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**Closed-form elasticity and elementary-effect sensitivity analysis of the
universal survival curve model for stereotactic radiotherapy fractionation**

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Abstract

Purpose The universal survival curve (USC) joins the linear-quadratic (LQ) description of the shoulder region to the log-linear multi-target asymptote at a transition dose, and is increasingly invoked to justify ablative fractionation. Which of its inputs actually controls predicted survival has not been established analytically. We derive closed-form elasticities for the USC, rank its inputs by two independent methods, and quantify the consequences for stereotactic schedules. **Methods** Continuity of value and gradient at the transition dose fixes the quadratic coefficient and the transition dose in terms of the radiosensitivity coefficient, the mean inactivation dose and the quasi-threshold dose. Dimensionless elasticities were derived in closed form and verified against central differences, and inputs were ranked independently by Morris elementary-effect screening over a fifteen per cent envelope. Biologically effective doses were compared between the two formulations for six clinical schedules and nine non-small-cell lung cancer cell lines. **Results** Dose dominated, with mean absolute elasticity 7.89, followed by the mean inactivation dose 6.64, the quasi-threshold dose 1.15 and the radiosensitivity coefficient 0.104. Morris screening reproduced this ordering. The two descriptions agreed for conventional fractionation but diverged sharply above the transition dose, the LQ formulation overstating biologically effective dose by 42 per cent for 54 Gy in three fractions and by 97 per cent for a single 30 Gy fraction. **Conclusion** Predicted survival is governed by delivered dose and the characteristic dose rather than by the radiosensitivity coefficient, so parameter-estimation effort should target the terminal slope of the survival curve.

Keywords Universal survival curve · Elasticity analysis · Morris elementary effects · Stereotactic body radiotherapy · Biologically effective dose · Linear-quadratic model

Introduction

Radiotherapy remains one of the principal curative modalities in oncology, and the quantitative link between physical dose and clonogenic cell survival underpins every decision about how that dose is fractionated. For half a century the linear-quadratic (LQ) formalism has provided that link [2, 13, 14]. Its two coefficients describe irreparable and repairable damage respectively, it is analytically tractable, and it reproduces the shouldered survival curves measured in clonogenic assays over the range of doses used in conventional fractionation.

The clinical adoption of stereotactic body radiotherapy has moved routine practice well outside that range. Schedules delivering 12 to 30 Gy in a single fraction are now standard for early-stage non-small-cell lung cancer [10-12], and at such doses the quadratic term of the LQ model causes the predicted survival curve to bend continuously downwards, whereas measured curves become log-linear once the repair capacity of the cell is saturated [4, 9]. Whether the LQ model may legitimately be extrapolated into the ablative regime has therefore been debated at length [3, 4, 8].

Several modifications have been proposed. The generalised LQ model of Wang and co-workers incorporates repair kinetics explicitly [7]; the linear-quadratic-linear construction of Astrahan appends a terminal straight segment [6]; the modified LQ model of Guerrero and Li interpolates towards the multi-target asymptote [5, 23]. The universal survival curve (USC) of Park and co-workers takes the most direct route: it retains the LQ expression below a transition dose and switches to the log-linear multi-target asymptote above it, requiring the two branches to meet smoothly [1]. The model is attractive because it is continuous in both value and gradient, requires no parameters beyond those already reported in clonogenic studies, and reduces to the LQ model at conventional dose per fraction.

That convenience conceals a question that has not been answered analytically. The USC is driven by three cell-line parameters together with the delivered dose, and these are not known with equal confidence: the radiosensitivity coefficient is routinely quoted, whereas the mean inactivation dose and the quasi-threshold dose are derived from the terminal slope and intercept of an assay that is noisiest precisely where those quantities are determined. If the model output is disproportionately governed by one of these inputs, then experimental effort, reporting standards and delivery tolerances should be directed towards it. Local derivatives cannot answer the question because the four inputs carry different units and different natural magnitudes; a dimensionless measure is required.

This work derives closed-form elasticities for the USC, verifies them against numerical differentiation, and ranks the inputs. The ranking is then reproduced by Morris elementary-effect screening, a global method that samples the whole plausible parameter envelope rather than a single operating point [18, 19]. A logistic surrogate is fitted to establish how much of the dose response survives compression into a two-parameter form, the consequences for biologically effective dose are evaluated across six clinical schedules, and the generality of the ranking is examined across nine non-small-cell lung cancer cell lines.

