Supplement 2

eMethods. Description of radiation dose adaptation

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

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

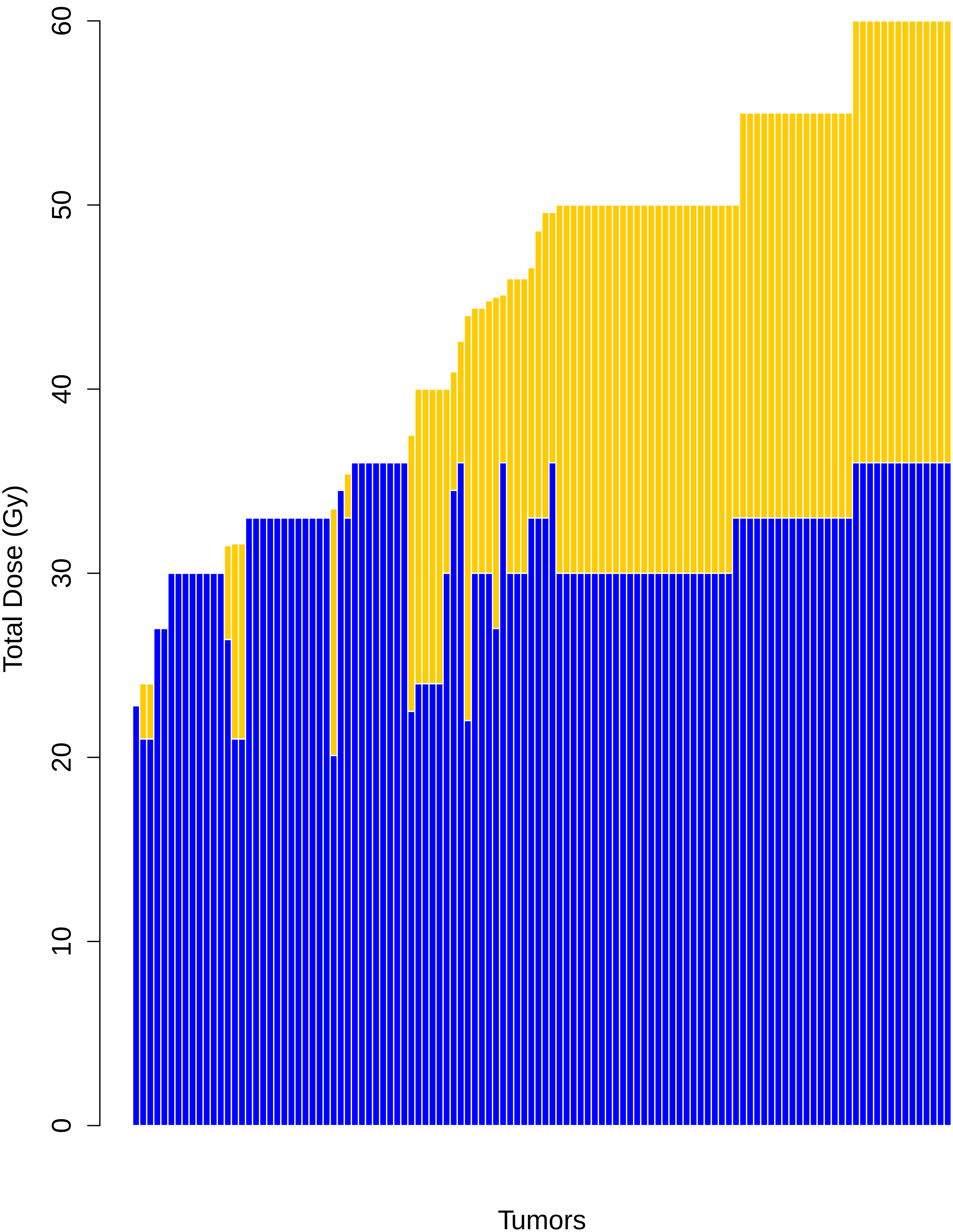
The term $(2d_2/3d_1)$ captures the difference in dose given during the first and second course of treatment. The unknown parameter γ was included to allow for the possibility that the damage (increase in ICGR15 normalized to dose) during the second course of treatment would be greater than the corresponding 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 $d_{2h} = \min((0.44- k_{1h})/(2(\gamma)b_{1h}),d_{1h})$

