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Editorial

The Linear–Quadratic Model and Implications for Fractionation

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For any new clinician practising radiotherapy, the diverse array of dose-fractionation regimens in routine clinical usage can seem bewildering. Understanding the clinical and laboratory rationale behind these schedules is an essential part of training, allowing personal practice to be grounded upon the many successes, and of course setbacks, of the last century.

Recognition of Fractionation Utility

Even 100 years ago clinicians recognised that by fractionating a course of radiotherapy a higher total dose could be delivered while remaining tolerable to the patient [1]. However, without robust clinical trial methodology and dosimetry, early regimens were generally devised by trial and error. This resulted in rich *in vivo* human datasets for commonly treated tumours: data unreproducible nowadays due to obvious ethical barriers. Leveraging this data, Strandqvist [2] was the first to note that responses of skin tumour control and skin toxicity (erythema) both followed a power law, related to the overall treatment time (with commensurate fraction size changes). Similar 'isoeffect' plots showing differential fraction size sensitivity were subsequently derived for several acute and late tissue reactions, with late effects showing steeper responses to changes in fraction size (Figure 1A) [3].

Cell Survival Assays and the Linear–Quadratic Model

A cellular basis for these *in vivo* observations is suggested through experiments irradiating cultured tumour cells *in vitro* with single fractions of X-rays: an increasing dose results in an exponential decrease in the viable cell proportion. On a semi-log plot, a curve with both linear and quadratic components fits the data well (Figure 1B) [4]:

$$\textit{Viable proportion of cells} = e^{-(\alpha \cdot d + \beta \cdot d^2)}$$

where:

α = linear term constant (Gy^{-1})
β = quadratic term constant (Gy^{-1})
d = dose of the fraction (Gy)

From this equation is derived the α/β ratio, a term allowing a description of the sensitivity of tissues to radiotherapy fraction size (Figure 1A). Most tumours, such as head and neck squamous cell carcinoma (HNSCC), exhibit high α/β ratios (e.g. α/β = 10 Gy is commonly used), indicating a lower sensitivity to fraction size [5]. In a similar manner, early (acute) normal tissue reactions (e.g. epithelial desquamation [6]) can also be described by high α/β ratios (Figure 1A: shallower isoeffect lines).

Some tumours now have strong evidence of a lower α/β ratio. A recent meta-analysis of eight prostate adenocarcinoma hypofractionation trials suggested an α/β ratio as low as 1.2 Gy [7]. For breast adenocarcinoma, a similar meta-analysis suggested an α/β ratio as low as 2.88 Gy [8]. Late toxicity reactions also exhibit generally lower α/β ratios, e.g. late rectal α/β ratio = 3–4.6 Gy [9,10] (Figure 1A: steeper isoeffect lines).

The underlying molecular mechanisms are worth consideration, but beyond the scope of this editorial [11].

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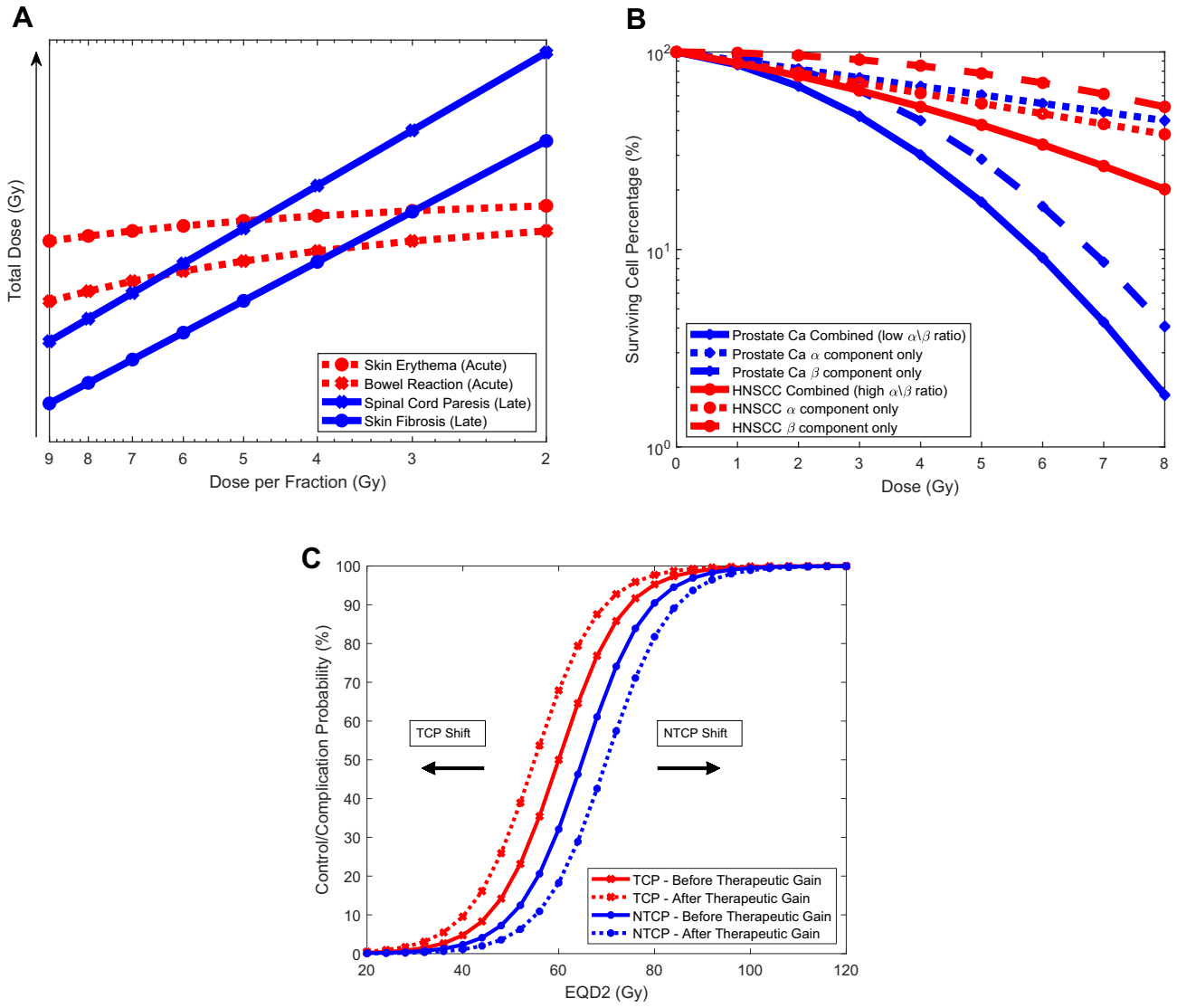