Methods

Radiobiological models

The LQ model expresses the surviving fraction S after a single dose d as

$$S = \exp(-(αd + βd^2)) \quad (1)$$

where $α$ (Gy^{-1}) and $β$ (Gy^{-2}) are the linear and quadratic coefficients of cell inactivation [2, 16]. The multi-target model instead treats the cell as carrying n targets, each inactivated with mean dose D_0 :

$$S = 1 - \left(1 - e^{-\frac{d}{D_0}}\right)^n \quad (2)$$

At doses large compared with D_0 this expression becomes log-linear [14, 15], and is conveniently written using the quasi-threshold dose D_q , the intercept of the terminal slope extrapolated back to unit survival:

$$-\ln S = \frac{d}{D_0} - \frac{D_q}{D_0} \quad (3)$$

The universal survival curve

The USC uses the LQ expression through the shoulder and the log-linear expression beyond it, the two meeting at a transition dose d_T [1]:

$$-\ln S(d) = \begin{cases} αd + βd^2, & d < d_T \\ \frac{d}{D_0} - \frac{D_q}{D_0}, & d \geq d_T \end{cases} \quad (4)$$

Requiring that the surviving fraction and its gradient be continuous at d_T removes two degrees of freedom and yields

$$β = \frac{(1 - αD_0)^2}{4D_0D_q} \quad (5)$$

$$d_T = \frac{2D_q}{1 - αD_0} \quad (6)$$

so that the model is fully specified by the triplet (α, D_0, D_q) . The gradient condition is what makes the construction smooth rather than merely continuous, and it is the reason β cannot be chosen independently. For the reference parameters used throughout this work these relations give the values reported in the Results.

Elasticity analysis

To compare inputs carrying different units, the dimensionless elasticity of the surviving fraction with respect to an input x was used:

$$E_x = \frac{\partial S / S}{\partial x / x} = \frac{\partial S}{\partial x} \cdot \frac{x}{S} \quad (7)$$

which is the fractional change in survival produced by a fractional change in x . Because the USC is piecewise analytic, every elasticity can be obtained in closed form. Differentiating the two branches gives, for the delivered dose,

$$E_D = \begin{cases} -(\alpha d + 2\beta d^2), & d < d_T \\ -\frac{d}{D_0}, & d \geq d_T \end{cases} \quad (8)$$

and, for the radiosensitivity coefficient in the shoulder region, where the dependence of β on α implied by Eq. 5 must be carried through the differentiation,

$$E_\alpha = -\alpha \left(d - \frac{(1 - \alpha D_0)d^2}{2D_q} \right), d < d_T \quad (9)$$

Corresponding expressions for D_0 and D_q follow in the same way and are given in the analysis code. Above the transition dose the elasticity with respect to α vanishes identically, since the log-linear branch does not contain that parameter. All closed forms were verified against central-difference derivatives on a grid of 500 points spanning 0.1 to 20.0 Gy, excluding a narrow interval around d_T where the gradient of the elasticity is discontinuous; agreement was to better than 1×10^{-7} for every input. Inputs were then ranked by the mean absolute elasticity over that grid.

Morris elementary-effect screening

Elasticities are local in the three cell-line parameters even when averaged over dose, so the ranking was tested independently by a global screening method. The elementary effect of input i at a point x is

$$EE_i = \frac{y(x + \Delta e_i) - y(x)}{\Delta} \quad (10)$$

where Δ is a fixed step on a normalised grid and e_i is the corresponding unit vector [18]. Trajectories were generated over an eight-level grid, each varying every input exactly once in random order, and 200 trajectories were used. The screening measures are the mean absolute elementary effect and its standard deviation across trajectories,

$$\mu^* = \frac{1}{r} \sum_{j=1}^r |EE_i^{(j)}| \quad (11)$$

A large μ identifies an influential input, while a large σ relative to μ indicates that the effect depends on where in the space it is evaluated, that is, non-linearity or interaction [19, 20]. The three cell-line parameters were varied by ± 15 per cent about their reference values and the dose over 0.1 to 20.0 Gy.

Surrogate regression

A Latin hypercube sample of 600 points [21, 22] was drawn over the same envelope and a three-parameter logistic function fitted to the resulting surviving fractions by non-linear least squares using the trust-region reflective algorithm [28]:

$$S(d) \approx \frac{L}{1 + \exp(k(d - d_{50}))} \quad (12)$$

with L a scale factor, k a steepness and d_{50} a location. Goodness of fit was summarised by

$$R^2 = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \bar{y})^2} \quad (13)$$

together with the root-mean-square error. The random number generator was initialised with a fixed seed (20260909) so that the sample is reproducible.

Model divergence and biologically effective dose

The extent to which the LQ description overstates cell kill was expressed as the ratio of logarithmic cell kill predicted by the two models at the same dose per fraction:

$$\rho(d) = \frac{\ln S_{LQ}(d)}{\ln S_{USC}(d)} \quad (14)$$

A value of unity indicates agreement and $\rho > 1$ indicates LQ overestimation. The clinical consequence was assessed through the biologically effective dose. In the LQ formulation, for n fractions of size d ,

$$BED_{LQ} = nd \left(1 + \frac{d}{\alpha/\beta} \right) \quad (15)$$

whereas the USC formulation normalises the model logarithmic cell kill by the radiosensitivity coefficient,

$$BED_{USC} = \frac{n}{\alpha} \cdot (-\ln S(d)) \quad (16)$$

The two coincide below the transition dose. Values were converted to the equivalent dose in 2 Gy fractions by

$$EQD_2 = \frac{BED}{1 + 2/(\alpha/\beta)} \quad (17)$$

and evaluated for six schedules spanning conventional fractionation to single-fraction ablation.

