Supplementary Online Content

Feng M, Suresh K, Schipper MJ, et al. Individualized adaptive stereotactic body radiotherapy for liver tumors in patients at high risk for liver damage: a phase 2 clinical trial. *JAMA Oncol*. Published online August 10, 2017. doi:10.1001/jamaoncol.2017.2303

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Description of radiation dose adaptation.

eFigure 1. Tumor dose, with the first part of treatment in blue and the second part of treatment in gold.

eFigure 2. Predicted and observed change in liver function for all patients after treatment adaptation

eMethods 1.

We describe here, in detail, the approach used to adapt treatment. Let k_{0h} k_{1h} and k_{2h} denote the ICG 15-minute retention proportions (ICGR15) for patient h at baseline, mid-treatment and 1 month post fraction 5 (or the planned timepoint for fraction 5 for patients who do not receive fractions 4 and 5). Let d_{1h} and d_{2h} denote the SBRT part 1 and part 2 dose per fraction values. At the mid-treatment timepoint for patient h, the goal was to select d_{2h} so that $k_{2h} < .44$ with high probability. The expected value of the final ICGR15 (k_{2h}) is given by

$$E[k_{2h}] = k_{1h} + (k_{1h} - k_{0h})(2d_{2h}/3d_{1h})\gamma \quad (1)$$

The term $(2d_2/3d_1)$ captures the difference in dose given during the first and second course of treatment. The unknown parameter γ was included to allow for the possibility that the damage (increase in ICGR15 normalized to dose) during the second course of treatment would be greater than the corresponding damage during the first course. Each time a patient in the trial reached their mid-treatment adaptation point, γ was calculated as described here. Let $b_{1h}=(k_{1h} - k_{0h})/(3d_{1h})$ and $b_{2h}=(k_{2h} - k_{1h})/(2d_{2h})$. The ratios of these sensitivities, denoted as $r_h = b_{2h}/b_{1h}$, were assumed to follow a Gaussian(μ,σ^2) distribution, with priors given by μ~Gaussian(1.5,0.25) and σ^2~Gamma(2.5,0.08). Given the priors and the observed data r_i ; i=1, 2, …,h-1, the posterior distribution for μ and σ^2, and the predictive distribution for future r_h, are easily calculated. Out of a desire to be conservative, γ in (1) was not estimated by the posterior mean μ. Rather it was estimated by the 90th percentile of the predictive distribution for r_h calculated as the median of $\mu+\Phi^{-1}(0.9)\sigma^2$, sampled from the posterior distribution. The algorithm for selecting d_{2h} for patient h, was:

1) If $(k_{1h} > .44)$, then $d_{2h} = 0$
2) If $(k_{lh} < .44)$ AND $(k_{1h} < k_{0h})$, then $d_{2h} = d_{1h}$
3) If $(k_{0h} < k_{lh} < .44)$, then $d_{2h} = \min((0.44- k_{1h})/(2(\gamma)b_{1h}),d_{1h})$

Note that the first term in the minimum function above is obtained by setting the left hand side of (1) to .44 and solving for d_{2h}.

Here is a calculation for a specific patient: This patient had an ICGR15 of 25% at baseline. At the mid-treatment timepoint (1 month post fraction 3) the ICGR15 had increased to 35%. Based on this, our model predicted that if we gave 20 Gy (2 more fractions of 10 Gy), the expected mean ICGR15 after the 5th fraction, would be 41% with an upper 90% prediction bound of 55%. Thus we decreased the dose to 10 Gy (5Gy per fraction) so that the resulting upper 90% prediction limit would be equal to 44%.