Fig 1. (A) Simulated isoeffect curves for early and late reactions showing the change in total dose required to produce the same clinical response (i.e. isoeffective) at differing doses per fraction. It can be noted that the late reactions, which have lower α/β ratios, have steeper curves than the acute reactions, which have higher α/β ratios. Adapted from data in Withers *et al.* [3]. (B) Cell survival curves demonstrating the linear–quadratic model. Simulated cell survival curves for single fraction radiotherapy to prostate cancer and head and neck squamous cell carcinoma (HNSCC). The separate α and β cell kill components are seen, together with their combination in the solid lines. Note the greater cell kill in response to increasing dose in prostate cancer, which has a lower α/β ratio. Values to produce the figure were prostate cancer $\alpha = 0.1$ Gy^{-1} $\beta = 0.05$ Gy^{-1}; HNSCC $\alpha = 0.12$ Gy^{-1} $\beta = 0.01$ Gy^{-1} [5]. (C) Tumour control probability (TCP) and normal tissue complication probability (NTCP) curves before (solid lines) and after (dashed lines) an intervention providing therapeutic gain. For an isoeffective EQD2 (maintaining the same TCP), a lower NTCP can be achieved. Alternatively, an isotoxic regimen (same NTCP) can provide a greater TCP. Increased heterogeneity of tumours or normal tissue will result in shallower curves.

Use of Models in Dose-Fractionation Regimen Comparison

In 1989, Fowler [12] proposed the biologically effective dose (BED), formulated from the linear–quadratic model, to compare dose-fractionation regimens [13].

$$BED = n \cdot d \cdot \frac{1+d}{\alpha/\beta} - K \cdot (T - T_k)$$

where:

n = total number of fractions
T = time of delivery (days)
T_k = kick-off day for repopulation (days)
K = daily BED equivalent repopulation (Gy.days^{-1})[1]

[1] The derivation of K is as follows:
$K = 0.693/(\alpha \cdot T_p)$
where T_p (effective doubling time) is derived from potential doubling time (T_{pot}) and the cell loss factor (φ):
$T_p = T_{pot}/(1 - \varphi)$

For faster repopulating tumours (e.g. HNSCC), changes in overall treatment time need to be considered (see Wither's famous dog-leg [14]), but for slower populating tumours, the right-side terms are commonly omitted in clinical practice. When deriving the α/β ratio from trial data, inclusion of a time factor term will alter the α/β ratio estimate. For example, in prostate adenocarcinoma, inclusion of a time factor in the meta-analysis cited above yielded a higher α/β ratio estimate of 2.7 Gy [7].

An alternative formulation is the equivalent dose in 2 Gy fractions (EQD2), which allows the comparison of dose-fractionation regimens to familiar 2 Gy per fraction schedules

$$EQD2 = n \cdot d \cdot \frac{\left(d + \frac{\alpha}{\beta}\right)}{\left(2 + \frac{\alpha}{\beta}\right)}$$

Terms for the effect of time on the EQD2 formulation exist [11], but are omitted for simplicity.

It is important to be very clear whether BED or EQD2 is used, as the units are not directly comparable (conversion is straightforward if the original α/β ratio is known [15]).