Reference data and implementation

The reference cell line was NCI-H460, with $\alpha = 0.33 \text{ Gy}^{-1}$, $D_0 = 1.25 \text{ Gy}$ and $D_q = 1.80 \text{ Gy}$. Nine non-small-cell lung cancer lines with published survival parameters were used to test generality [1, 24]. All computations were performed in MATLAB [27], with non-linear curve fitting carried out using the Curve Fitting Toolbox [28]; the analysis scripts are provided as supplementary material. No generative artificial intelligence tool was used to design the study, generate or analyse the data, or produce the results reported here.

Results

Model construction and continuity

For the reference parameters, Eqs. 5 and 6 give $\beta = 0.0384 \text{ Gy}^{-2}$, an α/β ratio of 8.60 Gy and a transition dose of 6.13 Gy. Figure 1a shows the resulting curve. Below d_T it is indistinguishable from the LQ curve and preserves the shoulder; above it, it follows the multi-target asymptote whose intercept on the dose axis is $D_q = 1.80 \text{ Gy}$. Figure 1b confirms that the construction is smooth: the gradient of the logarithmic cell kill rises linearly through the shoulder and joins the constant value $1/D_0 = 0.800 \text{ Gy}^{-1}$ exactly at d_T , with no step in either value or slope.

Figure 2 shows how the curve responds when each cell-line parameter is perturbed by ± 15 per cent. Varying α (Fig. 2a) produces almost no visible change, because the perturbation is partly compensated by the induced change in β required by Eq. 5, and because the parameter is absent from the high-dose branch. Varying D_0 (Fig. 2b) rotates the log-linear branch and displaces the curve by orders of magnitude at 18 Gy. Varying D_q (Fig. 2c) shifts the transition point and the intercept but leaves the terminal slope unchanged.

Closed-form elasticities

The closed-form expressions agreed with central differences to within $2.7\text{e-}08$ across the grid, confirming the derivation. Figure 3a shows how the four elasticities evolve with dose. The elasticity with respect to dose is negative and grows without bound, reaching 16.0 at 20 Gy; that with respect to D_0 is positive and of comparable magnitude,

since a larger mean inactivation dose means more surviving cells. The elasticity with respect to D_q saturates at the constant value $D_q/D_0 = 1.44$ above the transition dose, a direct consequence of the second branch of Eq. 4. The elasticity with respect to α is small throughout the shoulder and falls identically to zero above d_T .

Averaged over the dose range (Fig. 3b and Table 2), the ordering is dose 7.892, D_0 6.637, D_q 1.152 and α 0.104. Dose and the mean inactivation dose are therefore of the same order as one another and roughly seventy-six times more influential than the radiosensitivity coefficient.

Global screening

Morris screening over the full envelope reproduced the elasticity ranking. The mean absolute elementary effects were 15.35 for dose, 2.10 for D_0 , 0.34 for D_q and 0.022 for α (Fig. 4, Table 2). Dose lies far to the right of the plot with a standard deviation well below its mean effect, indicating a strong and consistently directed influence. The point for D_0 lies close to the line $\sigma = \mu$, showing that its effect depends appreciably on the values of the other inputs, as expected from its role in setting both the terminal slope and, through Eq. 5, the quadratic coefficient. The point for α sits in the lower left corner with σ exceeding μ , the signature of an input that is unimportant on average and acts only through interactions confined to the shoulder.

Surrogate behaviour

The logistic surrogate fitted the Latin hypercube sample with $R^2 = 0.9974$ and a root-mean-square error of 0.0125 (Fig. 5), with fitted parameters $L = 1.767$, $k = 0.669 \text{ Gy}^{-1}$ and $d_{50} = 0.354 \text{ Gy}$. Predicted and observed values lie on the identity line across the whole range (Fig. 5b) and the residuals show no systematic trend with dose (Fig. 5c), though their spread is largest below 5 Gy where the four inputs interact most strongly. That a two-parameter sigmoid reproduces better than ninety-nine per cent of the variance indicates that most of the information in the model is carried by the dose axis itself, consistent with the elasticity and screening results.

Divergence between the models and consequences for fractionation

Table 3 and Fig. 6 compare the two formulations across six schedules. For conventional fractionation at 2 Gy and for moderate hypofractionation at 2.75 Gy the two agree to better than one part in a thousand, both lying below the transition dose. Divergence appears as soon as the dose per fraction enters the ablative range. At 48 Gy in four fractions the LQ formulation returns a biologically effective dose 16.0 Gy higher than the USC formulation, a 16 per

cent overestimate; at 54 Gy in three fractions the discrepancy reaches 49.1 Gy, or 42 per cent; and for a single 30 Gy fraction the LQ value is 97 per cent higher. Expressed as equivalent dose in 2 Gy fractions, the three-fraction schedule differs by 39.9 Gy between the two descriptions, which is larger than the margin by which many dose-escalation trials have been separated.

