Chemoradiotherapy of locally-advanced non-small cell lung cancer: analysis of radiation dose-response, chemotherapy and survival-limiting toxicity effects

Michael G. Nix, Carl G. Rowbottom, Sindu Vivekanadan,
Maria A. Hawkins and John D. Fenwick

Summary: 2-year overall survival in 68 trial arms was best described by a model that accounted for classical radiobiological factors, chemotherapy effects and survival-limiting toxicity. The fitted α/β ratio was 4.0 Gy and repopulation negated 0.38 Gy/day. Modelled survival peaked at 80 (stage IIIA) and 87 Gy (IIIB) for radiotherapy and sequential chemoradiotherapy delivered in 2 Gy fractions over 40 days, and 67 (IIIA) and 73 Gy (IIIB) for concurrent chemoradiotherapy, before falling at higher doses.

Key words: NSCLC, radiotherapy, dose-escalation, chemotherapy, toxicity

Abstract

Purpose. To analyze changes in 2-year overall survival (OS_{2yr}) with radiotherapy (RT) dose, dose-per-fraction, treatment duration and chemotherapy use, in data compiled from prospective trials of RT and chemo-RT (CRT) for locally-advanced non-small cell lung cancer (LA-NSCLC).

Material and methods. OS_{2yr} data was analyzed for 6957 patients treated on 68 trial arms (21 RT-only, 27 sequential CRT, 20 concurrent CRT) delivering doses-per-fraction $\leq$4.0 Gy. An initial model considering dose, dose-per-fraction and RT duration was fitted using maximum-likelihood techniques. Model extensions describing chemotherapy effects and survival-limiting toxicity at high doses were assessed using likelihood-ratio testing, the Akaike Information Criterion (AIC) and cross-validation.

Results. A model including chemotherapy effects and survival-limiting toxicity described the data significantly better than simpler models (p <10^{-14}), and had better AIC and cross-validation scores. The fitted α/β ratio for LA-NSCLC was 4.0 Gy (95%CI: 2.8-6.0 Gy), repopulation negated 0.38 (95%CI: 0.31-0.47) Gy EQD2/day beyond day 12 of RT, and concurrent CRT increased the effective tumor EQD2 by 23% (95%CI: 16-31%). For schedules delivered in 2 Gy fractions over 40 days, maximum modelled OS_{2yr} for RT was 52% and 38% for stages IIIA and IIIB NSCLC respectively, rising to 59% and 42% for CRT. These survival rates required 80 and 87 Gy (RT or sequential CRT) and 67 and 73 Gy (concurrent CRT). Modelled OS_{2yr} rates fell at higher doses.

Conclusions. Fitted dose-response curves indicate that gains of ~10% in OS_{2yr} can be made by escalating RT and sequential CRT beyond 64 Gy, with smaller gains for concurrent CRT. Schedule acceleration achieved via hypofractionation potentially offers a further 5-10% improvement in OS_{2yr}. Further 10-20% OS_{2yr} gains might be made,

according to the model fit, if critical normal structures in which survival-limiting toxicities arise can be identified and selectively spared.

1. **Introduction**

Overall survival (OS) following radiotherapy (RT) for locally-advanced non-small cell lung cancer (LA-NSCLC) remains disappointing. While some dose-escalation trials have achieved promising results, [1] outcomes have been inconsistent, with median OS in better performing studies being 25-28 months. [2,3] Surprisingly, the RTOG-0617 phase III study of concurrent chemoradiotherapy (CRT) found a sub-unity median survival ratio (MSR) of 0.71 for 74 Gy in 37 daily fractions versus 60 Gy in 30 fractions. [2] Although hyperfractionated and moderately hypofractionated schedules have been trialled, [1,3-6] the standard-of-care remains 60-66 Gy in 30-33 fractions with some UK centres preferring 55 Gy in 20 fractions. Improved survival has recently been demonstrated using radio-immunotherapy [7] but the optimal RT schedule has yet to be determined.

A need therefore exists to reconcile apparently inconsistent trial results, to improve outcome prediction for modified RT of NSCLC. Partridge *et al* analyzed 2-year disease-free survival (DFS), demonstrating a dose-response using a probit tumour control probability (TCP) model. [8] Differences in dose-per-fraction and schedule duration were accounted for by standardizing to equivalent doses in 2 Gy fractions delivered over a fixed treatment duration (EQD2T), using the time-corrected linear-quadratic formalism. Values of α/β, λ and T_K parameters describing fractionation sensitivity, accelerated tumor proliferation and onset delay are not well established for NSCLC, [9-12], and therefore Partridge *et al* chose 10 Gy, 0.6 Gy/day and 21 days, similar to values obtained from analyses of outcomes for head-and-neck squamous cell carcinoma (HNSCC). [13]

A recent meta-analysis of randomized studies reported an MSR of 1.13 (p=0.002) for higher radiation dose arms in RT-only and sequential CRT trials, but 0.83 (p = 0.02) for higher dose arms in concurrent CRT trials [6], demonstrating the need for dose-response

models to describe differential chemotherapy effects and possible reductions in survival at high radiation doses. Here, we analyze 2-year OS rates (OS_{2yr}) compiled for ~7000 NSCLC patients from published phase I-III trials of RT alone and CRT. Starting from the Partridge model, we freely fit α/β, λ and T_k before parsimoniously extending the model to describe sequential and concurrent chemotherapy effects, and survival reductions at high doses due to radiation toxicity. [14]

2. **Materials and methods**

2.1. *Data*

Phase I-III trial data were identified from *PubMed*, *ScienceDirect* and *Google Scholar* searches for the MeSH term 'NSCLC radiotherapy dose-escalation'. Citation-following yielded further data. The dataset was limited to studies published after 1995 describing outcomes for >20 patients per trial arm. Reports missing unambiguous details of dose, fractionation, treatment duration, chemotherapy scheduling, stage-mix and OS_{2yr} data were excluded. Strongly hypofractionated schedules used to treat predominantly early-stage disease (dose-per-fraction >4.0 Gy) were also excluded, substantially weighting the dataset towards higher-stage disease.

Reported prescribed doses and doses-per-fraction were increased by 5% for North American trials not employing lung tissue heterogeneity corrections. [15] Doses prescribed in the RTOG-0617 study were also raised by 5% despite heterogeneity corrections having been applied, since prescription was to 95% of the planning target volume, generating physical isocentre doses similar to those of isocentrically-prescribed treatments planned without heterogeneity corrections. [16]

2.2. *Fitted dose-response models*

Three models have been fitted to OS_{2yr} data. The first accounts for dose, dose-per-fraction and schedule duration. The second contains two additional parameters describing systemic and local chemotherapy effects. The third contains two further parameters describing survival reductions at high doses, and one accounting for improvements in survival over time.

Model 1: Standard probit-EQD2

Model 1, based on that of Partridge *et al*, [8] describes TCP varying sigmoidally with EQD2T delivered to the tumor, $EQD2T_{tum}$

$$\mathrm{TCP} \;=\; \Phi\left[\frac{\mathrm{EQD2T_{tum}} - \mathrm{EQD2T_{tum,50}}}{m.\,\mathrm{EQD2T_{tum,50}}}\right] \times\; 100\% \qquad (1)$$

where ϕ is the cumulative normal distribution, $\mathrm{EQD2T_{tum,50}}$ is the tumor EQD2T required for 50% control, and *m* defines the dose-response gradient. $\mathrm{EQD2T_{tum}}$ was calculated as

$$\mathrm{EQD2T_{tum}} \;=\; D\left[\left(1+\left(\frac{d}{\alpha/\beta_{\,tum}}\right)\right)\Big/\left(1+\left(\frac{2}{\alpha/\beta_{\,tum}}\right)\right)\right] \;-\; \lambda.\,\mathrm{Max}[T-T_k,0] \qquad (2)$$

D and *d* being prescribed dose and dose-per-fraction, and *T* treatment duration. [8] Following Partridge's approach, cohort-specific OS was calculated as a weighted sum of modelled TCPs for each disease stage

$$\mathrm{OS_{2yr}^{Model1}} \;=\; 100\% \times \sum_i f_i \times \Phi\left[\frac{\mathrm{EQD2T_{tum}} - \mathrm{EQD2T_{tum,50}}(S_i)}{m.\,\mathrm{EQD2T_{tum,50}}(S_i)}\right] \qquad (3)$$

where f_i is the fraction of patients in the cohort with stage *i* (I, II, IIIA or IIIB) disease, and $\mathrm{EQD2T_{tum,50}}(S_i)$ the $EQD2T_{tum,50}$ for that stage. Initially, α/β_{tum}, λ and T_k values were fixed at the levels chosen by Partridge, and the five parameters *m* and

$\mathrm{EQD2T}_{\mathrm{tum},50}\left(S_{\mathrm{I,\,II,\,IIIA,\,IIIB}}\right)$ were fitted to achieve the best description of the data ('Partridge model'). Subsequently all eight model parameters were fitted ('Model 1').

