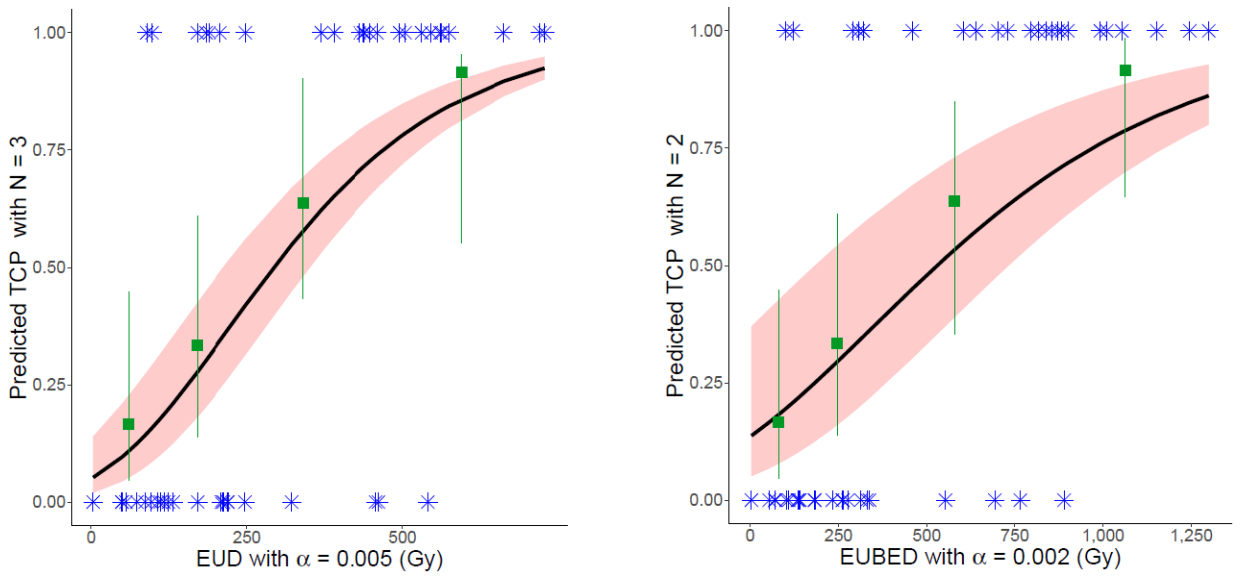

Supplemental Figure 1. TCP predictions (black curves) from the cell survival model fit compared to observed response proportions (green squares) by dose quartiles. EUD metrics correspond to the α and N that gave the best fit (Supplemental Table 7). The blue asterisk indicates the observed binary response for each lesion. The red shaded region shows the 95% CI for the model and the green lines indicate the 95% score-based CIs for the observations. Comparison with Fig. 3 of the main text demonstrate the superior performance of the logit model compared with this model.

Supplemental Table 1. Patient/lesion characteristics of the entire cohort and sub-cohort with mRECIST response.

	Total cohort	**Sub-cohort with mRECIST response**
Disease		
Primary	9 (41%)[a]	7 (58%)[b]
Liver Metastasis	13 (59%)[c]	5 (42%)[d]
Total Patients	22	12
Total Therapies	28	14
Number of lesions		
Primary	31 (35%)	21 (50%)
Liver Metastasis	58 (65%)	21 (50%)
Total Lesions	89	42
Cirrhotic livers	7 (32%)[e]	6 (50%)[e]
	Median [range]	
Administered activity (GBq)		
Hepatocellular carcinoma	2.5 [0.5 to 4.4]	1.9 [0.5 to 2.9]
Cholangiocarcinoma	3.2 [2.1 to 4.4]	4.4
Liver Metastasis	2.9 [0.6 to 5.8]	3.1 [0.7 to 3.9]
Specific activity of microspheres at administration (Bq/sphere)	866 [144 to 1456]	887 [182 to 1191]
Lesion volume (mL)		
Hepatocellular carcinoma	11.7 [2.3 to 57.7]	5.5 [2.3 to 53.6]
Cholangiocarcinoma	8.7 [4.0 to 130.8]	7.4 [4.0 to 130.8]
Liver Metastasis	9.3 [2.2 to 827.8]	8.1 [2.2 to 827.8]
Number of lesions per patient	3 [1 to 5]	3 [1 to 5]
Elapsed time between microsphere administration and ^{90}Y PET/CT (min)	153, [44 to 230]	138 [44 to 191]
Elapsed time between 90Y treatment and first follow-up (weeks)	11 [5 to 23]	13 [6 to 23]

[a]Includes hepatocellular carcinoma (7), cholangiocarcinoma (2)

[b]Includes hepatocellular carcinoma (6), cholangiocarcinoma (1)

[c]Includes neuroendocrine(5), colorectal(2), colon (2), pheochromocytoma (1), anal(1) and adrenal(2) disease.

