Appendix A

A1. Summary of models and their parameters

Table A1. Computational model summaries. All doses are in EQD2.

Model (No. of patients)	**Cross-reference**	**Parameters (95% CI)**
Dose conversion to EQD2 *(LQL)* *(n=192)*	Ref. 4	$^{\alpha}/_{\beta} = 2.5$ Gy DT = 5.0 Gy $^{\gamma}/_{\alpha} = 5.0$ Gy
Perfusion Reduction *HCC* *(n=23)*	Fig. 2	D50=23.5 (10.8-36.2); *k*=0.268 (0.207-0.329)
Dosimetric LKB *ALBI* *C-P* *Enzymatic changes* *(n=176)**	Fig. 1	D50=24.3 (22.0-26.5); γ_{50}=0.466 (0.195-0.737) D50=29.1 (26.5-31.7); γ_{50}=0.494 (0.217-0.772) D50=52.6 (50.4-54.7); γ_{50}=1.29 (0.963-1.62)
Dosimetric+imaging PA *ALBI* *C-P* *Enzymatic changes* *(n=176)**	Fig. 3	f50=0.515 (0.459-0.571); γ_{50}=1.05 (0.0564-2.05) f50=0.559 (0.502-0.616); γ_{50}=1.08 (0.0114-2.14) f50=0.920 (0.804-1.04); γ_{50}=1.52 (0.0924-2.94)

Dose+biomarkers LKB *(ALBI)* *change in TGF-β1* *change in Eotaxin* *(n=72)*	Fig. 4	D50=16.3 (-17.3-49.9); γ_{50}=0.408 (-0.565-1.38); δ=0.0893 (-3.56-3.74) D50=15.2 (-9.16-39.6); γ_{50}=0.416 (-0.524-1.36); δ=0.357 (-2.76-3.47)
Dose+biomarkers PA *(ALBI)* *change in TGF-β1* *change in Eotaxin* *(n=72)*	Fig. 5	f50=0.217 (-0.275-0.709); γ_{50}=0.651 (-0.998-2.30); δ=0.959 (-2.00-3.92) f50=0.427 (0.133-0.722);γ_{50}=0.652 (-0.106-2.36); δ=0.630 (-1.62-2.87)
Change in ICG *LKB* *PA* *(n=102)*	Fig. 6	D50=11.0 (-61.5-83.5); γ_{50}=0.434 (-0.590-1.46); δ=0.937 (-8.29-10.2) f50=0.482 (-0.984-1.95);γ_{50}=0.744 (-2.46-3.95); δ=0.148 (-3.07-3.37)

*Patients with terminal baseline toxicity were excluded.

A2. Sample implementation and comparison with known limits.

Table A2.1. LKB estimates of risk (Figure 1 model). Note the impact of the selected endpoint on estimated risk, which should be taken into consideration when applying these values for what would be considered as "safe dose."

Dose-volume limits	**EQD2 Conversion***	**Estimated Risk**			
		RILD (%)**	**ALBI (%)**	**C-P (%)**	**Enzymatic changes (%)**
MLD in 3 fx					
13	19.74	0.01	40.77	34.06	2.08
15	25.00	0.72	51.34	43.08	4.49
18	33.33	31.33	66.79	57.15	11.81
20	38.89	79.43	75.83	66.15	19.96
MLD in 5 fx					
13	14.73	0.00	32.28	27.05	1.00
15	18.33	0.00	38.71	32.34	1.76
18	24.40	0.48	50.19	42.07	4.15
20	28.89	6.27	58.73	49.64	7.25

*These estimates are approximate only due to nonlinearity in EQD2 conversion from 3D distributions into dose-volume histograms (assume a uniform distribution in the uninvolved liver).

**QUANTEC HCC liver model (Figure 2, Ref. 31).

Table A2.2 PA estimates of risk (Figures 2/3 model). Note the impact of the selected endpoint on estimated risk, which should be taken into consideration when applying these values for what would be considered as "safe dose."

Dose-volume limits	EQD2 Conversion*	Perfusion reduction (Figure 2)	Estimated Risk			
			RILD (%)**	ALBI (%)	C-P (%)	Enzymatic changes (%)
MLD in 3 fx						
13	19.74	0.49	0.00	44.37	36.42	3.66
15	25.00	0.50	0.00	47.79	39.53	4.25
18	33.33	0.52	1.16	51.71	43.16	5.02
20	38.89	0.53	22.12	53.81	45.12	5.48
MLD in 5 fx						
13	14.73	0.47	0.00	40.66	33.10	3.08
15	18.33	0.48	0.00	43.58	35.71	3.53
18	24.40	0.50	0.04	47.46	39.22	4.19
20	28.89	0.51	0.17	49.76	41.34	4.63

*These estimates are approximate only due to nonlinearity in EQD2 conversion from 3D distributions into dose-volume histograms (assume a uniform distribution in the uninvolved liver).

**Estimated based on PA model from Ref. 22.