2.2.1. Model 2: Adding chemotherapy effects

Survival is improved by chemotherapy-driven reductions in the distant failure-rate. [17,18]. Model 2 describes this effect via an additional factor

$$\mathrm{OS}_{\mathrm{2yr}}^{\mathrm{Model2}} = \left(\frac{\mathrm{OS}_{\mathrm{2yr-max}}}{100\%}\right) \mathrm{OS}_{\mathrm{2yr}}^{\mathrm{Model1}} \quad (4)$$

where $OS_{2yr\text{-}max}$ values <100% account for patients who died of distant metastases or unrelated causes despite achieving loco-regional control. For RT alone, $\mathrm{OS}_{\mathrm{2yr\text{-}max}}^{\mathrm{RT\text{-}only}}$ was fixed at 85%, based on a reported distant failure-rate of 15% post-surgery for patients who did not receive chemotherapy. [19] For CRT treatments, $OS_{2yr\text{-}max}^{CRT}$ was fitted to obtain the best match of the model to the data, a value >85% describing reduced distant failure-related mortality due to systemic effects of chemotherapy.

Survival is longer following concurrent than sequential CRT. [20, 21] This is accounted for by scaling the $EQD2T_{tum}$ doses of concurrent CRT treatments by an additional fitted parameter $\mathrm{RS}^{\mathrm{cCRT}}$ >1 to describe possible tumor radiosensitization by concurrent chemotherapy

$$\mathrm{EQD2T}_{\mathrm{tum}}^{\mathrm{cCRT}} = \mathrm{RS}^{\mathrm{cCRT}} \,.\, \mathrm{EQD2T}_{\mathrm{tum}} \quad (5)$$

Model 2 has ten fitted parameters. Its residuals revealed an unfitted trend for OS_{2yr} to rise with study publication year (see Supplementary Information), presumably reflecting advances in treatment and staging over time unrelated to CRT scheduling, and concurring with a reported trend for significantly longer survival in more recent studies [6]. Survival was therefore adjusted further via

$$\mathrm{OS}_{24\mathrm{m}}^{\mathrm{Model2b}} = \mathrm{OS}_{24\mathrm{m}}^{\mathrm{Model2}} \ (1 - R.Y) \quad (6)$$

Y being the number of years before 2016 a study was published, and *R* a fitted parameter describing survival benefit with time.

2.2.2. Model 3: Reduced survival at higher doses

Model 2 cannot describe falling survival at high doses. However, the concept of a therapeutic window implies that OS must rise, plateau and eventually fall as RT dose increases. To accommodate this, we extended the model to

$$\mathrm{OS}_{2\mathrm{yr}}^{\mathrm{Model3}} = \mathrm{OS}_{2\mathrm{yr}}^{\mathrm{Model2b}} \left(1 - \frac{SLT}{100\%}\right) \quad (7)$$

where the modelled survival-limiting toxicity-rate, *SLT*, is given by

$$SLT = \Phi\left[\frac{\mathrm{EQD2_{NT}} - \mathrm{EQD2_{NT,50}}}{m_{\mathrm{NT}}.\ \mathrm{EQD2_{NT,50}}}\right] \times 100\% \quad (8)$$

and increases sigmoidally with the normal tissue EQD2

$$\mathrm{EQD2_{NT}} = D\left[\left(1 + \left(\frac{d}{3}\right)\right) \Big/ \left(1 + \left(\frac{2}{3}\right)\right)\right] \quad (9)$$

calculated using α/β = 3 Gy. The fitted quantities m_{NT} and $\mathrm{EQD2}_{50,\mathrm{NT}}$ define the toxicity dose-response gradient and the $\mathrm{EQD2}_{\mathrm{NT}}$ at which survival is halved by toxicity, and bring the number of fitted parameters in Model 3 to 13.

2.3. *Statistical methods*

Models were fitted to $\mathrm{OS}_{2\mathrm{yr}}$ data using the maximum-likelihood method, via the *mle2* package within the 'R' language (v3.4.0). [22] Significances of improvements in model-fit were determined using likelihood-ratio testing. [23] Relative model performance in future data was estimated using the Akaike Information Criterion (AIC), which trades off

goodness-of-fit against a penalty term that rises with the number of fitted parameters to account for possible overfitting of the dataset. [24] Leave-one-out cross-validation was performed to check the AIC findings, calculating weighted sums-of-squared residuals.

For each model, asymptotic confidence intervals (CIs) were calculated on all fitted parameters. For the model judged best on AIC and cross-validation, profile-likelihood CIs were also determined. [22]

3. Results

3.1. *Data*

The dataset comprised 6957 patients treated on 68 trial arms of 40 studies, for which 2-year OS ranged from 6 to 68%. [1-5,25-64] Overall, 9% of patients were stage I, 9% stage II, 43% IIIA and 39% IIIB (AJCC 6th edition). RT alone, sequential and concurrent CRT treatments were given in 21, 27 and 20 arms respectively (Table 1).

Figure 1a shows observed OS_{2yr} plotted against prescribed physical dose. Although the data appear highly dispersed, local regression (LOESS, smoothing = 0.7) shows survival increasing with dose before plateauing at ~80 Gy. Physical dose and dose-per fraction are plotted against RT duration in Figure 1b and Supplementary Figure S1. Higher doses were typically given using longer schedules (Spearman's rho = 0.62, p <0.001), but dose-per-fraction and schedule duration were not significantly correlated (p = 0.66).

3.2. *Data fits*

Model fits to 2-year survival data are detailed in Table 2. The data were described significantly better when classical radiobiological parameters α/β, λ and T_K were fitted rather than fixed at the levels of the Partridge model ($p<10^{-5}$). The fit was further improved by additional terms describing chemotherapy effects ($p<10^{-19}$), longer survival in later

studies ($p<10^{-8}$, Supplementary Table S1 and Figure S2), and reduced survival at high dose-levels ($p<10^{-6}$). Model 3 included all these factors and described the data best (Figure 2).

Values of OS_{2yr} predicted by Model 3 are plotted in Figure 3a and rise with observed OS_{2yr}, with notably less data dispersion than in Figure 1. A plot of predicted and observed OS_{2yr} versus $EQD2T_{tum}$ shows no trend in residuals (Figure 3b). On AIC and cross-validation measures Model 3 substantially out-performed the other models (Table 2), indicating that its success was not due to over-fitting of this specific dataset.

The fitted α/β ratio was 4.0 Gy (profile-likelihood 95% CI: 3.0, 5.4 Gy) for Model 3, with a tumor repopulation rate λ of 0.38 Gy/day (95%CI: 0.30, 0.48 Gy/day) beginning at day 12 [95%CI: 12, 17] of RT. Relatively low α/β ratios were common to fits of Models 1, 2 and 3. For Model 2b a higher α/β value of 7.4 Gy (95%CI: 2.7, 12.4 Gy) was obtained, but Model 3 described the dataset substantially better. In fits of Models 1 and 2, tumor repopulation ran faster at 0.71 and 0.97 Gy/day starting at day 28, but again Model 3 described the data significantly better. The Model 3 fit described a maximum dose-response gradient of 1.25% (95% CI: 1.13, 1.42%) gain in OS_{2yr} per 1% increase in $EQD2T_{tum}$, in the absence of survival-limiting toxicity.