The ratio ρ rises monotonically above the transition dose (Fig. 6b), remaining within one per cent of unity through 6 Gy and reaching 1.97 at 30 Gy.

Generality across cell lines

Table 4 and Fig. 7 extend the analysis to nine non-small-cell lung cancer lines. The transition dose was 5.83 ± 0.89 Gy (range 4.12 to 7.09 Gy), so the ablative schedules in current use lie above d_T for every line examined. The elasticity ranking was preserved without exception: dose was the most influential input in 9 of nine lines and the radiosensitivity coefficient the least influential in 9 of nine (Fig. 7c). The degree of LQ overestimation at 24 Gy varied from 1.19 to 1.97 with a mean of 1.69, and tracked the α/β ratio inversely (Fig. 7b): the largest discrepancy occurred for NCI-H596, which has the broadest shoulder, and the smallest for NCI-H23, whose very high ratio makes its LQ curve nearly exponential already.

Discussion

Two independent methods, one local and analytic and one global and sampling-based, agree that the universal survival curve is governed by the delivered dose and by the mean inactivation dose, and that the radiosensitivity coefficient exerts comparatively little influence once the dose exceeds the transition point. The agreement matters because the two methods fail in different ways: elasticities are exact but evaluated about a single operating point, whereas elementary effects explore the whole envelope but only coarsely. That they produce the same ordering makes the conclusion robust to the choice of method.

The result is at first sight counter-intuitive, since α is the parameter most often quoted when a cell line is described as radiosensitive or radioresistant. Its unimportance here follows from the structure of the model rather than from any biological claim. Above d_T the surviving fraction depends only on D_0 and D_q , so the elasticity with respect to α is identically zero; below d_T its influence is partly cancelled by the compensating change in β that Eq. 5 enforces. In the ablative regime that motivates the USC in the first place, the parameter simply does not enter. The

practical implication is that experimental effort should be directed at the terminal slope of the survival curve, which fixes D_0 , rather than at the initial slope, which fixes α , even though the latter is easier to measure reliably.

The dominance of dose itself carries a separate implication. An elasticity of roughly eight means that a one per cent error in delivered dose produces an eight per cent error in predicted surviving fraction, and the figure grows with dose because the elasticity is proportional to d/D_0 on the log-linear branch. This provides a model-based argument for the tight delivery tolerances demanded in stereotactic practice, and suggests that the benefit of reducing geometric and dosimetric uncertainty is larger in the ablative regime than conventional fractionation would imply.

The comparison of biologically effective dose is the most directly clinical result. The two formulations are interchangeable at conventional dose per fraction, which is reassuring, but they diverge substantially in the range where stereotactic schedules operate. Reporting a single 30 Gy fraction as equivalent to a biologically effective dose of 135 Gy on LQ assumptions, when the USC returns 68 Gy, is not a minor discrepancy; it is large enough to change how two schedules are ranked against one another. Since cross-trial comparisons in stereotactic radiotherapy are routinely conducted in these units [10-12, 25], the choice of model is not a technicality.

These findings are consistent with the broader literature questioning naive extrapolation of the LQ model to large fraction sizes [4, 8, 9, 24]. They do not resolve the underlying controversy, since the USC is itself a phenomenological construction and the experimental data at very high dose per fraction remain sparse and, in places, contradictory [3, 25]. What the present analysis adds is a quantitative account of which inputs the discrepancy actually depends on, which was previously a matter of assertion.

Limitations

The analysis is confined to the USC as originally formulated and to single-fraction survival; it does not treat repopulation, reoxygenation, redistribution or intercellular signalling, and it assumes full repair between fractions when computing biologically effective dose. The cell-line parameters are taken from published clonogenic fits and inherit whatever uncertainty attaches to them; no confidence intervals are propagated, because the published values are generally reported without them. The Morris method ranks inputs but does not decompose variance, so interaction terms are detected but not quantified. Finally, the nine cell lines are all of pulmonary origin and all irradiated in vitro under aerobic conditions, so the ranking should not be assumed to hold under hypoxia, where the radiosensitivity coefficient is itself dose-modified [26].

Future work

Variance-based decomposition would quantify the interactions that the screening step only detects, and a Bayesian treatment of the clonogenic fits would allow parameter uncertainty to be propagated into the predicted survival rather than assumed away. Applying the same analysis to the generalised LQ and linear-quadratic-linear models [5-7] would show whether the dominance of D_0 is a property of the USC specifically or of high-dose extensions generally. Most usefully, the divergence in biologically effective dose is large enough at three fractions and below to be tested against clinical outcome data, and such a test would discriminate between the formulations in a way that in vitro data cannot.

