Fractionation Schedule Optimization for Lung Cancer Treatments using Radiobiological and Dose Distribution Characteristics

Innovation/Impact

Based on the Lyman-Kutcher-Burman (LKB) model for normal tissue complication probabilities we derive rigorous mathematical criteria on the normal tissue dose distributions determining the nature of an optimal dose per fraction schedule. For a normal tissue, the relationship between a simple dose distribution characteristic and the alpha-beta ratio determines whether a hypo- or a hyper-fractionated regimen is optimal. Empirical volume criteria can potentially be replaced by more robust, model-based characteristics.

Optimization Problem

Selecting the individual fraction doses d_i for each fraction i to maximize a linear-quadratic effect in the tumor E_T while constraining the normal tissue complication probability according to the LKB model yields the optimization problem:

$$\text{Max} \quad E_T(\{d_i\}) = \alpha_T \sum_i d_i + \beta_T \sum_i d_i^2 \qquad (1)$$

$$\text{s. t.} \quad \text{NTCP}(\{d_i\}; n, (\alpha/\beta)_S, m, TD50) \leq \Omega_{\text{NTCP}} \qquad (2)$$

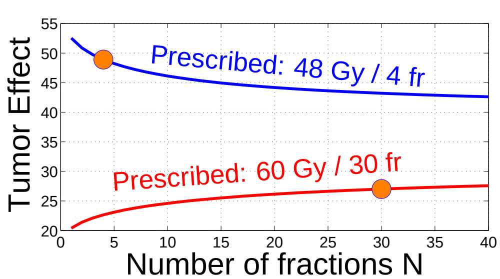
The NTCP is computed from the DVH of the normal tissue with alpha-beta ratio $(\alpha/\beta)_S$, dose reduction parameter n, as well as the Lyman-model parameters m and $TD50$.

The solution of this problem is surprisingly simple. If none of the parameters are time-dependent, all d_i are equal. However, the optimal number N of these equal fractions depends on the relative magnitude of the ratio of the alpha-beta ratios and a characteristic number of the dose distribution in the normal tissue (NT):

$$B < \left(\frac{\alpha}{\beta}\right)_S / \left(\frac{\alpha}{\beta}\right)_T \quad \Rightarrow N = 1 \qquad \text{(Hypo)} \qquad (3)$$

$$B > \left(\frac{\alpha}{\beta}\right)_S / \left(\frac{\alpha}{\beta}\right)_T \quad \Rightarrow N = \infty \qquad \text{(Standard/Hyper)} \qquad (4)$$

In (3) and (4), B is the *bifurcation number* and is scale-free, i.e. independent of the prescription dose. For serial structures ($n = 0$), $B = d_{max}/D$, where D is the tumor dose and d_{max} the NT maximum dose. For parallel structures, B is a ratio involving the first and second moments of the NT dose distribution, both easily derivable from the DVH. Equations (3) and (4) should be re-interpreted in a practical clinical context. The single dose solution $N = 1$ corresponds to hypofractionation and the infinite number of fractions case corresponds to standard or hyperfractionation. Figure 1 shows the tumor effect E_T for various isotoxic fractionations for the lung for 2 clinical non-small cell lung cancer (NSCLC) treatment plans. In accordance with the model, delivery of the dose in fewer or more fractions results in a larger tumor effect depending on whether Eq. (3) or (4) holds, respectively.



Patient Data Analysis

To establish the clinical relevance of the bifurcation number, it was tested if the inequalities (3) and (4) were consistent with clinically prescribed fractionations for NSCLC treatments at our institution. In lung cancer treatments fractionation protocols are strongly dependent on the configuration (size, location) of the GTV and its relative position to various organs at risk. The bifurcation numbers for lung and esophagus were computed from clinical treatment plans for 30 patients randomly selected from various fractionation protocols. Of the 30 patients, 13 were treated with standard 2 Gy fractionation (Group 1, red in Fig. 2), 4 with 60 Gy in 20 fractions (Group 2, green in Fig. 2), and 13 with $>$7.5 Gy per fraction (Group 3, blue in Fig. 2).

Results and Discussion

Figure 2 shows that the bifurcation numbers for both lung and esophagus are a perfect classifier (no misclassified patients in this cohort) for the hypo-fractionated and the conventional fractionation group. The variability of the bifurcation numbers within patients of the conventional fractionation group was much smaller than the variability of the treated ITV volumes or the ITV to lung volume ratios. The bifurcation numbers for the intermediate fractionation group 2 are in between.

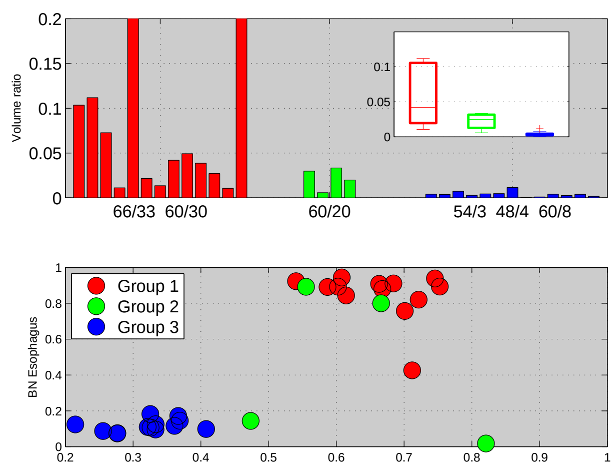


Figure 2: *Upper Panel: ITV to non-GTV lung volume ratios for all 30 patients stratified by fractionation group (red: standard 2 Gy, green: 3 Gy, blue: $>$ 7.5 Gy per fraction). Lower panel: Bifurcation number B of Non-GTV lung and esophagus for the same groups.*

Conclusions

Within the LQ model, the bifurcation number provides a mathematically sound foundation for the traditional radiobiological arguments for hypo/hyperfractionation, i.e. low/high tumor alpha-beta ratio and/or an anatomical configuration that allows large/little volume sparing of the normal tissue. The bifurcation number is consistent with current clinical fractionation protocols for NSCLC treatments. This framework may allow for prospective selection of an appropriate fractionation protocol once the dose distribution has been optimized.