3.3. *Dose-response curves*

Dose-response curves for OS_{2yr} described by Model 3 are plotted in Figure 4 for RT alone, sequential and concurrent CRT. For ease of comparison with a reference schedule delivering 60 Gy in 30 fractions over 6 weeks (40 days), OS_{2yr} is plotted against dose delivered in 2 Gy fractions over 40 days, $EQD2(40d)_{tum}$, where

$$EQD2(40d)_{tum} = EQD2T_{tum} + \lambda\,(40-T_K) = EQD2T_{tum} + 10.6\ \text{Gy} \quad \text{for Model 3} \qquad (10)$$

The plots show predicted OS_{2yr} peaking at 52% and 38% respectively for stages IIIA and IIIB NSCLC treated using RT alone, and at 59% and 42% for CRT treatments. For RT alone and sequential CRT, peak survival is reached at $EQD2(40d)_{tum}$ doses of 80 and 87 Gy for stages IIIA and IIIB respectively. For concurrent CRT, peak survival requires 67 and 73 Gy for IIIA and IIIB disease. Some of these dose-levels, 87 Gy for example, would exceed tolerance for serious toxicities [8]. At higher dose-levels the model fit describes falling survival, gains in tumor control being more than offset by survival-limiting toxicity.

Discussion

NSCLC OS_{2yr} data was described best by Model 3 (Table 2, Figure 2), which includes terms accounting for sequential and concurrent CRT, and toxicity-related reductions in survival at high doses. Although survival is known to be improved by CRT, [20] and is suspected to be limited by toxicity at high doses, [14, 65] to our knowledge this is the first time these factors have been included in comprehensive dose-response modelling for NSCLC.

The 4.0 Gy (95%CI: 3.0, 5.4 Gy) α/β ratio of the Model 3 fit is notably lower than the 10 Gy value often assumed for NSCLC [10], and allowed the model to describe the data significantly better ($p < .002$, likelihood-ratio). A similar value of 4.9 Gy (95%CI: 3.0, 6.8 Gy) was obtained when the radiobiological parameters of the standard Partridge model were freely-fitted (Model 1, Table 2), indicating that the result is robust and not an artefact of modelling CRT and toxicity-limited survival. We are unaware of such a low α/β ratio being previously reported for LA-NSCLC, but the 4.0 Gy α/β value is consistent with an observation of Partridge *et al.* [8] that hypofractionated schedules appeared to over-perform in plots of DFS versus $EQD2T_{tum}$ calculated for α/β = 10 Gy, and concurs with α/β estimates of 3.9 and 2.8 Gy obtained from fits to stage I NSCLC data [66, 67].

Tumor repopulation negates 0.38 Gy EQD2 per day of treatment extension beyond day 12 of RT according to the Model 3 fit, making RT acceleration worth ~3 Gy per week of schedule shortening. Since the fitted tumour α/β value of 4.0 Gy lies close to the generic late toxicity α/β ratio of 3 Gy, such acceleration might be achieved efficiently via moderate hypofractionation (dose-per-fraction >2 Gy) including simultaneous boost techniques. For example, 56 Gy in 20 fractions over 26 days offers a modelled 5% advantage in OS_{2yr} for stage IIIB NSCLC compared to 63 Gy in 30 fractions over 40 days, the two schedules being equivalent for late normal tissue damage (α/β = 3 Gy).

The fitted 0.38 Gy/day loss of EQD2 to repopulation is similar to an early estimate of 0.45 Gy/day made for NSCLC by Koukourakis *et al* [68], but is lower than estimates for HNSCC (~0.6 Gy/day starting 3-5 weeks into RT [13]), and depends strongly on the introduction of the toxicity term into Model 3. Fits of the simpler but less well-performing Models 1, 2 and 2b described higher loss-rates of 0.6-1.0 Gy/day typically starting at day 28 of RT, a consequence of these models using rapid repopulation rather than survival-limiting toxicity to fit the observed plateau in OS_{2yr} at high doses, albeit less well.

The systemic effect of chemotherapy compared to RT alone was described in the Model 3 fit by a 10% rise in $OS_{2yr\text{-}max}$, the overall survival achievable by a treatment if 100% of primary tumours were cured and no survival-limiting toxicity occurred. And the local effect of concurrent chemotherapy was described by a modelled 23% increase in effective tumor EQD2, greater than estimated previously [9] but consistent with the 0.86 hazard ratio reported by O'Rourke *et al* for concurrent rather than sequential CRT [20].

The model fit was significantly improved by the toxicity term, which was introduced to account for survival reductions at high dose-levels, and described survival-limiting toxicity rates of 4%, 11% and 22% at 50, 66 and 80 Gy $EQD2_{NT}$ respectively following RT alone or

sequential CRT, and 8%, 23% and 42% following concurrent CRT. These modelled rates suggest that survival in dose-escalation trials may have been reduced by toxicity, and are in line with data from a cause-of-death analysis [69], which reported an ~15% rate of non-malignant cardiac mortality at 2 years post-treatment for a curatively treated stage III cohort. Research is being carried out to identify mediastinal substructures in which survival-limiting toxicities arise, with a focus on heart [14], offering the prospect of improved outcomes if doses to these structures can be limited without compromising tumor coverage.

Whilst Model 3 was designed to parsimoniously account for several classical and novel dose-response factors, it nevertheless requires fitting of 13 parameters. This relative complexity is justified by the model's superior AIC and cross-validation scores, compared to those of simpler models. Further terms might provide a more complete description of the dataset, or might simply overfit it. We have investigated stage-specific survival-limiting toxicity terms, motivated by the observation that critical structures are less likely to receive high doses during RT of early-stage disease: resulting improvements in AIC score were marginal (Supplementary Information).

In summary, we have fitted a dataset of OS_{2yr} rates reported for many RT and CRT schedules using a model that combined a classical description of radiation dose-response with novel terms accounting for chemotherapy effects and survival reductions at high doses. The model fit had an α/β ratio of 4.0 Gy and described a rate of EQD2 loss due to tumor repopulation of 0.38 Gy/day, implying that moderate acceleration achieved via hypofractionation would produce useful survival gains.

The fit predicts maximal OS_{2yr} rates of 52% (stage IIIA) and 38% (IIIB) for RT alone when given in 2 Gy fractions over 6 weeks, and 59% (IIIA) and 42% (IIIB) for CRT, these peak

rates being achieved at prescribed doses of 80 Gy (IIIA) and 87 Gy (IIIB) for RT alone and sequential CRT, and 67 Gy (IIIA) and 73 Gy (IIIB) for concurrent CRT. According to the fit, 10-20% further improvements in OS_{2yr} might be achieved if normal tissues in which survival-limiting toxicities arise could be identified and spared without compromising tumor dose coverage.

Acknowledgements

MAH is funded by MRC grant MC_UU_00001/2. The authors have no conflicts of interest to report.

References:

1. Landau DB, Hughes L, Baker A, et al. IDEAL-CRT: A phase 1/2 trial of isotoxic dose-escalated radiation therapy and concurrent chemotherapy in patients with stage II/III non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1367-1377.

2. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617). Lancet Oncol. 2015;16(2):187-199.

3. van Baardwijk A, Reymen B, Wanders S, et al. Mature results of a phase II trial on individualised accelerated radiotherapy based on normal tissue constraints in concurrent chemo-radiation for stage III non-small cell lung cancer. Eur J Cancer. 2012;48(15):2339-2346.

4. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Parmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: Mature data from the randomised multicentre trial. Radiother Oncol. 1999;52(2):137-148.

5. Cannon DM, Mehta MP, Adkison JB, et al. Dose-limiting toxicity after hypofractionated dose-escalated radiotherapy in non-small-cell lung cancer. J Clin Oncol. 2013;31(34):4343-4348.

6. Ramroth J, Cutter DJ, Darby SC, et al. Dose and Fractionation in Radiation Therapy of Curative Intent for Non-Small Cell Lung Cancer: Meta-Analysis of Randomized Trials. Int J Radiat Oncol Biol Phys. 2016;96(4):736-747.

7. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018:379(24):2342-2350.

8. Partridge M, Ramos M, Sardaro A, Brada M. Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature. Radiother Oncol. 2011;99(1):6-11.

9. Fenwick JD, Nahum AE, Malik ZI, et al. Escalation and Intensification of Radiotherapy for Stage III Non-small Cell Lung Cancer: Opportunities for Treatment Improvement. Clin Oncol. 2009;21(4):343-360.

10. Fowler JF, Tomé WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. Int J Radiat Oncol. 2004;60(4):1241-1256.

11. Mehta M, Scrimger R, Mackie R, Paliwal B, Chappell R, Fowler J. A new approach to dose escalation in non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2001;49(1):23-33.

12. Bentzen SM, Saunders MI, Dische S. From CHART to CHARTWEL in non-small cell lung cancer: Clinical radiobiological modelling of the expected change in outcome. Clin Oncol. 2002;14(5):372-381.

13. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol (Madr). 1988;27(2):131-146.

14. Vivekanandan S, Landau DB, Counsell N, et al. The impact of cardiac radiation dosimetry on survival after radiation therapy for non-small cell lung cancer. Int J Radiat Oncol. 2017;99(1):51-60.

15. Papanikolaou N, Battista JJ, Boyer AL, Kappas C, Klein E, Mackie TR. AAPM Report 85: Tissue Inhomogeneity Corrections for Megavoltage Photon Beams. Report of the AAPM Radiation Therapy Committee Task Group 65.; 2004.

16. Frank SJ, Forster KM, Stevens CW, et al. Treatment planning for lung cancer: traditional homogeneous point-dose prescription compared with heterogeneity-corrected dose-volume prescription. Int J Radiat Oncol Biol Phys. 2003;56(5):1308-1318.

17. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small cell lung cancer. N. Engl. J. Med. 1990; 323: 940-945

18. Kotas M, Willner J and Flentje M. Sequential chemo-radiotherapy in non-small cell lung cancer. Lung Cancer 2001;33;61-64

19. Boyd J, Hubbs JL, Kim DW, Hollis D, Marks LB, Kelsey CR. Timing of local and distant failure in resected lung cancer: implications for reported rates of local failure. J Thorac Oncol. 2010;5(2):211-214.

20. O'Rourke N, Roqué i Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. In: Cochrane Database of Systematic Reviews. 2010:CD002140.

21. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J. Clin. Oncol. 2010;28:2181–90.

22. Ross GJS. Nonlinear Estimation. Springer; 1990.

23. Dudewicz EJ, Mishra SN. Modern Mathematical Statistics. New York : Wiley; 1988.

24. Konishi S, Kitagawa G. Information Criteria and Statistical Modeling. Springer; 2008.

25. Cox JD. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: Possible survival benefit with > 69.6 Gy in favorable patients with radiation therapy oncology group stage III non-small-cell lung carcinoma: J Clin Oncol. 1990;8(9):1543-1555.

26. Bonner JA, McGinnis WL, Stella PJ, et al. The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced nonsmall cell lung carcinoma. Cancer. 1998;82(6):1037-1048.

27. Ball D, Bishop J, Smith J, et al. A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-

small cell lung cancer: Final report of an Australian multi-centre trial. Radiother Oncol. 1999;52(2):129-136.

28. Sause W, Kolesar P, Taylor IV S, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest. 2000;117(2):358-364.

29. Curran WJ, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage iii non-small cell lung cancer: Randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103(19):1452-1460.

30. Hayman BJ, Martel MK, Haken RK Ten, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy : Update of a phase I trial. J Clin Oncol. 2001;19(1):127-136.

31. Kong F-M, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys. 2005;63(2):324-333.

32. Sim S, Rosenzweig KE, Schindelheim R, Ng KK, Leibel S. Induction chemotherapy plus three-dimensional conformal radiation therapy in the definitive treatment of locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):660-665.

33. Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. Int J Radiat Oncol. 2002;54(2):370-378.

34. Wu K-L, Jiang G-L, Liao Y, et al. Three-dimensional conformal radiation therapy for non-small-cell lung cancer: a phase I/II dose escalation clinical trial. Int J Radiat Oncol Biol Phys. 2003;57(5):1336-1344.

35. Schild SE, Bonner JA, Hillman S, et al. Results of a phase II study of high-dose thoracic radiation therapy with concurrent cisplatin and etoposide in limited-stage small-cell lung cancer (NCCTG 95-20-53). J Clin Oncol. 2007;25(21):3124-3129.

36. Bradley J, Graham M V., Winter K, et al. Toxicity and outcome results of RTOG 9311: A phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2005;61(2):318-328.

37. Belani CP. Phase III Study of the Eastern Cooperative Oncology Group (ECOG 2597): Induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non small cell Lung cancer. J Clin Oncol. 2005;23(16):3760-3767.

38. Skladowski K, Maciejewski B, Golen M, et al. Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: Long-term results of Phase III clinical trial. Int J Radiat Oncol. 2006;66(3):706-713.

39. De Ruysscher D, Wanders R, van Haren E, et al. HI-CHART: A Phase I/II study on the feasibility of high-dose continuous hyperfractionated accelerated radiotherapy in patients with inoperable NSCLC. Int J Radiat Oncol Biol Phys. 2008;71(1):132-138.

40. Bradley JD, Moughan J, Graham M V., et al. A Phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III NSCLC: Phase I Results of RTOG 0117. Int J Radiat Oncol Biol Phys. 2010;77(2):367-372.

41. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). Radiother Oncol. 2011;100(1):76-85.

42. Sapkota S, Kapoor R, Aggrawal AN. A randomized trial comparing conventional fractionation versus accelerated hyperfractionation with three dimensional conformal

radiotherapy (3D-CRT) and concurrent chemotherapy in unresectable non small cell lung cancer. Lung Cancer. 2013;80:S27.

43. Reinfuss M, Glinski B, Kowalska T, et al. Radiotherapy for stage III, inoperable, asymptomatic small cell lung cancer. Final results of a prospective randomized study (240 patients). Cancer Radiother. 1999;3(6):475-479.

44. Nabavizadeh N, Elliott DA, Chen Y, et al. Image guided radiation therapy (IGRT) practice patterns and IGRT's impact on workflow and treatment planning: Results from a national survey of american society for radiation oncology members. Int J Radiat Oncol. 2016;94(4):850-857.

45. Chen C, Uyterlinde W, Sonke JJ, De Bois J, Van Den Heuvel M, Belderbos J. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. Radiother Oncol. 2013;108(2):337-341.

46. Uyterlinde W, Chen C, Kwint M, et al. Prognostic parameters for acute esophagus toxicity in Intensity Modulated Radiotherapy and concurrent chemotherapy for locally advanced non-small cell lung cancer. Radiother Oncol. 2013;107(3):392-397.

47. Belderbos JSA, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66(1):126-134.

48. Thirion P, Holmberg O, Collins CD, et al. Escalated dose for non-small-cell lung cancer with accelerated hypofractionated three-dimensional conformal radiation therapy. Radiother Oncol. 2004;71(2):163-166.

49. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. Cancer. 2005;103(10):2118-2127.

50. Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2004;60(3):741-747.

51. Armstrong J, Raben A, Zelefsky M, et al. Promising survival with three-dimensional conformal radiation therapy for non-small cell lung cancer. Radiother Oncol. 1997;44(1):17-22.

52. Hayman JA, Martel MK, Ten Haken RK, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: Update of a phase I trial. J Clin Oncol. 2001;19(1):127-136.

53. Wurstbauer K, Deutschmann H, Kopp P, et al. NSCLC: Primary tumor size - Radiation dose-related accelerated, twice daily radiotherapy by target splitting, preceded by 2 cycles of chemotherapy - First results of a prospective study. In: Strahlentherapie Und Onkologie. 2007;183:38-40.

54. Qi J, Nakayama K, Cardiff RD, et al. Siah2-dependent concerted activity of HIF and FoxA2 regulates formation of neuroendocrine phenotype and neuroendocrine prostate tumors. Cancer Cell. 2010;18(1):23-38.

