

```
1 #####
2
3 # Example MIROpt Configuration File Objectives and Constraints for a Brain Case
4 # More information can be found on: https://github.com/openFLASH/conformalFLASH/ (accessed 04/09/2025)
5
6 #####
7
8 TargetROI: ct_target      # name for target ROI
9 ExternalROI: ct_BODY     # name for external ROI - the body contour
10 optFunction:
11 - name: maxDVH           # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average
12 of the percentile dose rate), minDRm (minimum median of the percentile dose rate), minDADRm (minimum median of the dose averaged dose rate)
13 ROIname: ct_target      # Name for the ROI to which the objective function needs to be applied
14 intersect: "            # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
15 remainder: "           # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
16 Dref: 10.5              # Reference dose in Gy
17 DRref: 0                # Not used
18 Vref: 0.02              # Reference volume in 1% only needed for minDVH and maxDVH functions
19 impw: 0.5               # Importance weight for the current objective function (impw > 0)
20 robust: 0               # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
21 - name: minDVH          # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average
22 of the percentile dose rate), minDRm (minimum median of the percentile dose rate), minDADRm (minimum median of the dose averaged dose rate)
23 ROIname: ct_target      # Name for the ROI to which the objective function needs to be applied
24 intersect: "            # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
25 remainder: "           # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
26 Dref: 10                # Reference dose in Gy
27 DRref: 0                # Not used
28 Vref: 0.95              # Reference volume in 1% only needed for minDVH and maxDVH functions
29 impw: 0.5               # Importance weight for the current objective function (impw > 0)
30 robust: 0               # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
31 - name: minDVH          # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average
32 of the percentile dose rate), minDRm (min$
33 ROIname: ct_target      # Name for the ROI to which the objective function needs to be applied
```

34 intersect: " # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
35 remainder: " # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
36 Dref: 9.5 # Reference dose in Gy#
37 DRref: 0 # Not used
38 Vref: 1.0 # Reference volume in 1% only needed for minDVH and maxDVH functions
39 impw: 0.85 # Importance weight for the current objective function (impw > 0)
40 robust: 0 # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
41 - name: max # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average of
42 the percentile dose rate), minDRm (min\$
43 ROIname: ct_BODY # Name for the ROI to which the objective function needs to be applied#
44 intersect: " # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
45 remainder: " # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
46 Dref: 12 # Reference dose in Gy
47 DRref: 0 # Not used
48 Vref: 0.95 # Reference volume in 1% only needed for minDVH and maxDVH functions
49 impw: 0.5 # Importance weight for the current objective function (impw > 0)
50 robust: 0 # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
51 - name: minDR # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average of
52 the percentile dose rate), minDRm (minimum median of the percentile dose rate), minDADRm (minimum median of the dose averaged dose rate
53 ROIname: ct_BODY # Name for the ROI to which the objective function needs to be applied
54 intersect: " # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
55 remainder: " # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
56 Dref: 2 # Dose (Gy / FRACTION) in OAR above which the dose rate condition must be respected
57 DRref: 40 # Reference dose rate in Gy/s
58 Vref: 0.98 # Not used
59 impw: 0.00000001 # Importance weight for the current objective function (impw > 0)
60 robust: 0 # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
61 - name: max # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average of
62 the percentile dose rate), minDRm (min\$
63 ROIname: ct_Brain # Name for the ROI to which the objective function needs to be applied
64 intersect: " # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
65 remainder: " # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed
66 Dref: 12 # Reference dose in Gy

67 DRref: 0 # Not used
68 Vref: 0.95 # Reference volume in 1% only needed for minDVH and maxDVH functions
69 impw: 0.5 # Importance weight for the current objective function (impw > 0)
70 robust: 0 # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0
71 - name: minDR # Type of objective function. Possible types are: min, max,max_mean, min_mean, minDVH, maxDVH, minDR (minimum average of
72 the percentile dose rate), minDRm (minimum median of the percentile dose rate), minDADRm (minimum median of the dose averaged dose rate)
73 ROIname: ct_Brain # Name for the ROI to which the objective function needs to be applied
74 intersect: " # The objective will be applied to "ROIname" intersect with "intersect". Blank if no intersection needed
75 remainder: " # The objective will be applied to "ROIname" remainder with "remainder". Blank if no remainder needed#
76 Dref: 2 # Dose (Gy / FRACTION) in OAR above which the dose rate condition must be respected
77 DRref: 40 # Reference dose rate in Gy/s
78 Vref: 0.98 # Not used
79 impw: 0.00000001 # Importance weight for the current objective function (impw > 0)
80 robust: 0 # Set robust to 1 if robustness optimization needs to be applied to this volume, otherwise set to 0