Conclusion

Closed-form elasticity analysis and Morris elementary-effect screening agree that predicted clonogenic survival under the universal survival curve model is governed by the delivered dose and by the mean inactivation dose, with the quasi-threshold dose of secondary importance and the radiosensitivity coefficient of little consequence above the transition dose. The ranking held for all nine non-small-cell lung cancer lines examined. Because the linear-quadratic and universal survival curve descriptions of biologically effective dose diverge by up to 97 per cent in the ablative range while agreeing at conventional dose per fraction, the choice between them materially affects how stereotactic schedules are compared. Effort in parameter estimation should be concentrated on the terminal slope of the survival curve, and the strong dependence of predicted survival on dose supports the tight delivery tolerances required in stereotactic practice.

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Author Contributions Both authors contributed to the study conception and design. Model derivation, software implementation and analysis were performed by Aryaveer Singh. Methodological supervision, software implementation, validation and interpretation were provided by Rajiv Kumar Singh. The first draft was written by

Aryaveer Singh and both authors commented on subsequent versions. Both authors read and approved the final manuscript.

Ethics Approval Not applicable. This study is a computational analysis of previously published data and involved no human participants or animals.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

Data Availability All data supporting the findings of this study are contained within the article. The analysis scripts that regenerate every reported value, table and figure will be provided as supplementary material by corresponding author upon reasonable request.

Use of Artificial Intelligence No generative artificial intelligence tool was used to design the study, generate or analyse data, or produce any scientific content. Artificial intelligence assisted copy editing was used only for language.

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Table 1 Radiobiological models considered in this work, with the parameters each requires and the dose range over which it is generally regarded as valid

Model	Parameters	Behaviour at high dose	Equation
Linear-quadratic	α, β	Continuous downward curvature	1
Multi-target	n, D_0	Log-linear	2
Multi-target (log form)	D_0, D_q	Log-linear	3
Universal survival curve	α, D_0, D_q	Log-linear above d_T	4

Table 2 Ranking of the four inputs for NCI-H460 by mean absolute elasticity over 0.1 to 20.0 Gy and by Morris elementary-effect screening (200 trajectories, ± 15 per cent envelope). The two methods give the same ordering

Input	Mean $ E_x $	Rank	μ^*	σ	Rank
Dose, D	7.892	1	15.347	1.818	1
Mean inactivation dose, D_0	6.637	2	2.100	1.472	2
Quasi-threshold dose, D_q	1.152	3	0.343	0.165	3
Radiosensitivity coefficient, α	0.104	4	0.022	0.047	4

Table 3 Biologically effective dose and equivalent dose in 2 Gy fractions for six schedules, computed for NCI-H460 under the linear-quadratic (Eq. 15) and universal survival curve (Eq. 16) formulations. The two agree below the transition dose of 6.13 Gy and diverge above it

Schedule	Dose / fractions	BED _{LQ} (Gy)	BED _{USC} (Gy)	Ratio	EQD2 _{LQ} (Gy)	EQD2 _{USC} (Gy)
Conventional	60 Gy / 30 fr	73.9	73.9	1.00	60.0	60.0
Moderate hypofx	55 Gy / 20 fr	72.6	72.6	1.00	58.9	58.9
SBRT peripheral	48 Gy / 4 fr	114.9	98.9	1.16	93.3	80.3
SBRT central	50 Gy / 5 fr	108.1	99.4	1.09	87.7	80.6
SBRT 3-fraction	54 Gy / 3 fr	167.0	117.8	1.42	135.5	95.6
Single fraction	30 Gy / 1 fr	134.6	68.4	1.97	109.2	55.5

341 **Table 4** Extended analysis across nine non-small-cell lung cancer cell lines. Survival parameters are previously published fitted values [1, 24]; β , α/β and d_T were derived from Eqs.
342 5 and 6. The ratio $p(24 \text{ Gy})$ is the linear-quadratic overestimation of logarithmic cell kill at a single fraction of 24 Gy (Eq. 14), and E_x values are mean absolute elasticities over 0.1
343 to 20.0 Gy

Cell line	Histology	$\alpha \text{ (Gy}^{-1}\text{)}$	$D_0 \text{ (Gy)}$	$D_q \text{ (Gy)}$	$\alpha/\beta \text{ (Gy)}$	$d_T \text{ (Gy)}$	$p(24 \text{ Gy})$	E_D	E_{D0}	E_{Dq}	E_a
NCI-H460	Large cell anaplastic	0.43	1.00	1.53	8.10	5.37	1.82	9.91	8.55	1.26	0.104
NCI-H661	Large cell anaplastic	0.08	1.40	3.15	1.79	7.09	1.86	6.91	5.15	1.73	0.034
NCI-H23	Adenocarcinoma	0.89	1.02	0.19	81.16	4.12	1.19	9.84	9.55	0.16	0.126
NCI-H522	Adenocarcinoma	0.34	1.10	2.11	8.05	6.74	1.63	8.92	7.30	1.49	0.129
NCI-H358	Adenocarcinoma	0.27	1.20	1.91	5.42	5.65	1.91	8.22	6.85	1.30	0.072
NCI-H290	Mesothelioma	0.59	1.30	0.76	42.95	6.52	1.23	7.67	7.00	0.46	0.210
NCI-H596	Adenosquamous	0.18	1.35	2.23	3.78	5.89	1.97	7.28	5.90	1.33	0.052
NCI-H647	Adenosquamous	0.30	1.50	1.49	8.87	5.42	1.78	6.61	5.72	0.82	0.074
NCI-H226	Squamous	0.26	1.60	1.65	8.05	5.65	1.78	6.18	5.27	0.84	0.069
Mean $\pm$ SD	–	0.37	1.27	1.67	18.69	5.83 $\pm$ 0.89	1.69	7.95	6.81	1.04	0.097