55. Maguire PD, Marks LB, Sibley GS, et al. 73.6 Gy and beyond: Hyperfractionated accelerated radiotherapy for non-small-cell lung cancer. J Clin Oncol. 2001;19(3):705-711.

56. Maguire J, Khan I, McMenemin R, et al. SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III Non-Small Cell Lung Cancer and good performance status. European Journal of Cancer. Vol 50; 2014:2939-2949.

57. King SC, Acker JC, Kussin PS, Marks LB, Weeks KJ, Leopold KA. High-dose, hyperfractionated, accelerated radiotherapy using a concurrent boost for the treatment of nonsmall cell lung cancer: Unusual toxicity and promising early results. Int J Radiat Oncol Biol Phys. 1996;36(3):593-599.

58. Din OS, Harden S V., Hudson E, et al. Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: Results from 4 UK centres. Radiother Oncol. 2013;109(1):8-12.

59. Adkison JB, Khuntia D, Bentzen SM, et al. Dose escalated, hypofractionated radiotherapy using helical tomotherapy for inoperable non-small cell lung cancer: preliminary results of a risk-stratified phase I dose escalation study. Technol Cancer Res Treat. 2008;7(6):441-447.

60. Kepka L, Tyc-Szczepaniak D, Bujko K. Dose-per-fraction escalation of accelerated hypofractionated three-dimensional conformal radiotherapy in locally advanced non-small cell lung cancer. J Thorac Oncol. 2009;4(7):853-861.

61. Harada H, Nishio M, Murakami H, et al. Dose-escalation study of three-dimensional conformal thoracic radiotherapy with concurrent S-1 and cisplatin for inoperable stage III non-small-cell lung cancer. Clin Lung Cancer. 2013;14(4):440-445.

62. Kaira K, Tomizawa Y, Yoshino R, et al. Phase II study of oral S-1 and cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. Lung Cancer. 2013;82(3):449-454.

63. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol. 2008;26(15):2457-2463.

64. Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: Radiation Therapy Oncology Group trial 98-01. J Clin Oncol. 2005;23(10):2145-2154.

65. Contreras JA, Lin AJ, Weiner A, Speirs C, et al. Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer. Radiother Oncol. 2018;128(3):498-504.

66. Santiago A, Barczyk S, Jelen U, Engenhart-Cabillic R, Wittig A. Challenges in radiobiological modeling: can we decide between LQ and LQ-L models based on reviewed clinical NSCLC treatment outcome data. Radiat Oncol. 2016;11:67.

67. Jeong J, Oh JH, Sonke JJ, et al. Modeling the cellular response of lung cancer to radiation therapy for a broad range of fractionation schedules. Clin Cancer Res. 2017;23(18):5469-5479.

68. Koukourakis M, Hlouverakis G, Kosma L, et al. The impact of overall treatment time on the results of radiotherapy for nonsmall cell lung carcinoma. Int J Radiat Oncol. 1996;34(2):315-322.

69. Robinson AG, Biot M, Young K, et al. Causes of death and subsequent treatment after initial radical or palliative therapy of stage III non-small-cell lung cancer. Curr Oncol. 2015; 22(5):333-340.

Table 1. Dataset details. ‘Accelerated’ achedules delivered >1 fraction-per-day; ‘hyperfractionated’ and ‘hypofractionated’ schedules gave doses-per-fraction of ≤1.6 and ≥3.0 Gy respectively. Accelerated and hyperfractionated categories overlap.

	68 trial arms, 6957 patients **Stage I/II = 17%** (1211 patients)*, **Stage IIIA/IIIB = 83%** (5746 patients)**					
Schedules	RT alone: 21 Accelerated: 8 Hyperfractionated: 6 Hypofractionated: 1		Sequential CRT: 27 Accelerated: 4 Hyperfractionated: 1 Hypofractionated: 0		Concurrent CRT: 20 Accelerated: 6 Hyperfractionated: 5 Hypofractionated: 0	
Patient No.	1571 Stage I/II = 397 Stage IIIA/IIIB = 1174		3023 Stage I/II = 720 Stage IIIA/IIIB = 2303		2363 Stage I/II = 94 Stage IIIA/IIIB = 2269	
	Mean	Range	Mean	Range	Mean	Range
Dose† (Gy)	64.7	40.0-81.0	70.8	55.0-96.6	67.3	55.0-77.7
Dose-per-fraction (Gy)	2.10	1.26-4.00	2.10	1.68-2.75	2.02	1.26-2.75
Number of fractions	33.1	10-58	33.8	20-46	35.2	20-58
RT duration (days)	35.3	12-55	43.0	16-64	41.4	21-52
OS_{2yr} (%)	34.0	6-56	36.1	18-59	44.9	23-68

*1174 patients were split 50/50% stage I versus II; the split for a further 37 patients was not published and 50/50% was assumed.

**5682 patients were split 52/48% stage IIIA vs IIIB, with a 50/50 split assumed for the other 64 patients.

†Tabulated doses have been increased by 5% for trials not employing heterogeneity corrections.

Table 2: Degrees of freedom (DoF), parameter values and 95% CIs for fits of Models 1-3.

Parameter		Partridge Model	Model 1 Probit-EQD2T	Model 2 CRT effects added	Model 3 CRT, publication date and toxicity effects added	
		Fit, DoF= 63 (asymptotic 95% CI)	**Fit, DoF= 60 (asymptotic 95% CI)**	**Fit, DoF = 58 (asymptotic 95% CI)**	**Fit, DoF = 55 (profile-likelihood 95% CI)**	**(asymptotic 95% CI)**
Fitted parameters						
$\alpha/\beta_{\text{tum}}$	Gy	10†	4.9 (3.0, 6.8)	4.2 (2.1, 6.2)	**4.0 (3.0, 5.4)**	(2.3, 5.6)
λ	Gy/day	0.6†	0.71 (0.58, 0.83)	0.97 (0.72, 1.21)	**0.38 (0.30, 0.48)**	(0.26, 0.51)
T_k	Days	21†	28 (27, 29)	28 (27, 29)	**12 (12*, 17)**	(10, 14)
$\text{EQD2T}_{\text{tum,50}}(S_{\text{IIIa}})$	Gy	69 (63, 74)	69 (63, 74)	75 (66, 84)	**51 (45, 57)**	(44, 59)
$\Delta\ \text{EQD2T}_{\text{tum,50}}(S_{\text{I}})$	Gy	-12 (-22, -3)	-11 (-19, -4)	-33 (-45, -22)	**-11 (-21, -6)**	(-20, -2)
$\Delta\ \text{EQD2T}_{\text{tum,50}}(S_{\text{II}})$	Gy	38 (9, 77)	49 (13, 85)	17 (-13, 47)	**-4.2 (-11.3, 2.4)**	(-13.6, 5.1)
$\Delta\ \text{EQD2T}_{\text{tum,50}}(S_{\text{IIIb}})$	Gy	9 (-1, 16)	8 (-2, 18)	13 (-5, 31)	**13.2 (4.6, 20.4)**	(1.3, 25.2)
m	-	0.62 (0.51, 0.73)	0.66 (0.57, 0.75)	0.82 (0.65, 1.00)	**0.39 (0.25, 0.55)**	(0.15, 0.62)
$\text{OS}_{\text{24m-max}}^{\text{Ch-RT}}$	%	-	-	96 (89, 103)	**95 (89, 103)**	(86, 104)
$\text{RS}^{\text{Conc-Ch-RT}}$	-	-	-	1.29 (1.19, 1.39)	**1.23 (1.16, 1.31)**	(1.12, 1.34)
R	per year	-	-	-	**0.018 (0.013, 0.020)**	(0.014, 0.024)
$\text{EQD2}_{\text{NT,50}}$	Gy	-	-	-	**105 (97, 116)**	(94, 115)
m_{NT}	-	-	-	-	**0.30 (0.15, 0.80)**	(-0.08, 0.69)
Fixed parameters						
$\text{OS}_{\text{24m-max}}^{\text{RT-only}}$	%		-	85	85	
α/β_{NT}	Gy		-	-	3	
Fit quality measures						
AIC		9147.2	9136.0	9050.4	8985.0	
Cross-validation score		439.1	423.7	363.5	215.1	
Likelihood-ratio *p* value**		-	$5\text{x}10^{-6}$	$3\text{x}10^{-20}$	$2\text{x}10^{-15}$	

† Parameters fixed at values derived from HNSCC by Partridge et.al. * For T_K the profile-likelihood 95% confidence interval lower limit is fixed at 12 days. **Significance of the difference in fit quality between a model and the immediately simpler model in the table.