Function	Constraint	Dose	ROI	Description
■ Physical composite objective				
Min dose		Plan (RBE)	PTVT1_30.0	Min dose 9.80 Gy (RBE)
Max dose		Plan (RBE)	BODY	Max dose 10.10 Gy (RBE)
Max DVH		Plan (RBE)	Brain	Max DVH 2.00 Gy (RBE) to 2.00% volume
Max DVH		Plan (RBE)	04_1_Ring_Difference	Max DVH 6.00 Gy (RBE) to 13.00% volume
Min DVH	★	Plan (RBE)	PTVT1_30.0	Min DVH 9.90 Gy (RBE) to 100.00% volume
Max DVH	★	Plan (RBE)	PTVT1_30.0	Max DVH 10.30 Gy (RBE) to 2.00% volume
Min DVH	★	Plan (RBE)	PTVT1_30.0	Min DVH 10.00 Gy (RBE) to 95.00% volume

Figure S1: Dose objectives and constraints for a margin-based FLASH-PT plan generated for an example brain case using RayStation.

Function	Constraint	Dose	ROI	Description	Robust
■ Physical composite objective					
Max DVH		Plan (RBE)	GTVT1_30.0	Max DVH 10.50 Gy (RBE) to 2.00% volume	★
Min DVH		Plan (RBE)	GTVT1_30.0	Min DVH 9.50 Gy (RBE) to 95.00% volume	★
Min DVH		Plan (RBE)	GTVT1_30.0	Min DVH 10.00 Gy (RBE) to 95.00% volume	★
Max dose		Plan (RBE)	Brain	Max dose 10.60 Gy (RBE)	
Max dose		Plan (RBE)	BODY	Max dose 10.50 Gy (RBE)	
Max DVH		Plan (RBE)	04_1_Ring_Difference	Max DVH 8.00 Gy (RBE) to 3.00% volume	

Figure S2: Dose objectives and constraints for a robust FLASH-PT plan generated for an example brain case using RayStation.