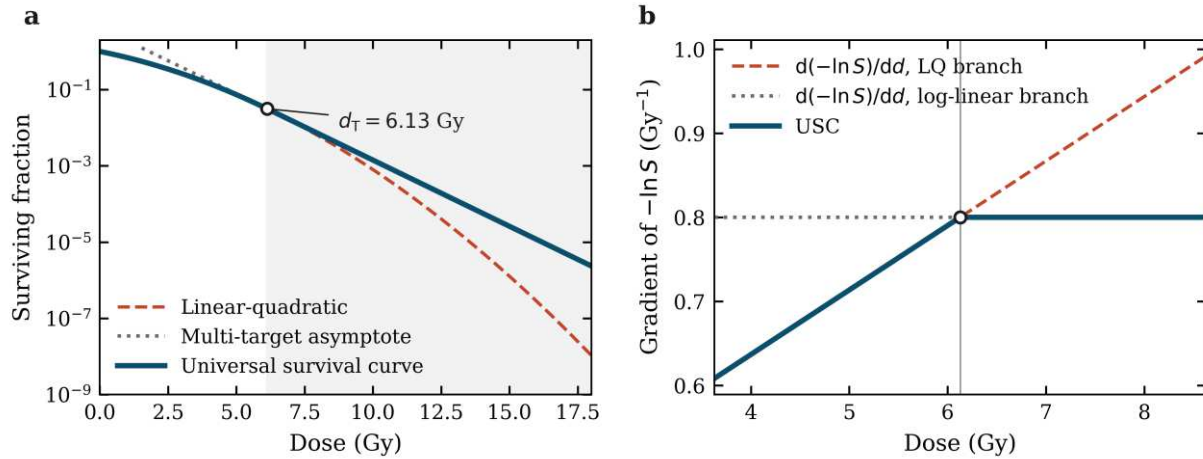


Fig. 1 Construction of the universal survival curve for NCI-H460. **a** The model follows the linear-quadratic expression below the transition dose $d_T = 6.13$ Gy (shaded region marks the log-linear regime) and the multi-target asymptote above it. **b** Gradient of the logarithmic cell kill near the transition, showing that the two branches meet with matching value and slope, as required by Eqs. 5 and 6

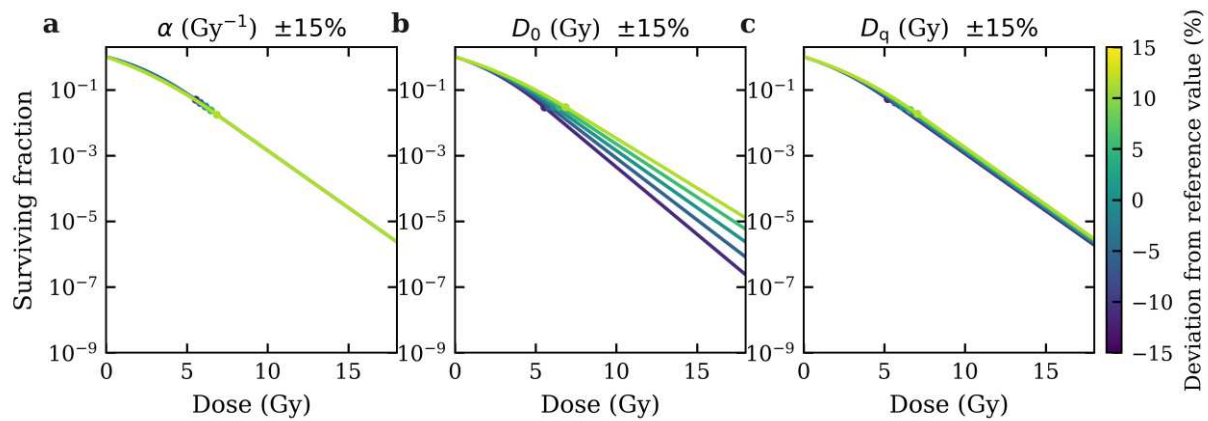


Fig. 2 Response of the survival curve to a ± 15 per cent perturbation of each cell-line parameter about its reference value.
a Radiosensitivity coefficient α . **b** Mean inactivation dose D_0 . **c** Quasi-threshold dose D_q . Dots mark the transition dose for each perturbed curve