[d]Includes neuroendocrine (3), pheochromocytoma (1), and adrenal (1) disease.

[e]All cases correspond to hepatocellular carcinoma

Supplemental Table 2. Summary of dose metrics and dose – shrinkage model R^2 values (with 95% CI) for the full dataset and the subset of lesions with mRECIST assessment. The ADxx, BEDxx and Vxx values presented are those that provided the best shrinkage model fit.

	All lesions (N=89)			Subset of lesions with mRECIST (N=42)			
Metric	**Median, Mean [Min,Max]**	**Dose - shrinkage model R^2 (95% CI)**	**p-value***	**Response**	**Median, Mean [Min,Max]**	**Dose - shrinkage model R^2 (95% CI)**	**p-value***
AD (Gy)	268, 359 [1, 1271]	RECIST: 0.074 (0.010, 0.194)	0.007	RECIST	270, 398 [2, 1271]	0.338 (0.137, 0.572)	0.0001
				mRECIST	270, 398 [2, 1271]	0.423 (0.163, 0.622)	<0.0001
BED (Gy)	404, 663 [1, 4337]	RECIST: 0.043 (0.005, 0.100)	0.038	RECIST	438, 763 [2, 4337]	0.257 (0.064, 0.408)	0.001
				mRECIST	438, 763 [2, 4337]	0.334 (0.135, 0.584)	0.0001
ADxx (Gy)	449, 573 [2, 2727]	RECIST: 0.089 (0.017, 0.204) (AD10)	0.005	RECIST	439, 550 [3, 1835]	0.335 (0.139, 0.544) (AD20)	0.0001
				mRECIST	38, 475 [2, 1535]	0.409 (0.163, 0.612) (AD30)	<0.0001
BEDxx (Gy)	140, 251 [0, 1334]	RECIST: 0.021 (0.0002, 0.087) (BED90)	0.106	RECIST	145, 248 [1, 894]	0.174 (0.002, 0.419) (BED90)	0.007
				mRECIST	354, 602 [2, 2085]	0.392 (0.059, 0.610) (BED50)	<0.0001
Vxx (AD) (%)	63, 60 [0, 100]	RECIST: 0.115 (0.016, 0.272) (V200)	0.0003	RECIST	18, 35 [0, 99]	0.273 (0.076, 0.532) (V450)	0.001
				mRECIST	14, 31 [0, 98]	0.414 (0.063, 0.606) (V500)	<0.0001
Vxx(BED) (%)	75, 67 [0, 100]	RECIST: 0.124 (0.013, 0.280) (V200)	0.0002	RECIST	37, 45 [0, 100]	0.248 (0.054, 0.486) (V500)	0.002
				mRECIST	37, 45 [0, 100]	0.403 (0.108, 0.582) (V500)	<0.0001

*p-value of dose metric from linear mixed model of shrinkage.

Supplemental Table 3. Dose-shrinkage (mRECIST) models for primary and metastatic lesions with AD metrics as covariates. Results for RECIST are not shown, but similar to mRECIST the slopes and intercepts of the models for the 2 groups were not significantly different. Coefficients for each group come from fully interacted linear models of the form:

$$\widehat{Shrinkage}_{ij} = \beta_{0g} + b_{0g} + \beta_{1g} * Dose_{ij} + b_{1g} * Dose_{ij} + \epsilon_{ij}, i = 1, \dots, n, j = 1, \dots, n_i, g = 1,2$$

Where $\beta_{0g} = \begin{cases} \beta_{01}, \ if\ metastatic\ lesion \\ \beta_{02}, if\ primary\ lesion \end{cases}$ and $\beta_{1g} = \begin{cases} \beta_{11}, \ if\ metastatic\ lesion \\ \beta_{12}, if\ primary\ lesion \end{cases}$ and $b_{0g} =$ random intercept and $b_{1g} =$ random slope. So, there is a different slope and intercept depending on whether lesion is primary or metastatic.

Dose Metric	Group	Coefficient	Estimate (SE)	p-value for dose - shrinkage	p-value for whether intercepts differ	p-value for whether slopes differ
EUD, α=0.0002	Primary	Intercept	8.080 (13.714)	0.567	0.960	0.726
		Slope	0.073 (0.034)	0.043		
	Mets	Intercept	8.938 (9.422)	0.362		
		Slope	0.087 (0.017)	<0.0001		
V500	Primary	Intercept	18.549 (9.426)	0.073	0.763	0.131
		Slope	0.518 (0.209)	0.020		
	Mets	Intercept	14.293 (10.113)	0.183		
		Slope	0.967 (0.197)	<0.0001		
DOSE30	Primary	Intercept	6.764 (14.291)	0.645	0.822	0.994
		Slope	0.066 (0.031)	0.044		
	Mets	Intercept	10.805 (10.263)	0.313		
		Slope	0.066 (0.014)	<0.0001		
Mean Dose	Primary	Intercept	7.975 (13.703)	0.571	0.900	0.822
		Slope	0.073 (0.034)	0.042		
	Mets	Intercept	10.115 (9.454)	0.306		
		Slope	0.082 (0.016)	<0.0001		

Supplemental Table 4. Dose-shrinkage (mRECIST) models for primary and metastatic lesions with BED metrics as covariates. Results for RECIST are not shown, but similar to mRECIST the slopes and intercepts of the models for the 2 groups were not significantly different.