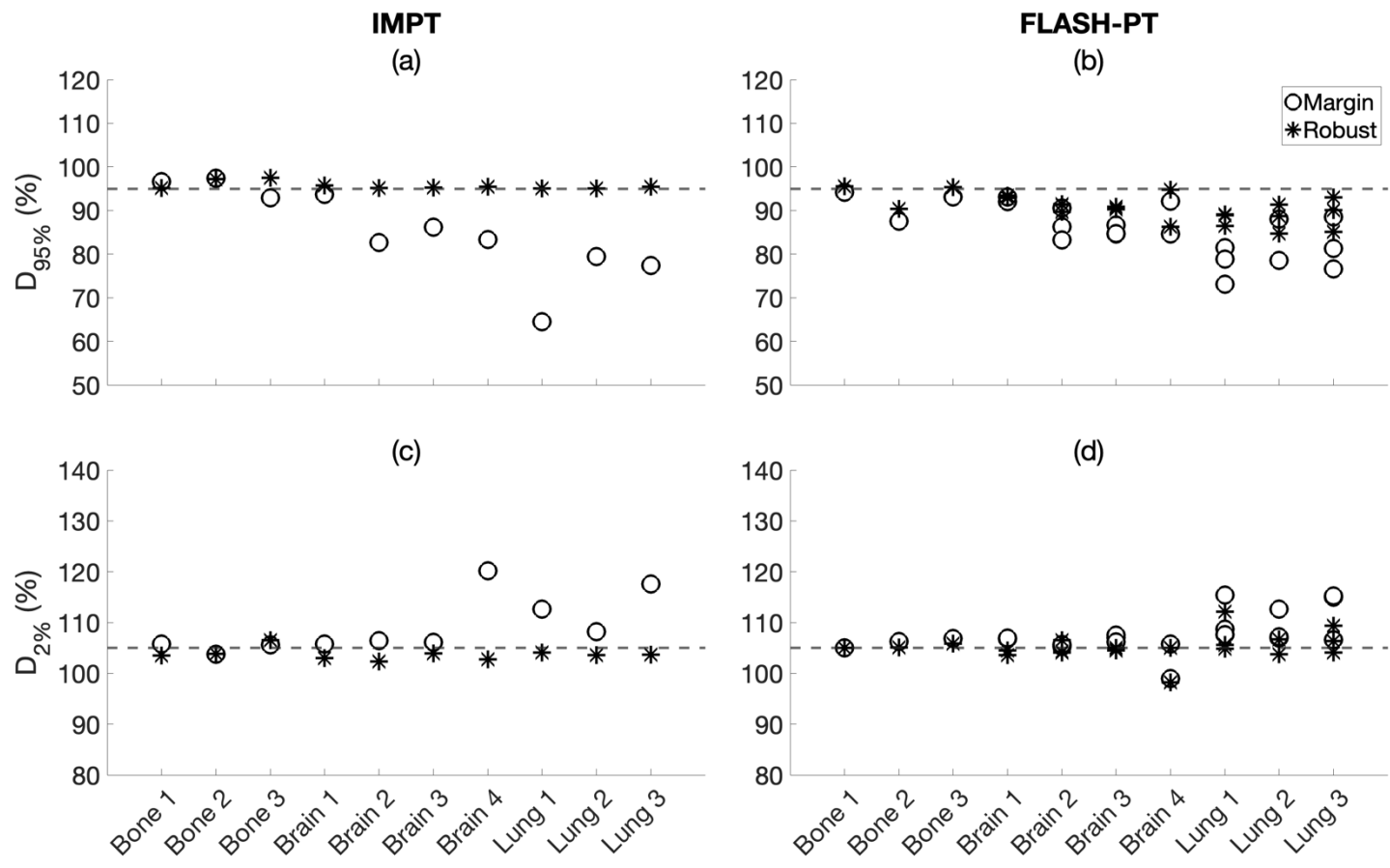


Figure S3: Worst-case scenario comparisons between margin (o) and robust (*) optimisation techniques for intensity modulated proton therapy (IMPT) and Bragg peak FLASH proton therapy (FLASH-PT). The worst-case scenarios were evaluated for $D_{95\%}$ and $D_{2\%}$ of the target volumes and are shown for each individual patient case for both IMPT and FLASH-PT, and for each individual fraction for FLASH-PT. Grey dashed lines indicate target dose limits of $D_{95\%} = 95\%$ for (a) and (b), and $D_{2\%} = 105\%$ for (c) and (d).

Cases Considered	Margin WC D_{95%} (%)	Robust WC D_{95%} (%)	Margin WC D_{2%} (%)	Robust WC D_{2%} (%)
All	86.50	90.64	106.89	105.00
Bone	93.13	95.38	106.25	105.13
Brain	86.50	91.10	105.98	104.50
Lung	81.27	88.93	108.73	106.33

Table S1: Median values of the worst-case (WC) scenario D_{95%} (%) and D_{2%} (%) for margin-based and robust Bragg peak FLASH proton therapy treatment plans, shown for all patient cases, as well as for the individual target sites.

