Letter regarding Meade et al. entitled “Models of acute mucosal tolerance to radiotherapy alone applied to synchronous chemo-radiation schedules in head and neck cancer”

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To the Editor,

We read with interest a recent article in *Tumor Biology* [1], in which Meade et al. helpfully compared the mucosal tolerability of several concurrent chemo-radiation schedules used to treat head-and-neck squamous cell carcinoma (HNSCC) with the predictions of three tolerance models developed for radiation-only schedules [2–4]. Meade et al. added estimates of the radiation-equivalent biologically effective doses for cell kill contributed by the chemotherapy components of the various schedules ($BED_{ck-chemo}$) to the BEDs contributed by radiation alone (BED_{ck-RT}), thereby generating total BED values (BED_{ck-tot}) which were compared with duration-specific tolerance ceilings specified by the three models. The study concluded that this BED-summation approach was useful but that the tolerance ceilings may need further adjustment in the chemo-radiation setting and noted that an accelerated schedule used in the RTOG 0129 study [5] was predicted to be intolerable by all three models, despite current indications that it may be tolerable.

We were a little surprised that our tolerance ceiling model (denoted by Meade et al. as $F_{en}BED_{ck}$) did not correctly predict the tolerance of the accelerated RTOG 0129 schedule, since we had fitted the model to a large radiation-only dataset using discriminant analysis [2], and Meade and colleagues very carefully obtained a BED_{ck-tot} value for the delivered schedule, by adding to its radiation-only BED_{ck-RT} dose a $BED_{ck-chemo}$ value of 2.9 Gy₁₀ individually estimated for the chemotherapy regimen used in the schedule.

In this context two observations should be made about our model. Firstly, it is most simply written as

$$F_{en} BED_{ck}(T) = 2.158 \times T / \sin(T/32.2) - 3.5 Gy_{10} \quad (1)$$

for $T \leq 50$ days

in which the sine function argument is specified in radians, and T is defined as the total radiotherapy duration including both the first and last days of treatment [2], which is 1 day longer than the definition of duration used in the other two tolerance models [3, 4] and by Meade et al. [1]. Therefore, schedule durations tabulated by Meade et al. should be increased by 1 day before being used in equation (1). Making this correction for the accelerated RTOG 0129 schedule raises its $F_{en}BED_{ck}$ ceiling to 87.7 Gy₁₀ which lies slightly above the schedule's BED_{ck-tot} value of 87.3 Gy₁₀ (Table 4 of reference [1]), meaning that the model in fact classifies the schedule as lying just *within* tolerance.

Secondly, our model is supported by tolerance data *only up to schedule durations of 50 days* (Figs. 1–5 of reference [2]); consequently, the tolerance boundary was defined only up to 50 days duration in Eq. (10) of our article. Meade and colleagues note that beyond this duration, the boundary might rise rapidly as $2.158 \times T - 3.5 Gy_{10}$. While this speculative extension is supported by theoretical considerations, fits to animal data, and observations of mucosal healing towards the end of long radiotherapy schedules [6–8], it is not yet supported by clinical determinations of tolerability. Therefore, it should be viewed as hypothesis-generating at best, rather than as a firm indication of tolerability beyond 50 days duration. Thus, the ceilings obtained by Meade et al. for durations of 52 and 58 days using the extended model should be viewed with considerable caution.

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Meade and colleagues noted further that a planned chemo-radiation schedule described by Bensadoun et al. [9] required lengthening when used clinically and thus might be considered intolerable. Delivery of 90.0 Gy₁₀ BED_{ck-RT} over 46 days was planned, to which Meade et al. added a generic BED_{ck-chemo} value of 5.1 Gy₁₀ to obtain a BED_{ck-tot} of 95.1 Gy₁₀. Since this lies below the $F_{\text{en}}\text{BED}_{\text{ck}}$ ceiling of 96.8 Gy₁₀ for 46 days duration, it was concluded that the model misclassifies the schedule as being tolerable. However, Meade et al. subsequently estimated a specific BED_{ck-chemo} value of 11.7 Gy for the chemotherapy regimen used in this schedule, and adding this to the schedule's 90.0 Gy₁₀ BED_{ck-RT} dose leads to a total BED_{ck-tot} of 101.7 Gy, which lies above the ceiling defined by our model, correctly classifying the schedule as intolerable.

In summary, Meade and colleagues have conducted important new work analyzing the mucosal tolerability of HNSCC chemoradiotherapy schedules. Tolerability depends on treatment duration and BED_{ck-RT} and BED_{ck-chemo} doses, the use of biological response modifiers such as cetuximab, and probably also the spatial and temporal patterns of dose deposition [2, 10, 11], and therefore its prediction is challenging. Consequently it is vital in such work that existing tolerability models are used precisely as they are defined, and only over the range of durations for which data support them, both to maximize the accuracy of predictive outcomes modelling and to allow significant differences between modelled and actual outcomes to be definitively attributed to effects not already included within the existing models.

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Conflicts of interest None

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