Dose Metric	Group	Coefficient	Estimate (SE)	p-value for dose - shrinkage	p-value for whether intercepts differ	p-value for whether slopes differ
EUBED, α=0.0005	Primary	Intercept	10.416 (12.317)	0.414	0.982	0.796
		Slope	0.043 (0.019)	0.033		
	Mets	Intercept	10.789 (9.746)	0.290		
		Slope	0.049 (0.010)	<0.0001		
V500	Primary	Intercept	13.871 (10.635)	0.217	0.692	0.152
		Slope	0.450 (0.179)	0.018		
	Mets	Intercept	7.726 (10.771)	0.487		
		Slope	0.814 (0.171)	<0.0001		
BED50	Primary	Intercept	12.222 (12.056)	0.331	0.799	0.856
		Slope	0.041 (0.019)	0.040		
	Mets	Intercept	16.367 (10.355)	0.140		
		Slope	0.045 (0.011)	0.0003		
Mean BED	Primary	Intercept	9.963 (12.094)	0.426	0.278	0.260
		Slope	0.043 (0.018)	0.026		
	Mets	Intercept	27.473 (9.559)	0.014		
		Slope	0.021 (0.006)	0.002		

Supplemental Table 5. Mean AD and BED metrics for (mRECIST) responding vs. nonresponding lesions. The ADxx, BEDxx and Vxx values presented are those that provided the best shrinkage model fit.

Dose Metric	**Mean (SD) for Responding lesions [Min, Max]**	**Mean (SD) for Nonresponding lesions [Min, Max]**	**p-value**
AD (Gy)	559 (291) [90, 1271]	183 (136) [2, 574]	<0.0001
V500 (AD) (%)	50 (31) [0, 98]	6 (17) [0, 72]	<0.0001
DOSE30 (Gy)	665 (341) [98, 1535]	221 (159) [2, 638]	<0.0001
BED (Gy)	1129 (946) [102, 4337]	255 (210) [2, 809]	<0.0001
V500 (BED) (%)	68 (32) [0, 100]	15 (25) [0, 94]	<0.0001
BED50 (Gy)	888 (500) [95, 2085]	221 (209) [2, 793]	<0.0001

Supplemental Table 6. AUC and log likelihood for logit function fits to EUD and EUBED for a range of α values. Step size was made finer around the optimal α value.

	EUD		EUBED	
α	AUC	-2logL	AUC	-2logL
0.0001	0.8819	394.2	0.9028	397.8
0.0002	0.8796	394.1	0.9028	396.8
0.0005	0.8773	394.2	0.9028	396.2
0.0008	0.8727	394.4	0.9051	396.6
0.001	0.8727	394.5	0.9028	396.9
0.002	0.8727	395.5	0.8843	398.6
0.005	0.8495	397.8	0.8588	401.5
0.008	0.8403	399.3	0.8449	402.8
0.01	0.8333	400.1	0.8356	403.4
0.1	0.787	403.6	0.7894	405

Supplemental Table 7. Cell survival TCP model fit AUC and log likelihood for a range of α values (at optimal N). TCP for each lesion *j* in *k* th patient was expressed as: $TCP_{jk} = e^{-N*exp(-\alpha*EUBED_{jk})}$ with N identified as the number of partially controlled tumor sub-volumes. Note that this N is not the clonogen cell number as in the basic Poisson model, because the end point used in the current study is short-duration partial control and not cure. Optimal values of α and N were estimated using profile likelihood methods as described in the text for the logit model. Comparison of the results below with results of Table 1 of the main text show that in terms of AUC, the logit model performed better.

	EUD			**EUBED**		
α	**N**	**AUC**	**-2logL**	**N**	**AUC**	**-2logL**
0.0001	1	0.841	67.114	1	0.861	65.208
0.001	1	0.839	56.705	1	0.868	52.6
0.002	1	0.839	53.638	2	0.851	47.411
0.005	3	0.817	47.472	3	0.824	48.486
0.008	4	0.806	50.148	5	0.808	55.62
0.01	5	0.803	53.809	6	0.799	61.554
0.03	20	0.775	104.232	23	0.768	124.875
0.06	58	0.761	185.031	64	0.761	220.028
0.1	134	0.75	292.422	---	---	---

*For EUBED with α = 0.1 model failed to converge and no estimate was identified