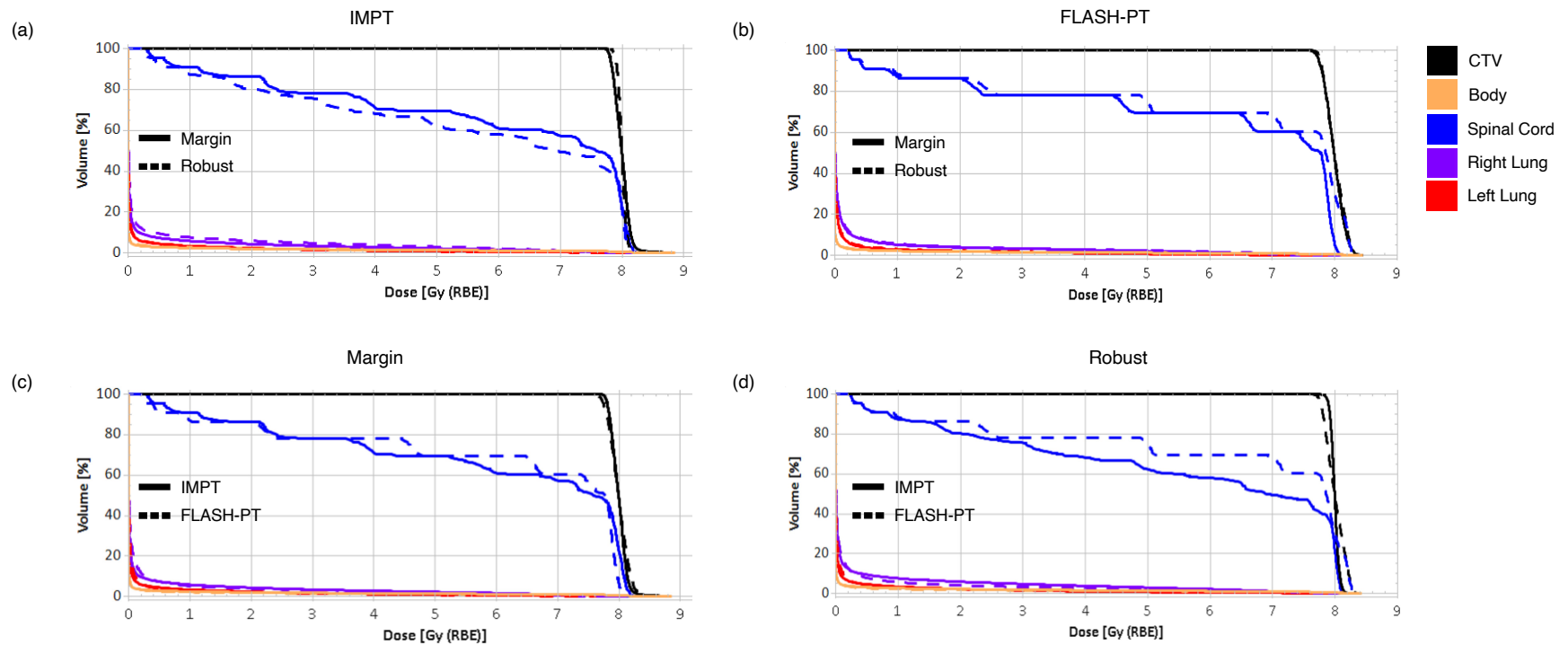


Figure S4: Dose volume histograms (DVHs) for RayStation plans simulated for an example bone case (Bone 1). Treatment techniques (margin vs. robust) are compared for both (a) IMPT and (b) FLASH-PT plans. Comparisons of IMPT and FLASH-PT plans are made for (c) margin-based and (d) robust plans. Treatment planning system comparisons could not be made for any bone case as MIROpt plans could not be generated due to target size constraints.