Figure 1. a) Observed OS_{2yr} vs. prescribed physical dose for the analyzed trial arms. LOESS regression (solid line) indicates dose-response in the region 40-80 Gy. b) Physical dose vs. RT schedule duration (RT only - open, sequential chemo-RT - striped, concurrent CRT - closed; larger symbols indicate better OS_{2yr}).

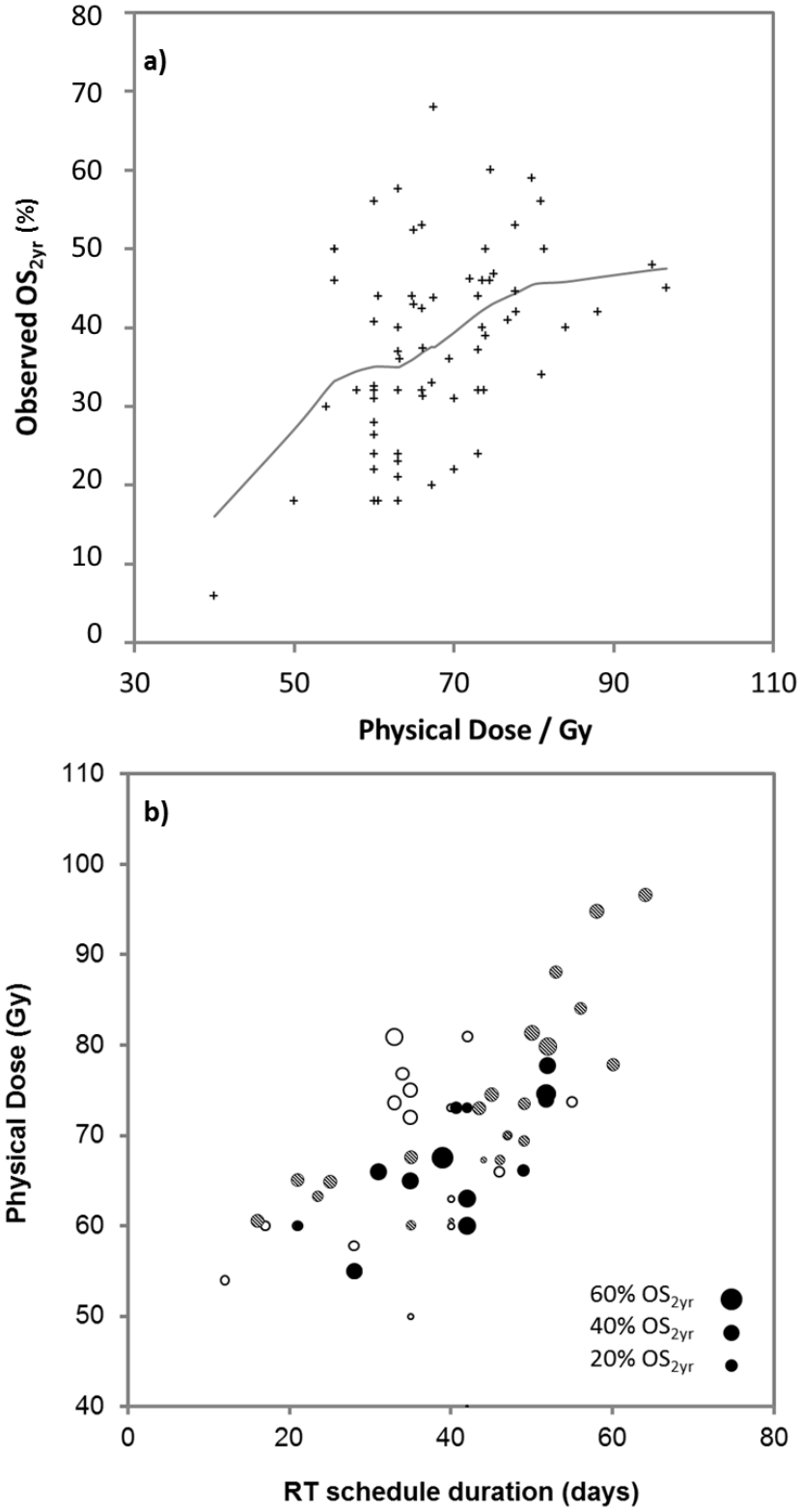


Figure 2. Calibration plots of predicted versus observed OS_{2yr} across the dataset, for fits of Models 1-3. Patients per trial arm are represented by areas of plotted points. Weighted least-square fits to the data (solid lines) are shown along with the line-of-identity. The gradients of the plots increase with improving fit quality.

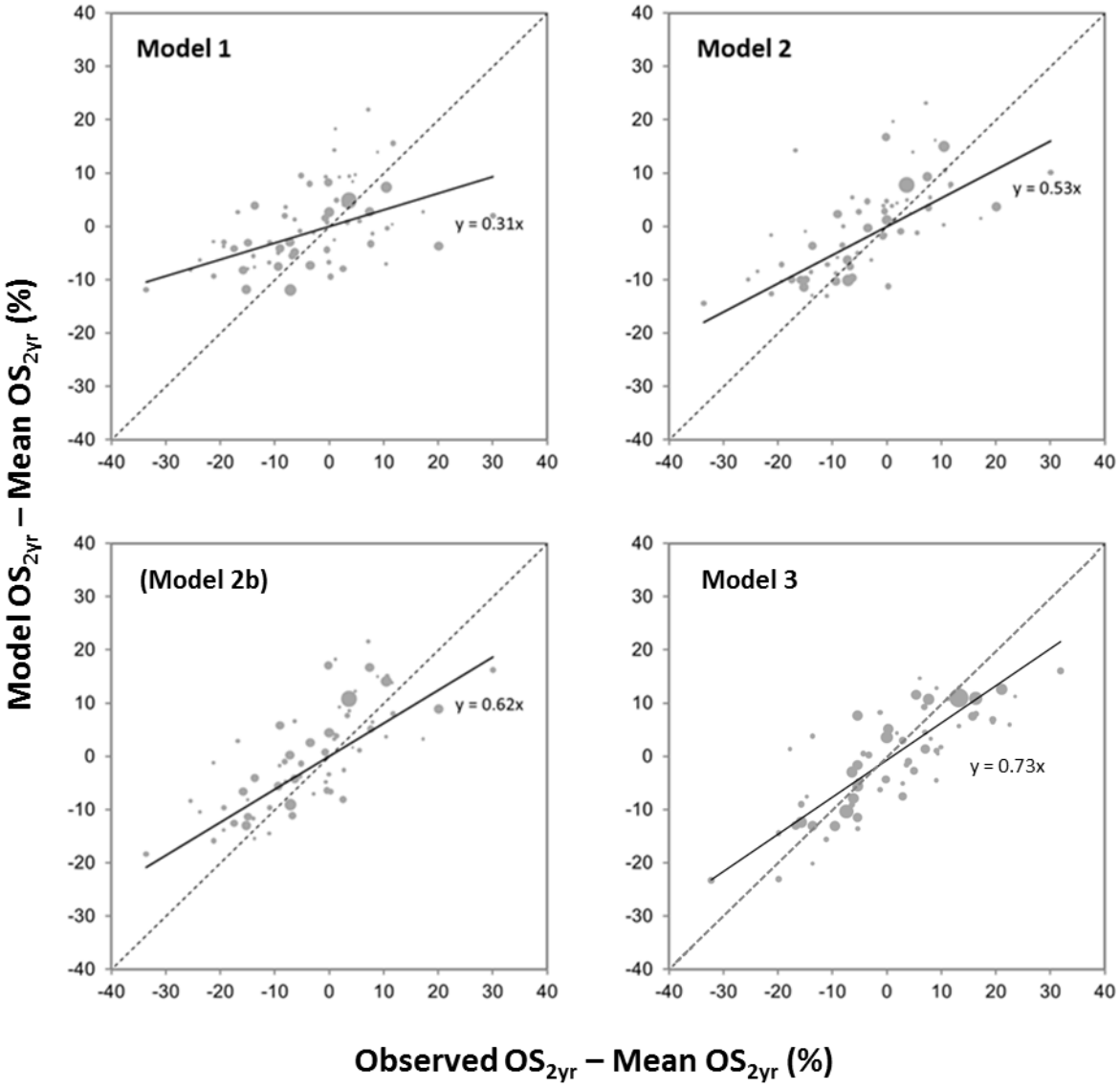


Figure 3. a) Observed (closed) and predicted (open) OS_{2yr} rates plotted against $EQD2T_{tum}$. b) Residuals (grey). Symbol sizes reflect patient numbers per trial arm.

