

Supplementary material for Tucker SL, et al. Is there an impact of heart exposure on the incidence of radiation pneumonitis? Analysis of data from a large clinical cohort. Acta Oncol 2014;53:590–6.

SUPPLEMENTARY MATERIALS

Details of the NTCP modeling:

Univariate analyses of dose-volume quantities describing lung or heart exposure were performed using the probit NTCP model:

$$(1) \quad \text{NTCP} = \frac{1}{2\pi} \int_{-\infty}^t e^{-u^2/2} du$$

where

$$(2) \quad t = b_0 + b_1 X_1$$

X_1 represents the covariate of interest and b_0 and b_1 represent the unknown model parameters.

For consistency with the Lyman-Kutcher-Burman model, the model was re-parameterized so that the fitted parameters were $X_{50} = -b_0 / b_1$ and $m = -1/b_0$, i.e.

$$(3) \quad t = \frac{X_1 - X_{50}}{m X_{50}}$$

When X_1 has units of dose, we use the notation D_{50} for X_{50} , and when X_1 has units of volume, the notation V_{50} is used.

For some analyses, the covariate employed was effective dose, defined as

$$(4) \quad D_{eff} = \left(\sum (D_i)^{1/n} v_i \right)^n$$

where D_i is the dose to fraction v_i of the organ at risk, n is the volume parameter, and the sum extends over all dose bins in the DVH.

Multivariate LKB modeling was performed by including an additional covariate, X_2 , in equation (2), i.e.

$$(5) \quad t = b_0 + b_1 X_1 + b_2 X_2$$

or equivalently

$$(6) \quad t = \frac{X_1 - X_{50}}{m X_{50}} + b_2 X_2$$

For the RP endpoint studied by Huang et al., multivariate modeling was also performed using their best-fitting logistic model:

$$(7) \quad \text{NTCP} = \frac{1}{1 + e^{-X}}$$

where $X = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3$, with $X_1 = \text{lung D35}$, $X_2 = \text{maximum lung dose}$, and $X_3 = \text{heart D10}$.

Models were fitted to data using a mixture model approach to account for censoring and differences in extent of patient follow-up. The distribution of event times was modeled using a lognormal distribution with density function

$$(8) \quad f(t) = \frac{1}{\sigma t \sqrt{2\pi}} e^{-(\ln t - \mu)^2 / 2\sigma^2}$$

which has parameters μ and σ .

Model fits and comparisons:

Models fitted in the present study are listed below. Shown are the parameter estimates obtained and their 95% profile-likelihood confidence intervals, together with AIC values and P-values for comparisons of nested models.

For models 1-14, the endpoint was Grade ≥ 3 RP. Models 1--3 include covariates describing lung exposure alone. Models 4--9 test the addition of heart factors to models 2--3. Models 10--12 include heart factors only. Model 14 is the best-fitting model published by Huang et al., and is compared with a version of the model in which the heart covariate is omitted (model 13).

- Model 1: Univariate LKB model with MLD as the covariate.
 $D_{50} = 31.4$ (28.1, 38.1) Gy
 $m = 0.45$ (0.36, 0.60)
 AIC = 1036.898
- Model 2: Univariate LKB model with D_{eff} ($n=0.5$) as the covariate.
 $D_{50} = 41.6$ (38.7, 47.4) Gy
 $m = 0.32$ (0.25, 0.43)
 AIC = 1032.388
- Model 3: Univariate LKB model with D_{eff} as the covariate, n estimated from data.
 $D_{50} = 40.9$ (31.2, 52.8) Gy
 $m = 0.32$ (0.22, 0.48)
 $n = 0.52$ (0.27, 0.95)
 AIC = 1034.368
 Comparison with Model 1: P = 0.033
- Model 4: Multivariate LKB model with MLD and heart D10 as covariates.
 $D_{50} = 29.8$ (23.2, 45.5) Gy
 $m = 0.45$ (0.36, 0.59)
 $b_2 = -0.0014$ (-0.0093, 0.0064) Gy⁻¹
 AIC = 1038.767
 Comparison with Model 1: P = 0.717
- Model 5: Multivariate LKB model with MLD and heart V65 as covariates.
 $D_{50} = 33.1$ (28.2, 44.8) Gy
 $m = 0.47$ (0.37, 0.63)
 $b_2 = 0.63$ (-0.80, 2.04)