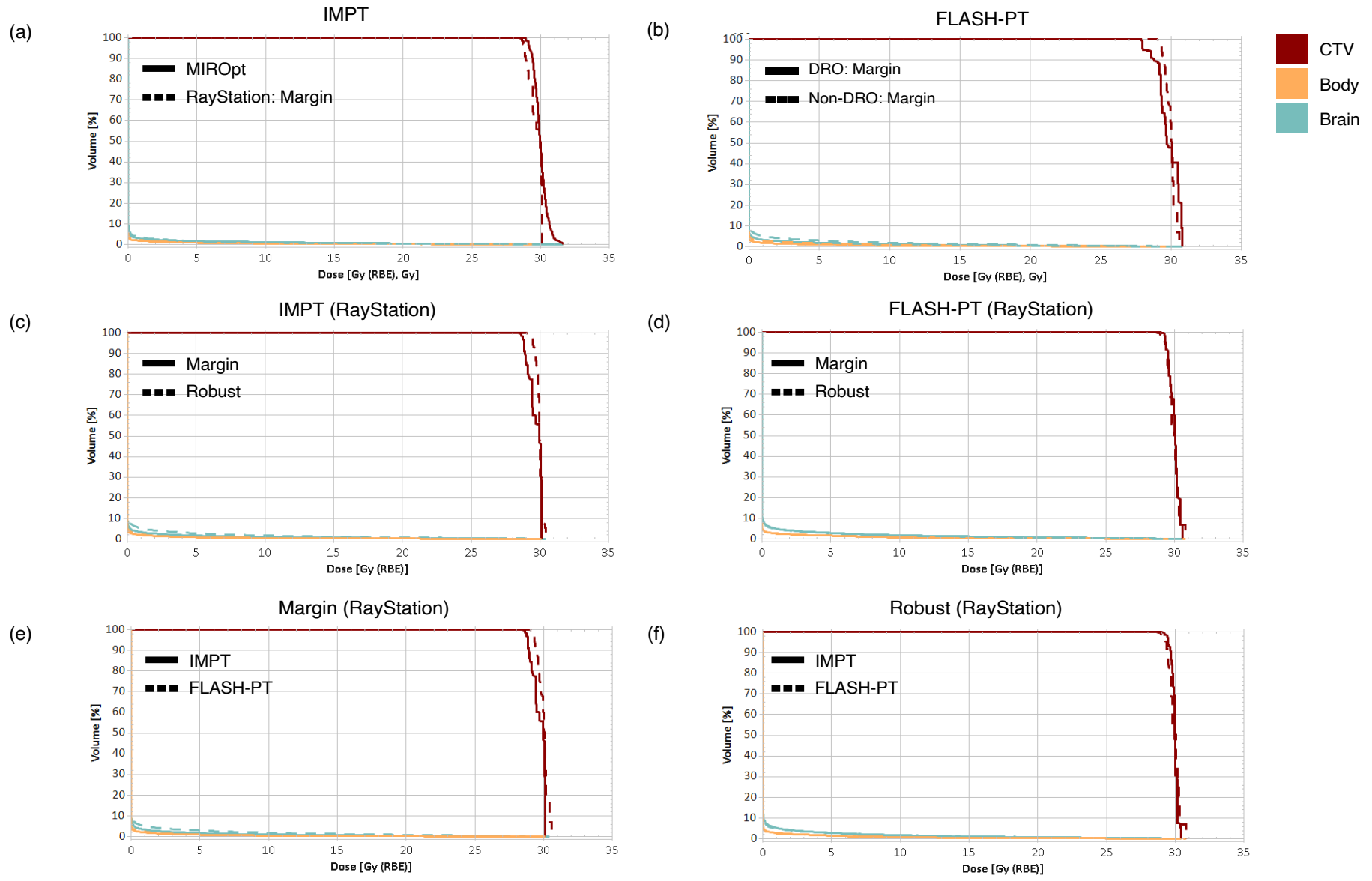


Figure S5: Dose volume histograms (DVHs) for an example brain case (Brain 2). Treatment planning system comparison (MIROpt vs. RayStation) is made for (a) IMPT plans, with (b) comparisons between dose rate optimised (DRO) and non-dose rate optimised (non-DRO) FLASH-PT, treatment techniques (margin vs. robust) are then compared for both (c) IMPT and (d) FLASH-PT plans simulated using RayStation. Comparisons between IMPT and FLASH-PT plans are then shown for both (e) margin-based and (f) robust IMPT and FLASH-PT plans.