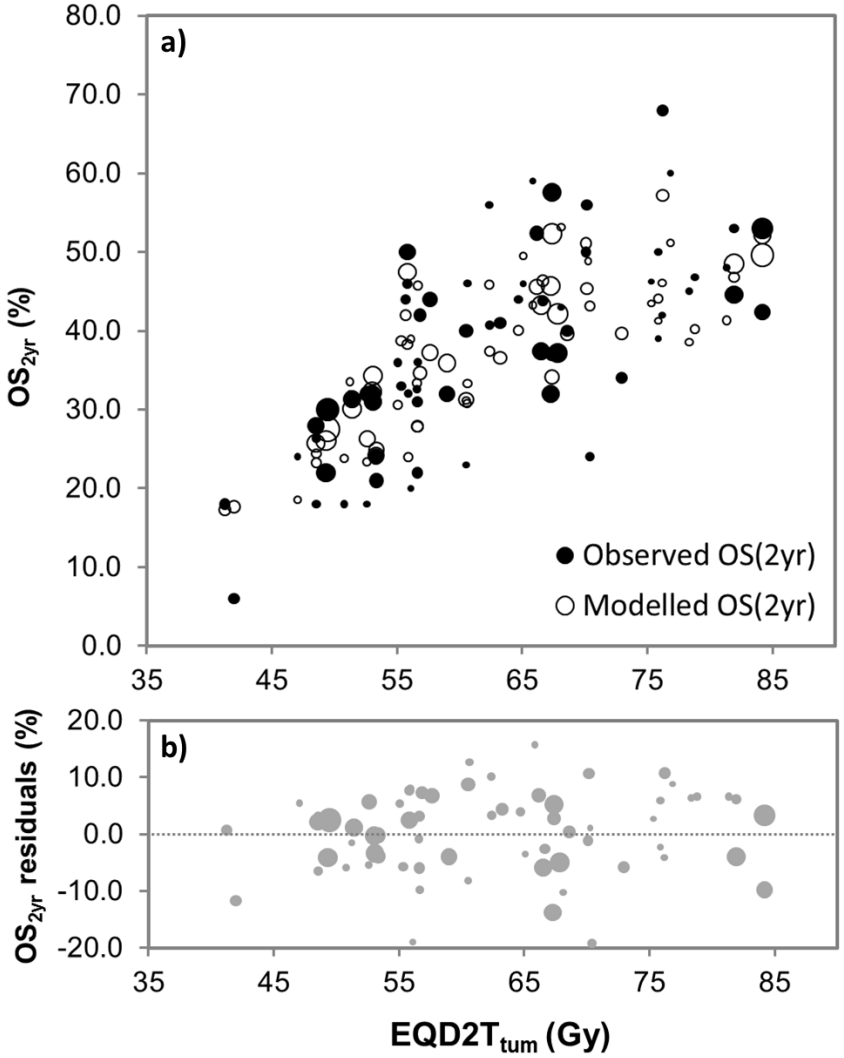
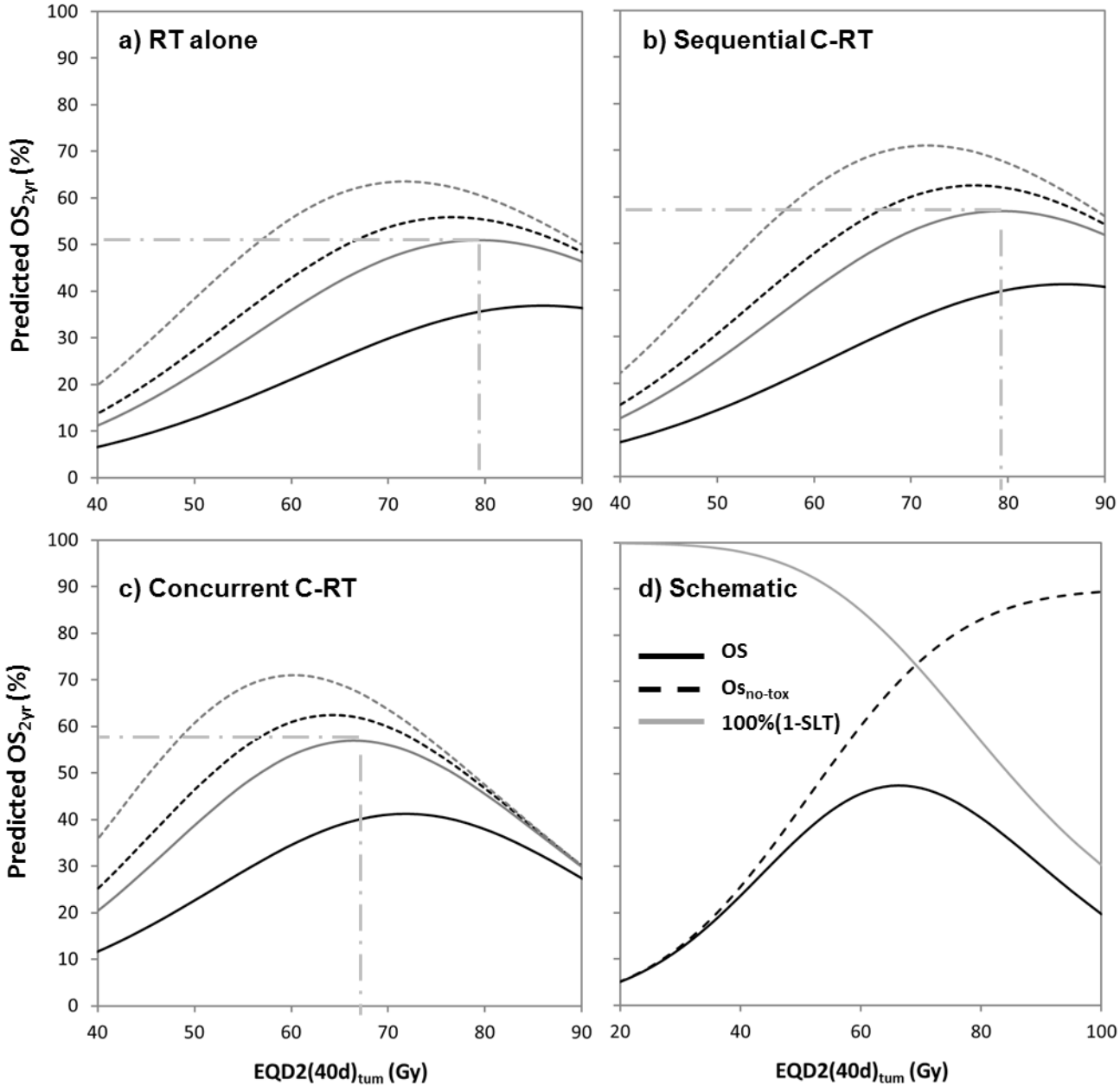


Figure 4. (a-c) OS_{2yr} dose-response curves calculated from the Model 3 fit for (a) RT alone, (b) sequential CRT, (c) concurrent CRT. Curves for stage I, II, IIIA and IIIB NSCLC are plotted as dashed grey, dashed black, solid grey and solid black lines. The peaks of the IIIA curves are picked out. (d) Schematic showing composition of OS as a product of survival unlimited by toxicity ($OS_{no\text{-}tox}$) and (100% - survival-limiting toxicity percentage rate).



