the primary liver tumor data. The top and bottom panels differ in the way errors have been estimated.[7]

Conflict of interest: none.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2018.02.012.

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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.

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