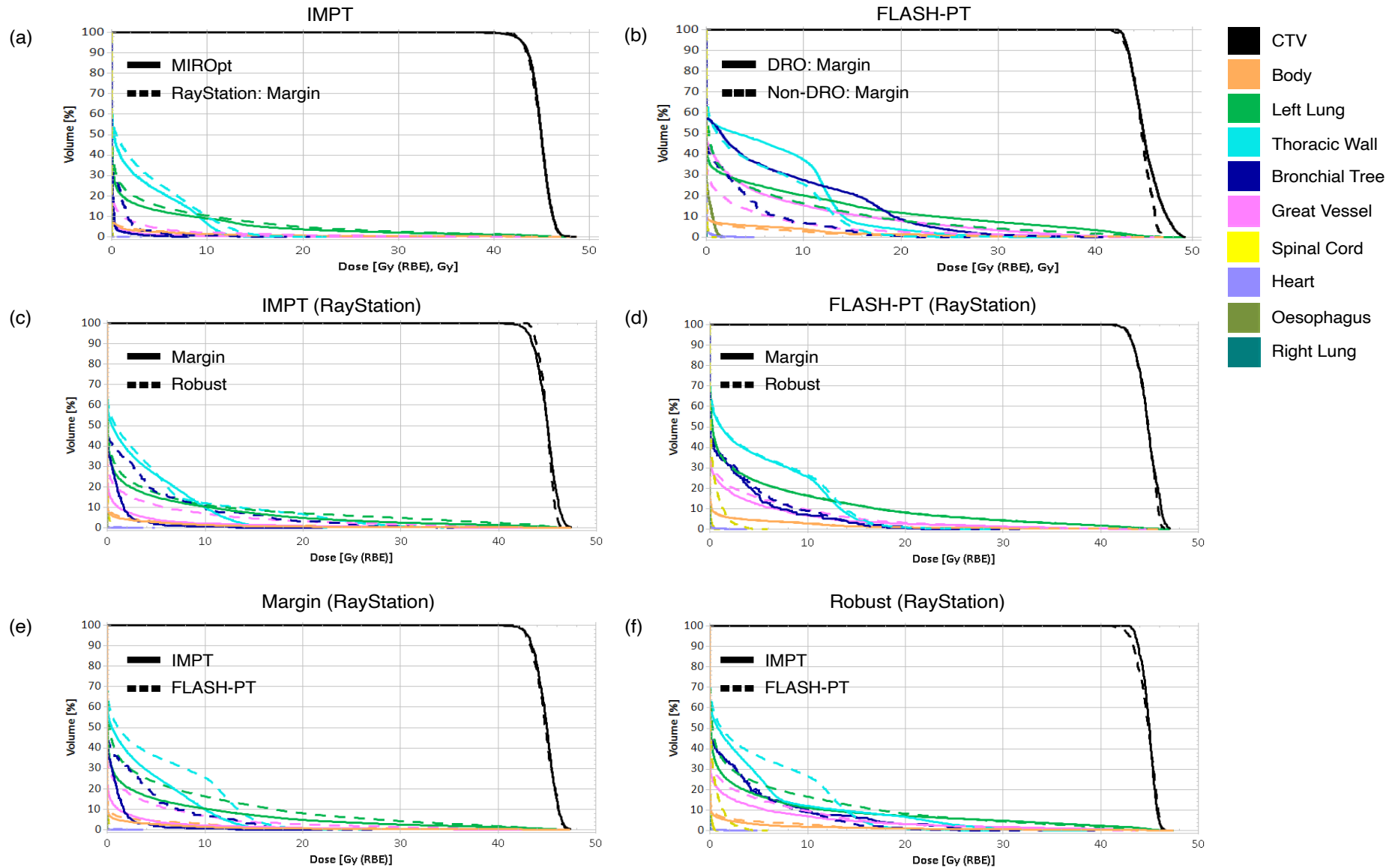


Figure S6: Dose volume histograms (DVHs) for an example lung case (Lung 2). Treatment planning system comparison (MIROpt vs. RayStation) is made for (a) IMPT plans, with (b) comparisons between dose rate optimised (DRO) and non-dose rate optimised (non-DRO) FLASH-PT, treatment techniques (margin vs. robust) are then compared for both (c) IMPT and (d) FLASH-PT plans simulated using RayStation. Comparisons between IMPT and FLASH-PT plans are then shown for both (e) margin-based and (f) robust IMPT and FLASH-PT plans.

Table S2: Intensity modulated proton therapy doses to the spinal cord for the different bone cases (Bone 1, Bone 2, Bone 3) and treatment planning techniques (margin-based and robust optimisation), generated using RayStation. The dose protocol used for these cases is RTOG 0631 [39].

Patient			Bone 1		Bone 2		Bone 3	
Technique			Margin	Robust	Margin	Robust	Margin	Robust
Protocol	OAR	Constraint						
RTOG 0631	Spinal Cord	10 Gy < 10% volume (%)	0	0	0	0	0	0
RTOG 0631	Spinal Cord	Max 10 Gy (D1%) (Gy)	8.2	8.11	8.2	8.28	8.06	8.09

Table S3: Bragg peak FLASH proton therapy doses to the spinal cord for the different bone cases (Bone 1, Bone 2, Bone 3) and treatment planning techniques (margin-based and robust optimisation), generated using RayStation. The dose protocol used for these cases is RTOG 0631 [39].