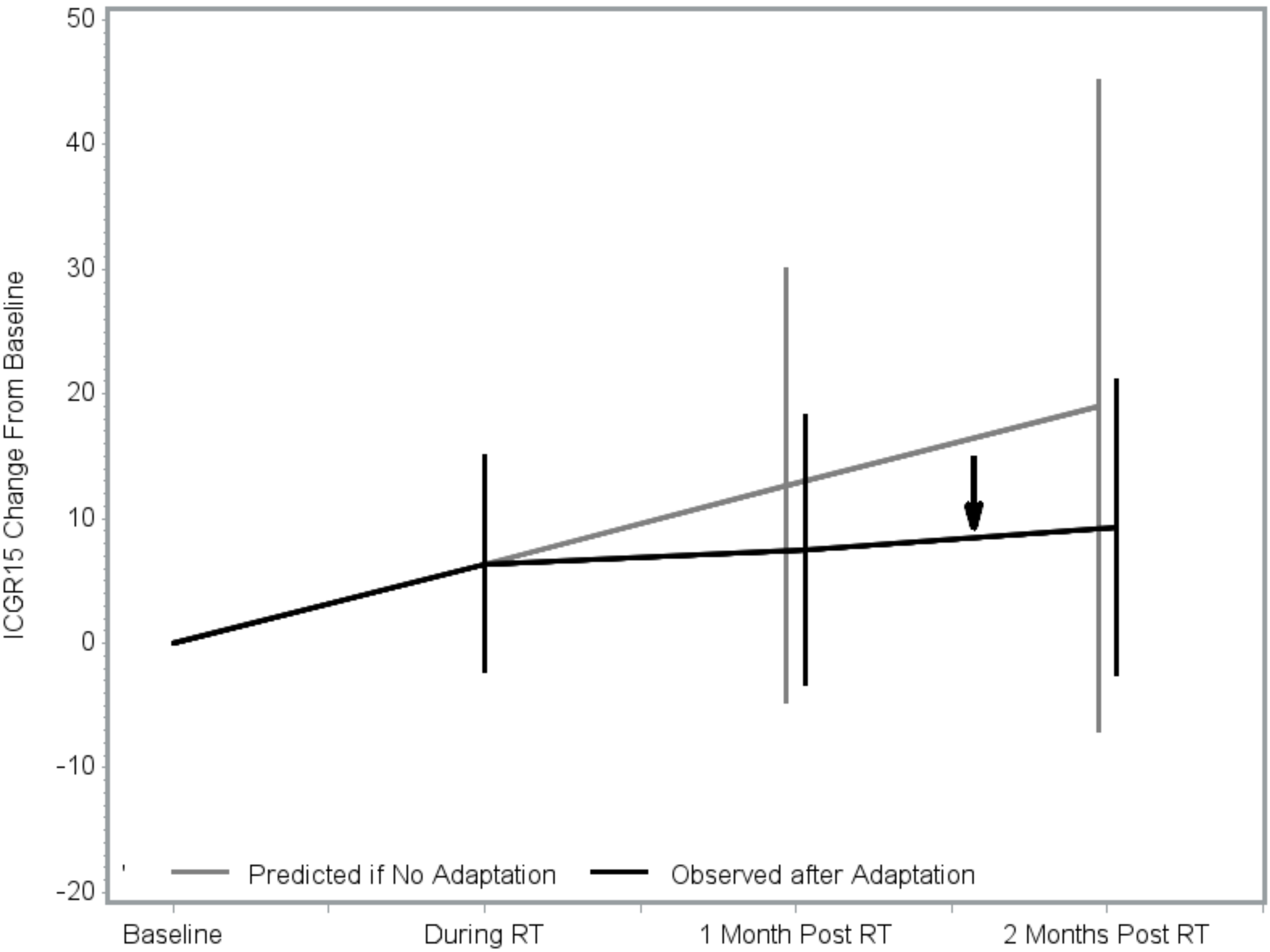
Note that the first term in the minimum function above is obtained by setting the left hand side of (1) to .44 and solving for d_{2h}.

eFigure1. Tumor dose, with the first part of treatment in blue and the second part of treatment in gold.

eFigure2. Predicted and observed change in liver function for all patients after treatment adaptation.



Total Dose (Gy)
0
10
20
30
40
50
60
Tumors


ICGR15 Change From Baseline
50
40
30
20
10
0
-10
-20
Predicted if No Adaptation
Observed after Adaptation
Baseline
During RT
1 Month Post RT
2 Months Post RT