Supplementary Information

Study of stage-specific survival limiting toxicity rates

Goodness-of-fit measures (likelihood-ratio, AIC, leave-one-out cross validation) all indicated that Model 3 was preferred over simpler models despite its relative complexity. Here we explore whether a more complex model might further improve the data description.

Early-stage NSCLC tumors are smaller with less mediastinal involvement, and thus critical normal structures in patients with early-stage disease are potentially less likely to receive prescription-level doses, reducing rates of survival-limiting toxicity in these patients.

We therefore tested a variant of Model 3 in which the fraction $f(S_I)$ of patients with stage I disease who might possibly experience survival-limiting toxicity (because critical structures received the prescribed dose) was freely fitted rather than being assumed to be 100%. The fitted value of $f(S_I)$ was 51%, and while the model was preferred on AIC and cross-validation to Model 3, the difference was marginal (Table S2). When the fraction was freely fitted for all stages (rather than just for stage I and being fixed at 100% for the rest) the resulting model was disfavoured on AIC and cross-validation, indicating a risk of overfitting. Overall, therefore, in the main part of the study we chose to limit model complexity to that of Model 3.

Table S1. Degrees of freedom (DoF), parameter values and 95% confidence intervals for the Model 2b fit.

Parameter		Model 2b CRT and publication date effects added Fit, DoF = 57 (asymptotic 95% CI)
		Fitted Parameters
$\alpha/\beta_{\text{tum}}$	Gy	7.5 (2.7, 12.4)
λ	Gy/day	0.59 (0.42, 0.77)
T_k	Days	12 (10, 14)
$\text{EQD2T}_{\text{tum},50}(S_{\text{IIIa}})$	Gy	54 (45, 62)
$\Delta\ \text{EQD2T}_{\text{tum},50}(S_{\text{I}})$	Gy	-25 (-34, -16)
$\Delta\ \text{EQD2T}_{\text{tum},50}(S_{\text{II}})$	Gy	3 (-14, 20)
$\Delta\ \text{EQD2T}_{\text{tum},50}(S_{\text{IIIb}})$	Gy	16 (-8, 32)
m	-	0.94 (0.68, 1.21)
$\text{OS}_{24\text{m-max}}^{\text{Ch-RT}}$	%	93 (86, 99)
$\text{RS}^{\text{Conc-Ch-RT}}$	-	1.22 (1.13, 1.30)
R	per year	0.018 (0.015, 0.022)
$\text{EQD2}_{\text{NT},50}$	Gy	-
m_{NT}	-	-
		Fixed Parameters
$\text{OS}_{24\text{m-max}}^{\text{RT-only}}$	%	85
α/β_{NT}	Gy	-
		Fit quality measures
AIC		9012.1
Cross-validation score		261.1
Likelihood-ratio p value†		2×10^{-9}

† Significance of the difference in fit quality relative to model 2.

Table S2. Effect of fitting the fraction f(S_I) of stage I patients in whom critical normal structures receive the prescribed dose-level and survival-limiting toxicities can occur (set to 100% for all stages in Model 3, and fitted for stage I only in the modified model).

Parameter		Model 3 CRT, publication date and toxicity effects added	
		Fit, DoF = 55; f(S_I) set to 1 (asymptotic 95% CI)	Fit, DoF = 54; f(S_I) fitted (asymptotic 95% CI)
		Fitted parameters	
α/β_{tum}	Gy	4.0 (3.0, 5.4)	4.2 (2.2, 6.2)
λ	Gy/day	0.38 (0.30, 0.48)	0.38 (0.26, 0.49)
T_k	Days	12 (12*, 17)	12 (10, 14)
$EQD2T_{tum,50}(S_{IIIa})$	Gy	51 (45, 57)	47 (38, 57)
$\Delta\ EQD2T_{tum,50}(S_I)$	Gy	-11 (-21, -6)	-5.2 (-17.1, 6.7)
$\Delta\ EQD2T_{tum,50}(S_{II})$	Gy	-4.2 (-11.3, 2.4)	-3.6 (-12.0, 4.8)
$\Delta\ EQD2T_{tum,50}(S_{IIIb})$	Gy	13.2 (4.6, 20.4)	8.9 (1.5, 16.2)
m	-	0.39 (0.25, 0.55)	0.28 (0.15, 0.40)
$OS_{24m\text{-}max}^{Ch\text{-}RT}$	%	95 (89, 103)	95 (86, 105)
$RS^{Conc\text{-}Ch\text{-}RT}$	-	1.23 (1.16, 1.31)	1.19 (1.10, 1.27)
R	per year	0.018 (0.013, 0.020)	0.018 (0.014, 0.025)
$EQD2_{NT,50}$	Gy	105 (97, 116)	100 (85, 115)
m_{NT}	-	0.30 (0.15, 0.80)	0.63 (-0.44, 1.70)
$f(S_I)$	-	1	0.51 (-0.02, 1.04)
		Fixed parameters	
$OS_{24m\text{-}max}^{RT\text{-}only}$	%	85	85
α/β_{NT}	Gy	3	3
		Fit quality measures	
AIC		8985	8984.7
Cross-validation score		215.1	217.3

*For T_K the profile-likelihood 95% confidence interval lower limit is fixed at 12 days.

Figure S1. Dose-per-fraction plotted against RT duration for the trial arms analyzed. Patient numbers-per-trial arm are represented by areas of plotted points.

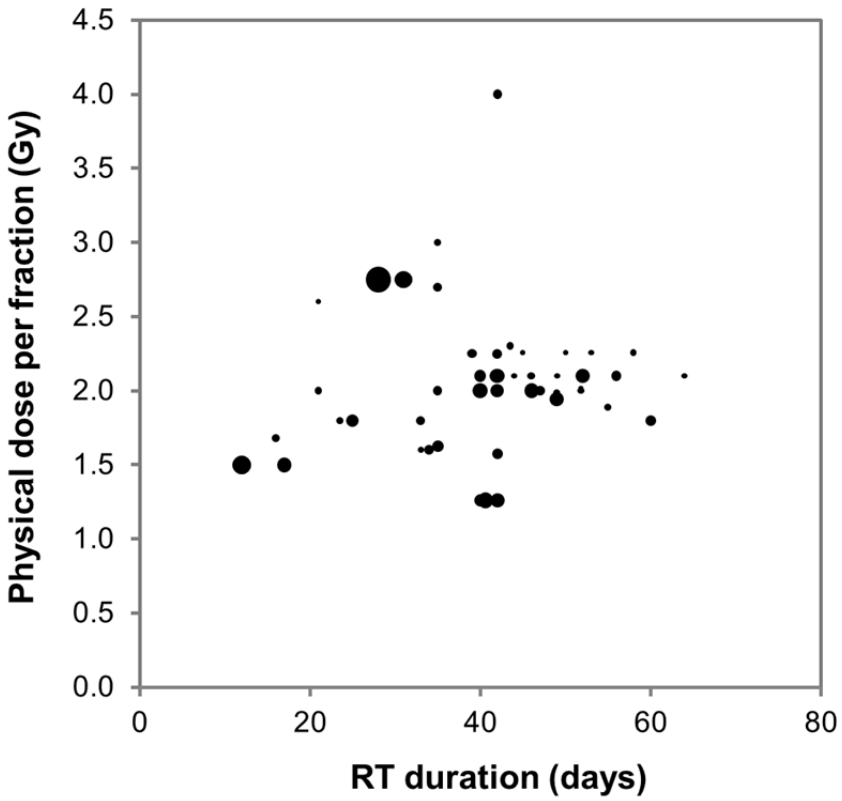


Figure S2: Model 2 fit residuals (differences between observed and fitted OS_{2yr}) versus year of publication. Symbol sizes reflect patient numbers per trial arm. The solid line is a weighted least squares linear fit to the data.