

EDITORIAL

FRACTIONATION AND LATE RECTAL TOXICITY

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Late rectal bleeding is well established as a key dose-limiting end point in prostate radiotherapy (1–6) and is an important consideration in cervical cancer radiotherapy (7–9). Consequently, much effort has been devoted to establishing dose–response relations for rectal bleeding (1–8). Clinically, however, little has been directly established about the response of this end point to changes in fractionation (as quantified, for example, by the α/β ratio [8]), though there have been increasing suggestions in the literature that at least part of the late rectal response is a “consequential” late effect, directly correlated with early rectal damage (10–12). If this is the case, one might expect that the response of this end point to changes in fractionation might be intermediate between a classic late effect (typical α/β value: 1 to 3 Gy) and a classic early response (typical α/β value: 8 to 10 Gy); indeed, the α/β ratios estimated for late rectal damage in rodents do seem to be in this intermediate range (13–19).

So new clinical data on the response of late rectal damage to changes in fractionation are of interest, both from a mechanistic standpoint and also because there has been much recent interest in hypofractionated prostate radiotherapy (20, 21). Akimoto *et al.* (22) report in this issue on late rectal bleeding after hypofractionated radiotherapy of the prostate, in which they delivered 69 Gy in 3 Gy fractions, using three-dimensional conformal radiotherapy (3D-CRT) without rectal blocking or explicit dose–volume histogram (DVH) based criteria. Akimoto *et al.* (22) report a late Radiation Therapy Oncology Group (RTOG) Grade 2 complication rate of 25% (mean follow-up, 31 months), virtually identical to that reported by the M.D. Anderson Cancer Center (5) using a 3D-CRT dose of 78 Gy delivered in conventional 2 Gy fractions. Akimoto *et al.* (22) report also, as have others (2, 23, 24), that diabetes is a highly significant predictor of late rectal sequelae.

As well as being of interest in their own right, these new hypofractionation data allow, for the first time, a quantitative estimate of the α/β ratio for late rectal bleeding, quantifying how rectal bleeding risks would be expected to change with changes in fractionation. This is possible be-

cause there is already a considerable amount of data in the literature on late rectal bleeding after conventionally fractionated (1.8 or 2 Gy fractions) radiotherapy delivered with a similar technique to that of Akimoto *et al.* (22) (i.e., 3D-CRT without rectal blocking or use of explicit DVH criteria). Because of the uniformity in fraction size among these earlier data, it has not been possible to make a quantitative estimate of the α/β ratio (i.e., the sensitivity to changes in fraction size). With the new 3 Gy fraction data, however, it is now possible to globally analyze the 1.8 Gy, 2 Gy, and 3 Gy per fraction data using the standard linear-quadratic model to generate an estimate of the α/β ratio for late rectal bleeding.

There are many reports in the literature of late genitourinary sequelae risks after 3D-CRT with conventional fractionation (2–5, 25–28); we chose to analyze the 3 largest series in the United States: from the M.D. Anderson Cancer Center (MDACC) (5), from Memorial Sloan-Kettering Cancer Center (MSKCC) (2), and from RTOG protocol 9406 (4), each of which used an approach to treatment planning similar to that of Akimoto *et al.* (22). The highest dose points in the MSKCC and RTOG studies (81 and 79 Gy respectively) were excluded, because rectal blocks or DVH-based treatment planning was used (2, 3). We also excluded the corresponding Fox Chase Cancer Center series, because almost all of their 3D-CRT patients were treated using rectal blocks (25). We excluded all French, British, and Australian studies (26–29), because the diabetes prevalence in those countries is dramatically different from that in both the United States and Japan (Estimated year 2000 prevalences above age 20 in the United States, Japan, the United Kingdom, France, and Australia are, respectively, 6.9%, 7.6%, 2.1%, 2.1%, and 2.7% [30]).

Thus the new Japanese data, together with the MDACC, MSKCC, and RTOG data, were fitted to the standard linear-quadratic formalism for normal-tissue complications in which the probability of RTOG grade ≥ 2 late rectal toxicity, $P_{\text{RTOG}2}$, is written in terms of K , the number of tissue-rescuing units (31), and their survival, S , after a dose D delivered in N fractions (18):

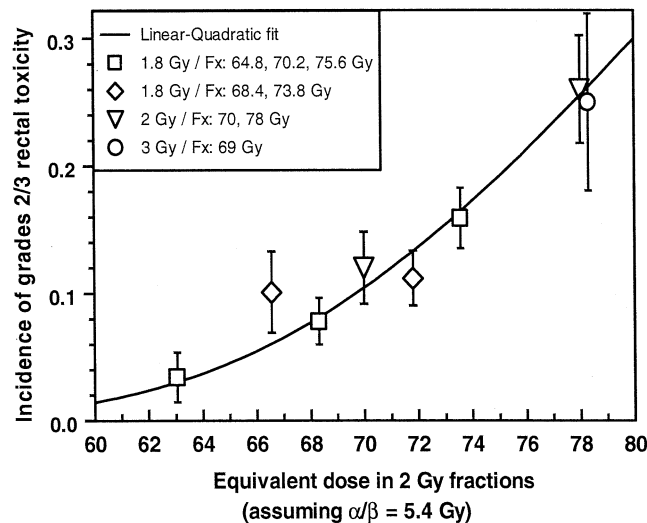


Fig. 1. Incidence of RTOG grade ≥ 2 late rectal toxicity as a function of equivalent total dose if delivered in 2 Gy fractions (doses converted using $\alpha/\beta = 5.4$ Gy). Curve represents the linear-quadratic model fit. Data points all used 3D-CRT with no rectal block or DVH-based treatment planning criteria (open square, from MSKCC, 1.8 Gy/fraction (2); diamond, from RTOG protocol 9406, 1.8 Gy/fraction (4); open triangle, from MDACC, 2 Gy/fraction (5); open circle, from Akimoto *et al.* (22), 3 Gy/fraction).

$$P_{RTOG2} = \exp(-K S)$$

where $S = \exp(-\alpha D - \beta D^2)/N$.

Data fitting used standard iteratively reweighted least squares (32), with parameter confidence limits estimated using synthetic data simulation (33). The estimated value of α/β value for RTOG grade ≥ 2 late rectal toxicity is 5.4 ± 1.5 Gy. Figure 1 shows the data and the model fit, in which all the doses have been “converted” to equivalent 2 Gy fractionated doses, using the 5.4 Gy α/β value.

This α/β estimate—which can also be roughly estimated with a “back-of-the envelope” calculation based on the equivalent rectal toxicity of 69 Gy in 3 Gy fractions (22) to 78 Gy in 2 Gy fractions (5)—is indeed intermediate between typical values for early- and late-responding tissues,

giving credence to the notion that at least some late rectal damage is a direct consequence of early-responding damage (10–12). The 5.4 Gy α/β value is also consistent with most estimates for late rectal damage in rodents (13–19).

As well as being of interest from a mechanistic standpoint, the α/β estimate allows us to predict, with more confidence, the risks of late genitourinary complications for alternate fractionation schemes. For example, the estimated 5.4 ± 1.5 Gy α/β value for late rectal damage may well be higher than that for most prostate cancers (where α/β estimates have generally been in the range from 1 to 3.5 Gy [29, 34–41]). This suggests that hypofractionation at the appropriate dose, besides providing logistical convenience, could improve the therapeutic outcome of prostate cancer radiotherapy.

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