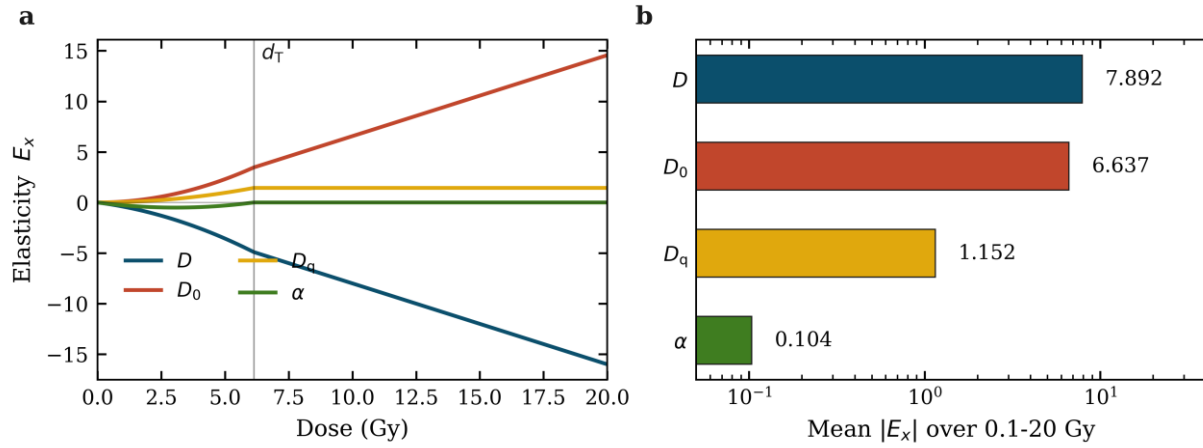


Fig. 3 Closed-form elasticities of the surviving fraction. **a** Elasticity of each input as a function of dose; the vertical line marks d_T , above which the elasticity with respect to α vanishes and that with respect to D_q saturates. **b** Mean absolute elasticity over 0.1 to 20.0 Gy on a logarithmic scale

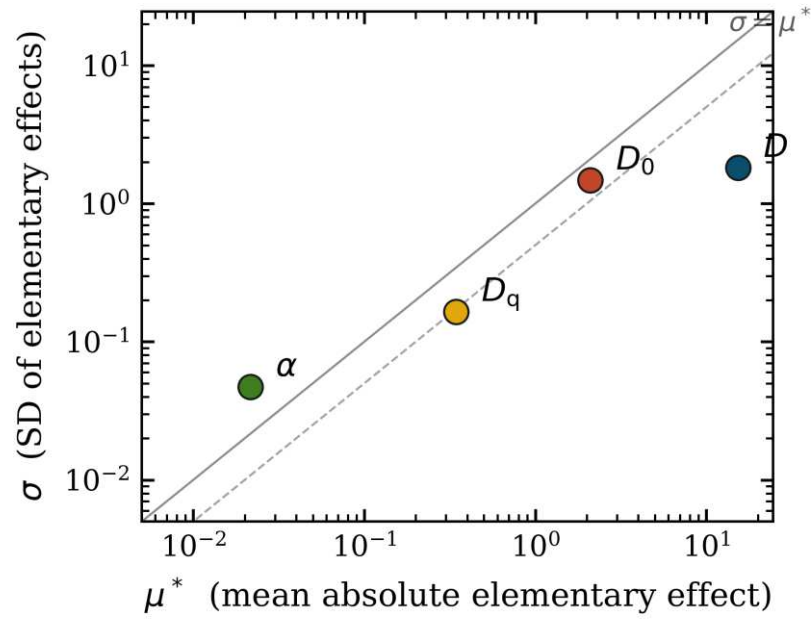


Fig. 4 Morris elementary-effect screening over the ± 15 per cent envelope (200 trajectories). Inputs far to the right are influential; those lying above the line $\sigma = \mu$ have effects that depend strongly on the rest of the parameter space. Dose dominates, while α^* is both weak and interaction-dominated