Patient			Bone 1		Bone 2		Bone 3	
Technique			Margin	Robust	Margin	Robust	Margin	Robust
Protocol	OAR	Constraint						
RTOG 0631	Spinal Cord	10 Gy < 10% volume (%)	0	0	0	0	0	0
RTOG 0631	Spinal Cord	Max 10 Gy (D1%) (Gy)	8.07	8.28	8.52	8.77	8.47	8.27

Table S4: Intensity modulated proton therapy doses to organs at risk (OAR) for the different brain cases (Brain 1, Brain 2, Brain 3, Brain 4), dose rate optimisations (dose rate optimised (DRO) and non-dose rate optimised (non-DRO)), and treatment planning techniques (margin-based and robust optimisation). Protocols used are from CORSAIR [37]. OAR dose constraints are given for each OAR, protocol, patient case, and treatment planning system/technique. Dashes (-) indicate that the specific OAR/constraint did not apply to that specific patient case. Brain 1 and Brain 4 were palliative and so the target volumes both exceeded 20 cm³; the first constraint could therefore not be applied to these cases. The Brain Stem was not contoured for Brain 4 due to complete overlap with the CTV; for Brain 2 and Brain 3 the target was not located near the Brain Stem and so it was not applicable as an OAR.

Patient			Brain 1			Brain 2			Brain 3			Brain 4		
System and Technique			DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust
Protocol	OAR	Constraint												
CORSAIR	Brain + target volume	D20cm ³ < 20 Gy (Gy) (optimal)	Target volume > 20 cm ³	Target volume > 20 cm ³	Target volume > 20 cm ³	8.45	7.52	7.84	4.96	5.97	7.85	Target volume > 20 cm ³	Target volume > 20 cm ³	Target volume > 20 cm ³
CORSAIR	Brain stem	D _{max} (0.035) < 18 Gy (Gy) (optimal)	-	-	-	-	-	-	-	-	-	0.00	0.00	0.00

Table S5: Bragg peak FLASH proton therapy doses to organs at risk (OAR) for the different brain cases (Brain 1, Brain 2, Brain 3, Brain 4), dose rate optimisations (dose rate optimised (DRO) and non-dose rate optimised (non-DRO)), and treatment planning techniques (margin-based and robust optimisation). Protocols used are from CORSAIR [37]. OAR dose constraints are given for each OAR, protocol, patient case, and treatment planning system/technique. Dashes (-) indicate that the specific OAR/constraint did not apply to that specific patient case. Brain 1 and Brain 4 were palliative and so the target volumes both exceeded 20 cm³; the first constraint could therefore not be applied to these cases. The Brain Stem was not contoured for Brain 4 due to complete overlap with the CTV; for Brain 2 and Brain 3 the target was not located near the Brain Stem and so it was not applicable as an OAR.

Patient			Brain 1			Brain 2			Brain 3			Brain 4		
System and Technique			DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust
Protocol	OAR	Constraint												
CORSAIR	Brain + target volume	D20cm ³ < 20 Gy (Gy) (optimal)	Target volume > 20 cm ³	Target volume > 20 cm ³	Target volume > 20 cm ³	8.77	14.81	14.08	5.12	6.79	12.26	Target volume > 20 cm ³	Target volume > 20 cm ³	Target volume > 20 cm ³
CORSAIR	Brain stem	D _{max} (0.035) < 18 Gy (Gy) (optimal)	-	-	-	-	-	-	-	-	-	0.00	0.00	0.00

Table S6: Intensity modulated proton therapy doses to organs at risk (OAR) for the different lung cases (Lung 1, Lung 2, Lung 3), dose rate optimisations (dose rate optimised (DRO) and non-dose rate optimised (non-DRO)), and treatment planning techniques (margin-based and robust optimisation). Protocols used are the UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy and CORSAIR [37,38]. OAR dose constraints are given for each OAR, protocol, patient case, and treatment planning system/technique. Dashes (-) indicate that the specific OAR/constraint did not apply to that specific patient case. For Lung 1, the target was not located near the Great Vessel or the Bronchial Tree and so these were not applicable as OARs.