AIC = 1038.149
 Comparison with Model 1: P = 0.387

- Model 6: Multivariate LKB model with MLD and MHD as covariates.
 $D_{50} = 32.8$ (26.3, 50.1) Gy
 $m = 0.46$ (0.36, 0.61)
 $b_2 = 0.0024$ (-0.010, 0.015) Gy⁻¹
 AIC = 1038.756
 Comparison with Model 1: P = 0.706
- Model 7: Multivariate LKB model with D_{eff} ($n=0.5$) and heart D10 as covariates.
 $D_{50} = 40.0$ (34.2, 52.3) Gy
 $m = 0.31$ (0.24, 0.43)
 $b_2 = -0.0017$ (-0.0091, 0.0059) Gy⁻¹
 AIC = 1034.200
 Comparison with Model 2: P = 0.665
- Model 8: Multivariate LKB model with D_{eff} ($n=0.5$) and heart V65 as covariates.
 $D_{50} = 42.0$ (37.9, 51.1) Gy
 $m = 0.32$ (0.24, 0.45)
 $b_2 = 0.149$ (-1.35, 1.63) Gy⁻¹
 AIC = 1034.350
 Comparison with Model 2: P = 0.844
- Model 9: Multivariate LKB model with D_{eff} ($n=0.5$) and MHD as covariates.
 $D_{50} = 43.3$ (37.6, 56.6) Gy
 $m = 0.32$ (0.25, 0.45)
 $b_2 = 0.0034$ (-0.0082, 0.0149) Gy⁻¹
 AIC = 1034.064
 Comparison with Model 1: P = 0.569
- Model 10: Univariate LKB model with heart D10 as the covariate.
 $D_{50} = 131$ (101, 239) Gy
 $m = 0.77$ (0.61, 1.01)
 AIC = 1055.718
- Model 11: Univariate LKB model with heart V65 as the covariate.
 $V_{50} = 0.456$ (0.308, 1.029)
 $m = 1.04$ (0.90, 1.24)
 AIC = 1057.122
- Model 12: Univariate LKB model with MHD as the covariate.
 $D_{50} = 65.2$ (49.3, 113.6) Gy
 $m = 0.85$ (0.70, 1.05)
 AIC = 1053.516
- Model 13: Multivariate logistic model with $X_1 =$ lung D35, $X_2 =$ maximum lung dose.
 $b_0 = -4.75$ (-8.36, -1.14)
 $b_1 = 0.055$ (0.035, 0.076) Gy⁻¹
 $b_2 = 0.034$ (-0.019, 0.085) Gy⁻¹
 AIC = 1037.530

Model 14: Multivariate logistic model with $X_1 = \text{lung D35}$, $X_2 = \text{maximum lung dose}$,
 $X_3 = \text{heart D10}$
 $b_0 = -4.74 (-8.36, -1.13)$
 $b_1 = 0.053 (0.029, 0.079) \text{ Gy}^{-1}$
 $b_2 = 0.033 (-0.020, 0.085) \text{ Gy}^{-1}$
 $b_3 = 0.0013 (-0.0116, 0.0146) \text{ Gy}^{-1}$
AIC = 1039.489
Comparison with Model 13: $P = 0.841$

For models 15-27, the endpoint was Grade ≥ 2 RP. Model 15 was fitted first, to obtain estimates of μ and σ to be used in fits of the remaining models. Previous experience has shown that estimates of these parameters are very stable, since they are determined by the observed distribution of event times, and are largely unaffected by the assumed relationship between dose-volume factors and NTCP. Models 16--18 include covariates describing lung exposure alone. The LKB volume parameter estimated for Grade ≥ 2 RP (model 18) is not significantly different from $n=1$, corresponding to MLD. However, fits based on D_{eff} ($n=0.5$) are included to demonstrate that the results are not highly dependent on the specific value of n assumed. Models 19--24 test the addition of heart factors to models 16--17. Models 25--27 include heart factors only.