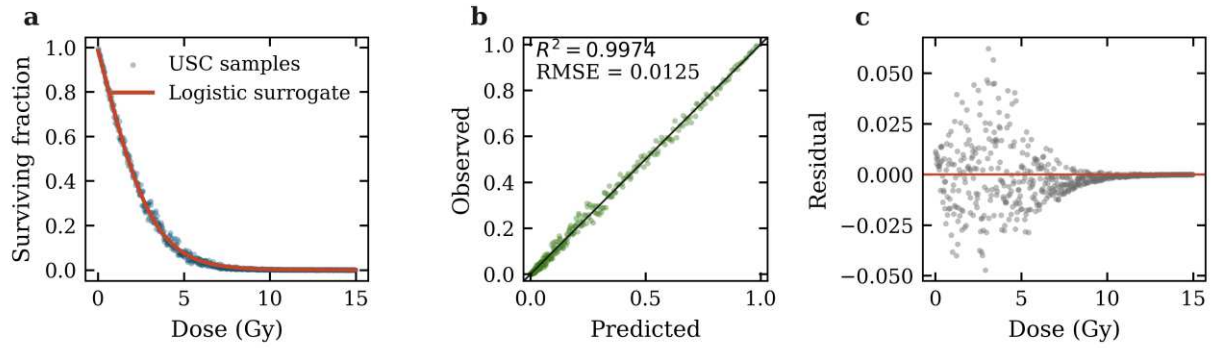


Fig. 5 Logistic surrogate fitted to a Latin hypercube sample of 600 points. **a** Sampled surviving fractions with the fitted function. **b** Predicted against observed values with the identity line. **c** Residuals against dose, showing no systematic trend

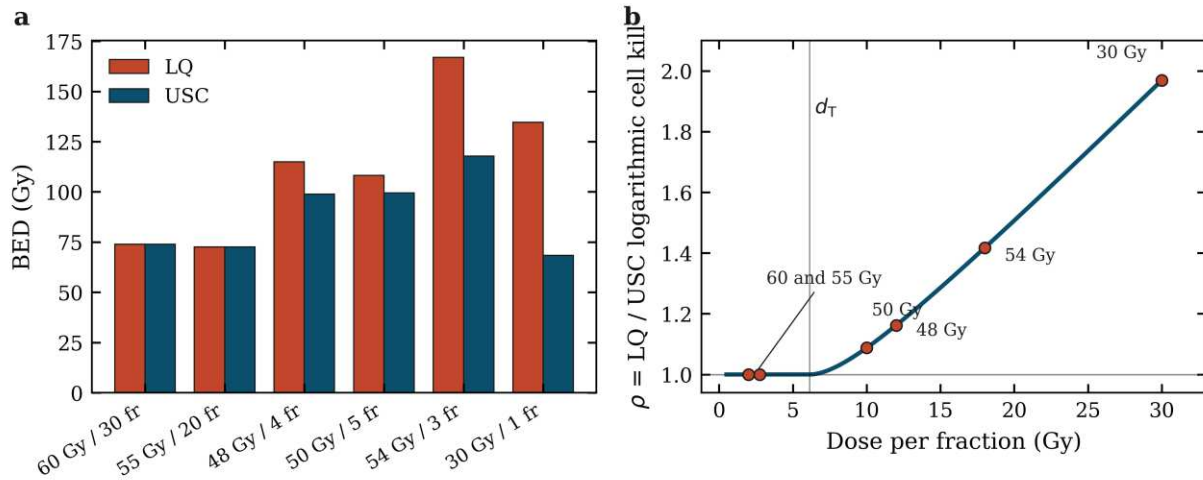


Fig. 6 Consequences for clinical fractionation. **a** Biologically effective dose for six schedules under the linear-quadratic and universal survival curve formulations. **b** Ratio ρ of logarithmic cell kill against dose per fraction, with the six schedules marked; the two descriptions agree below d_T and diverge progressively above it

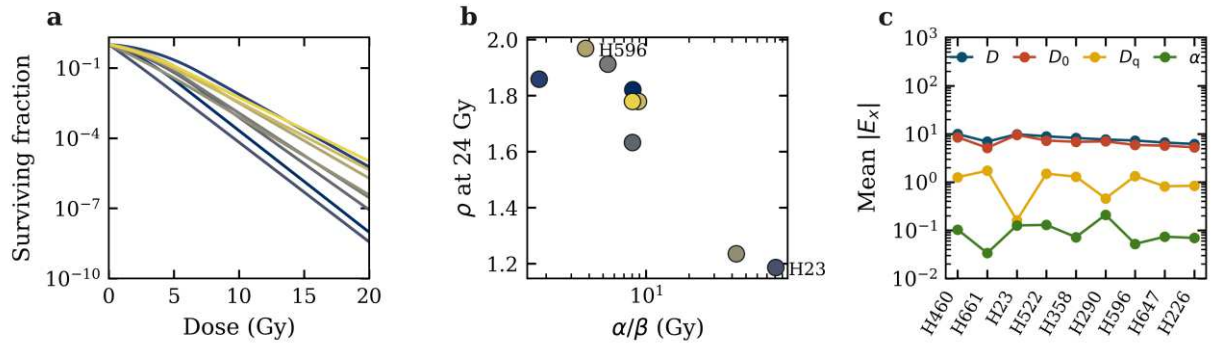


Fig. 7 Analysis across nine non-small-cell lung cancer cell lines. **a** Universal survival curves for all nine lines. **b** Linear-quadratic overestimation at 24 Gy against the α/β ratio. **c** Mean absolute elasticity of each input for every line; the ordering $D > D_0 > D_q > \alpha$ is preserved throughout