Patient			Lung 1			Lung 2			Lung 3		
System and Technique			DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust
Protocol	OAR	Constraint									
3 fx UK Consensus (Stereotactic)	Heart	$D_{\max}(0.5 \text{ cm}^3) < 24 \text{ Gy}$ (optimal)	0.08	0.12	0.29	0.06	0.11	0.99	4.99	8.04	11.78
3 fx UK Consensus (Stereotactic)	Great Vessel	$D_{\max}(0.5 \text{ cm}^3) < 45 \text{ Gy}$ (mandatory)	-	-	-	6.69	22.97	39,16	25.2	36.91	43.51
CORSAIR	Great Vessel	$D_{10\text{cm}^3} < 39 \text{ Gy}$ (optimal)									
CORSAIR	Lung	$D_{\text{mean}} < 8 \text{ Gy}$ (optimal)	-	-	-	0.09	0.66	4.1	2.74	5.8	12.38
CORSAIR	Lung	$V_{20 \text{ Gy}} < 15\%$ (mandatory)	2.03	2.69	4.06	2.44	2.99	3.82	2.02	2.48	3.09
CORSAIR	Lung	$V_{20 \text{ Gy}} < 10\%$ (optimal)	2.88	4.05	6.76	3.58	4.74	7.05	5.8	4.03	5.01
CORSAIR	Spinal Cord	$D_{\max}(0.1 \text{ cm}^3) < 18 \text{ Gy}$ (optimal)	2.88	4.05	6.76	3.58	4.74	7.05	5.8	4.03	5.01
3 fx UK Consensus (Stereotactic)	Bronchial Tree	$D_{\max}(0.5 \text{ cm}^3) < 30 \text{ Gy}$ (optimal)	0	0	0	0.09	0.05	0.47	0	0	0

Table S7: Bragg peak FLASH proton therapy doses to organs at risk (OAR) for the different lung cases (Lung 1, Lung 2, Lung 3), dose rate optimisations (dose rate optimised (DRO) and non-dose rate optimised (non-DRO)), and treatment planning techniques (margin-based and robust optimisation). Protocols used are the UK Consensus on Normal Tissue Dose Constraints for Stereotactic Radiotherapy and CORSAIR [37,38]. OAR dose constraints are given for each OAR, protocol, patient case, and treatment planning system/technique. Dashes (-) indicate that the specific OAR/constraint did not apply to that specific patient case. For Lung 1, the target was not located near the Great Vessel or the Bronchial Tree and so these were not applicable as OARs. Bold values indicate that they exceeded the optimal dose constraint, whereas bold and underlined values indicate that they exceeded the mandatory dose constraints.

Patient			Lung 1			Lung 2			Lung 3		
System and Technique			DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust	DRO: Margin	Non-DRO: Margin	Non-DRO: Robust
Protocol	OAR	Constraint									
3 fx UK Consensus (Stereotactic)	Heart	$D_{\max}(0.5 \text{ cm}^3) < 24 \text{ Gy}$ (Gy) (optimal)	0.01	0.34	0.38	2.66	1.31	1.71	20.29	17.79	17.19
3 fx UK Consensus (Stereotactic)	Great Vessel	$D_{\max}(0.5 \text{ cm}^3) < 45 \text{ Gy}$ (Gy) (mandatory)	-	-	-	38.98	35.33	34.46	<u>45.29</u>	40.02	40.83
CORSAIR	Great Vessel	$D_{10\text{cm}^3} < 39 \text{ Gy}$ (Gy) (optimal)	-	-	-	13.03	4.81	7.43	29.05	22.71	27.57
CORSAIR	Lung	$D_{\text{mean}} < 8 \text{ Gy}$ (Gy) (optimal)	3.82	3.93	4.52	5.73	4.67	4.73	2.88	3.54	3.59
CORSAIR	Lung	$V_{20 \text{ Gy}} < 15\%$ (%) (mandatory)	6.72	5.81	6.58	<u>11.66</u>	7.98	8.22	5.01	5.95	5.51
CORSAIR	Lung	$V_{20 \text{ Gy}} < 10\%$ (%) (optimal)	6.72	5.81	6.58	<u>11.66</u>	7.98	8.22	5.01	5.95	5.51
CORSAIR	Spinal Cord	$D_{\max}(0.1 \text{ cm}^3) < 18 \text{ Gy}$ (Gy) (optimal)	0	0	0	0	0.41	3.86	0	0	0
3 fx UK Consensus (Stereotactic)	Bronchial Tree	$D_{\max}(0.5 \text{ cm}^3) < 30 \text{ Gy}$ (Gy) (optimal)	-	-	-	18.94	6.51	8.23	0.01	3.84	3.72