Model 15: Univariate LKB model with D_{eff} as the covariate, n estimated from data, parameters of latency distribution for Grade >2 toxicity also estimated from data
 $D_{50} = 27.2 (19.0, 37.1) \text{ Gy}$
 $m = 0.54 (0.36, 0.89)$
 $n = 0.66 (0.38, 1.16)$
 $\mu = 1.42 (1.36, 1.48)$
 $\sigma = 0.45 (0.41, 0.49)$
AIC = 1754.948

Model 16: Univariate LKB model with MLD as the covariate.
 $D_{50} = 21.1 (19.5, 23.1) \text{ Gy}$
 $m = 0.71 (0.54, 1.028)$
AIC = 1751.135

Model 17: Univariate LKB model with D_{eff} ($n=0.5$) as the covariate.
 $D_{50} = 32.1 (30.5, 34.1) \text{ Gy}$
 $m = 0.46 (0.35, 0.67)$
AIC = 1749.980

Model 18: Univariate LKB model with D_{eff} as the covariate, n estimated from data.
 $D_{50} = 27.2 (19.0, 37.1) \text{ Gy}$
 $m = 0.54 (0.36, 0.89)$
 $n = 0.66 (0.38, 1.16)$
AIC = 1750.954
Comparison with Model 16: 0.140

Model 19: Multivariate LKB model with MLD and heart D10 as covariates.
 $D_{50} = 23.4 (17.9, 36.4) \text{ Gy}$

- $m = 0.72 (0.54, 1.051)$
 $b_2 = 0.0026 (-0.0042, 0.0094) \text{ Gy}^{-1}$
 AIC = 1752.582
 Comparison with Model 1: $P = 0.457$
- Model 20: Multivariate LKB model with MLD and heart V65 as covariates.
 $D_{50} = 20.6 (18.6, 23.5) \text{ Gy}$
 $m = 0.69 (0.52, 1.01)$
 $b_2 = -0.35 (-1.72, 1.02)$
 AIC = 1752.882
 Comparison with Model 1: $P = 0.615$
- Model 21: Multivariate LKB model with MLD and MHD as covariates.
 $D_{50} = 19.8 (16.8, 24.7) \text{ Gy}$
 $m = 0.69 (0.52, 1.00)$
 $b_2 = -0.0042 (-0.0157, 0.0073) \text{ Gy}^{-1}$
 AIC = 1752.617
 Comparison with Model 1: $P = 0.472$
- Model 22: Multivariate LKB model with D_{eff} ($n=0.5$) and heart D10 as covariates.
 $D_{50} = 34.8 (29.3, 47.0) \text{ Gy}$
 $m = 0.49 (0.35, 0.74)$
 $b_2 = 0.0029 (-0.0037, 0.0095) \text{ Gy}^{-1}$
 AIC = 1751.216
 Comparison with Model 2: $P = 0.382$
- Model 23: Multivariate LKB model with D_{eff} ($n=0.5$) and heart V65 as covariates.
 $D_{50} = 31.2 (29.3, 33.8) \text{ Gy}$
 $m = 0.43 (0.33, 0.63)$
 $b_2 = -0.76 (-2.18, 0.67) \text{ Gy}^{-1}$
 AIC = 1750.890
 Comparison with Model 2: $P = 0.296$
- Model 24: Multivariate LKB model with D_{eff} ($n=0.5$) and MHD as covariates.
 $D_{50} = 31.6 (28.4, 36.8) \text{ Gy}$
 $m = 0.46 (0.34, 0.68)$
 $b_2 = -0.0014 (-0.0121, 0.0094) \text{ Gy}^{-1}$
 AIC = 1751.917
 Comparison with Model 1: $P = 0.803$
- Model 25: Univariate LKB model with heart D10 as the covariate.
 $D_{50} = 58.6 (49.5, 71.5) \text{ Gy}$
 $m = 1.44 (1.04, 2.34)$
 AIC = 1766.406
- Model 26: Univariate LKB model with heart V65 as the covariate.
 $V_{50} = 0.149 (0.073, 0.675)$
 $m = 4.77 (2.90, 13.4)$
 AIC = 1783.394
- Model 27: Univariate LKB model with MHD as the covariate.
 $D_{50} = 27.5 (20.4, 42.0) \text{ Gy}$
 $m = 2.42 (1.62, 4.76)$
 AIC = 1776.980