The Therapeutic Ratio and Dose Fractionation

In approaching rationale treatment schedule design, it is helpful to first consider the concepts of tumour control probability (TCP), the likelihood of achieving local control and the normal tissue complication probability (NTCP), which differs for each toxicity end point. In radical plans, disease control is of primary importance, so tumour BED must be sufficient to achieve a clinically acceptable TCP. The therapeutic ratio describes the ratio of TCP:NTCP, which may be better or worse depending on the relative curve positions and steepness (Figure 1C gives a therapeutic gain example). Rationally designing dose-fractionation schedules to maximise the therapeutic ratio is desirable.

From a dose-fractionation perspective, these goals may be achieved by alterations to the total physical dose, fraction size and the total duration of treatment schedule. It is important to note that many other radiotherapy innovations also aim to increase the therapeutic ratio, e.g. radiosensitisers, highly conformal planning and motion management.

Hyperfractionation

Hyperfractionation describes radiotherapy delivery at less than 1.8 Gy per fraction. If the tumour α/β ratio exceeds late toxicity α/β ratios, then the therapeutic ratio may be widened by hyperfractionation. This may offer reduced normal tissue BED at a fixed tumour BED (isoeffective) or increased tumour BED at a fixed late normal BED (isotoxic).

Because of concerns over tumour repopulation and arduous regimen durations, hyperfractionated regimens have commonly been delivered at more than one fraction per day (issues discussed in *Acceleration* below). For a purer example of hyperfractionation, EORTC 22791 showed improved local control, while maintaining late isotoxicity with a hyperfractionated, non-accelerated regimen for HNSCC (70 Gy/35–40 fractions/7–8 weeks/1 fraction per day versus 80.5 Gy/70 fractions/7 weeks/2 fractions per day) [16].

Hypofractionation

Hypofractionation describes the administration of radiotherapy at more than 2.0 Gy per fraction. It is common to subdivide hypofractionation into moderate (>2.0–5.0 Gy per fraction) and extreme/profound (≥5.0 Gy per fraction) [17,18]. If late normal tissue effect α/β ratios exceed the tumour α/β ratio, hypofractionation widens the therapeutic ratio, providing lower late toxicity at a constant tumour BED. More profoundly, hypofractionated regimens may induce novel cell kill mechanisms, such as tumour vascular disruption or increased anti-tumour immune reactivity [19], although dose escalation alone might be explanatory [20].

Hypofractionation requires fewer patient exposures, reducing overall healthcare costs, and is often combined with an accelerated (compressed) treatment schedule. Hypofractionation without acceleration was undertaken in the three-armed START-A adjuvant breast radiotherapy hypofractionation trial (50 Gy/25 fractions/5 weeks versus 41.6 Gy or 39 Gy/13 fractions/5 weeks), designed to estimate breast cancer and normal tissue α/β ratios, without confounding influence from treatment time changes [21]. This informed the START-B trial, which improved the therapeutic ratio: 40.05 Gy/15 fractions/3 weeks non-inferior for local control, better for late side-effects, versus 50 Gy/25 fractions/5 weeks.

Acceleration

Accelerated radiotherapy regimens have a shorter overall treatment time than the reference regimen; a beneficial feature for patients. These are particularly attractive in tumours where a dose regimen's duration reaches the tumour accelerated repopulation phase, e.g. traditionally at day 28 in HNSCC [14]. Drawbacks include: worsened acute toxicity, logistical difficulties of multiple daily exposures and the possibility of increased consequential late effects [22] arising from excess acute toxicity.

Many accelerated regimens are complicated by simultaneous changes to the fractionation. The Danish Head and Neck Cancer Group (DAHANCA) 6/7 trials provided a pure investigation of the effect of acceleration in HNSCC, randomising patients between the standard five fractions per

week versus six fractions per week [23]. The total dose and fractionation were unchanged. A statistically significant improvement in locoregional control (60% versus 70%, $P < 0.001$) was seen. Acute toxicity was significantly worse, but late toxicity comparable, unsurprising given the faster schedule but preserved total dose.

The Continuous, Hyperfractionated, Accelerated Radiotherapy (CHART) trial for locally advanced HNSCC randomised patients between conventional (66 Gy/33 fractions/6.5 weeks/daily) versus CHART (54 Gy/36 fractions/12 days/3 fractions per day). Statistically similar rates of long-term local control were seen [24]. If acceleration allows lower total dose, then lower late toxicity is anticipated. However, failure to allow sufficient time between same-day fractions for normal tissue repair may increase late toxicity. For a 6 h fraction gap, a repair half-life of 1.2 h or less is needed for 95% interfractional repair. Late toxicity with CHART showed less improvement than predicted, suggesting incomplete interfraction repair, with repair half-lives for some late effects estimated to be as high as 4.9 h [25].

Conclusions

The linear–quadratic model continues to find direct clinical application. Large ongoing randomised controlled trials continue to evaluate advances in dose fractionation. Examples are the PACE (NCT01584258) and FAST-FORWARD (ISRCTN19906132) trials examining the role of profoundly hypofractionated, accelerated radiotherapy for, respectively, localised prostate cancer and adjuvant breast treatment.

Conflicts of Interest

The authors declare no conflicts of interest.

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