University of Miami Miller School of Medicine, Brain / Base-of-Skull RapidPlanPT Model Description

Created at Sylvester Comprehensive Cancer Center (SCCC)
Radiation Oncology Department

Note: *The University of Miami does not take any responsibility for improper use of their RapidPlanPT models. RapidPlanPT knowledge-based planning and its models are not intended to replace clinical decisions, provide medical advice, or endorse any particular radiation plan or treatment procedure. The patient's medical professionals are solely responsible for and must rely on their professional clinical judgment when deciding how to plan and provide radiation therapy. You should validate every DVH estimation model before implementing it clinically.*

Purpose:

This document describes the context in which the SCCC brain / base-of-skull model should be used, as well as how it was configured and validated.

The SCCC brain / base-of-skull model was created by the Radiation Oncology Department, University of Miami Miller School of Medicine at Sylvester Comprehensive Cancer Center. This model is designed to be used for intensity modulated proton therapy (IMPT) treatment plans with both single and multiple Clinical Target Volumes (CTVs).

A fine-tuning process for increasing plan quality and testing model-generated plans was described for clinical viability. The model estimates the DVH for brain, brainstem, hippocampus, chiasm, optic nerves, eyes, lens, pituitary gland, lacrimal gland, and spinal cord.

The SCCC proton brain / base-of-skull model is intended to be used for DVH estimates for proton brain / base of skull treatments with or without simultaneous integrated boost (SIB) to CTVs. The model library includes both SIB and non-SIB plans although the majority of the cases in the plan library are non-SIB cases. The prescription doses for the plans included in the model library were 50 – 60Gy with 1.8-2 Gy per fraction or to 35 Gy with 3-3.5 Gy per fraction. Gliomas account for many brain patients: RTOG (46Gy with 14Gy boost) is followed for most of the cases - but sometimes EORTC (60Gy no boost when overlapping with OAR's and dose is reduced to below tolerance at those structures).

Target and OAR contouring guidelines:

There are a variety of guidelines that we use based on what we are treating. The most common brain things we treat with protons are 1) gliomas, either IDH-mutated or recurrent glioblastoma are recommended to consider for protons per NCCN and ASTRO, 2) meningiomas and other benign tumors (pituitary adenoma, glomus tumors), 3) CSI for metastatic leptomeningeal disease mostly or other rare varieties of primary CNS malignancies (like germinomas, medulloblastoma, higher grade ependymomas).

The SCCC brain/base of skull model was created using the following guidelines. Every patient must have a planning CT. The CT simulation scan must encompass the entire head to include the most superior aspect of the patient through the entire head. Axial slice thickness should not exceed 2.5mm and smaller axial cuts are recommended.

The use of MRI guided contouring is recommended. The MRI axial slice thickness should match the CT slice thickness as much as possible. The fused pre- and post-operative axial T1 post-contrast and axial T2-FLAIR MRI sequences co-registered to the planning CT image set for contouring.

The clinical target volumes (CTV) and the organs at risk (OARs) are contoured on the planning CT.

Target name	Guidelines
CTV	For glioblastoma, postoperative cavity, and surrounding enhancement, with a volumetric 2 cm expansion for the initial and boost phases of the treatment. Customize the CTV to exclude expansions into regions deemed not at-risk due to natural boundaries of tumor spread. For base of skull (meningioma), the GTV was determined on the basis of pre- and post-operative MRIs, Multiplanar T1 post-contrast and pre-contrast T1, T2, and FLAIR images were required. Neither cerebral edema nor the dural tail were included within the GTV, however, hyperostotic bone or directly invaded bone was included. The clinical target volume (CTV) was the GTV + 1 cm. It was permissible to reduce the CTV margin to 0.5 cm around natural barriers to tumor growth such as uninvolved skull.

OAR contouring guidelines:

OAR name	Guidelines
Hippocampus(R+L)	Bilateral hippocampal contours (contoured in one structure); will be generated from the CT simulation image set fused to MRI image sets.
Brainstem	Seen on both MRI image set CT simulation image set. In craniocaudal direction, delineate the midbrain, pons, and medulla oblongata (up to the tip of C3 dens).
Spinal Cord	Superior aspect to begin at the distal edge of the brainstem through inferior aspect of the image set.
Lens(R/L)	Use CT image set only for creation; bilateral contoured separately.
Optic Nerve (R/L)	Use CT image set only for creation; bilateral contoured separately. Delineate from the posterior edge of eyeball to the optic chiasm.
Eye(R/L)	Best generated from CT simulation image set; delineate the entire globe of the eye; bilateral contoured separately.
Optic Chiasm	Structure best visualized on MRI image set and confirmed on CT image set; located above the pituitary fossa which is located within the

	sella turcica. Use coronal and sagittal images and T1-wigted MRI sequences for better delineation.
Lacrimal Gland(R/L)	Structure sits superior and lateral to the globe of the eye; best generated on CT simulation image set and verified using MRI; bilateral contoured separately.

References for contouring and planning guidelines:

The additional contouring guidelines for glioblastoma cases are cited below.

Kruser, T.J., Bosch, W.R., Badiyan, S.N. et al. NRG brain tumor specialists consensus guidelines for glioblastoma contouring. J Neurooncol 143, 157–166 (2019). https://doi.org/10.1007/s11060-019-03152-9.

IDH-mutated tumors (astrocytomas, oligodendrogliomas) can be treated upfront with protons since these patients have relatively good prognosis of around 10yr median os at least. For such patients, the same contouring techniques are used, but with reduced CTV margin. The trials that detail what we use for what is in the second citation below in table 2- that paper is the ASCO SNO guideline from 2022.

Therapy for Diffuse Astrocytic and Oligodendroglial Tumors in Adults: ASCO-SNO Guideline Nimish A. Mohile, Hans Messersmith, Na Tosha Gatson, Andreas F. Hottinger, Andrew Lassman, Jordan Morton, Douglas Ney, Phioanh Leia Nghiemphu, Adriana Olar, Jeffery Olson, James Perry, Jana Portnow, David Schiff, Anne Shannon, Helen A. Shih, Roy Strowd, Martin van den Bent, Mateo Ziu, and Jaishri BlakeleyJournal of Clinical Oncology 2022 40:4, 403-426.

The glioblastomas that are treated using protons are at times prescribed with 35 Gy in 10 fractions - that is based on RTOG 1205 (cited below). We treat GTV = CTV with that is the bottom line although a 5mm margin can be added if the disease is not previously in field. Cited below and the protocol has constraints. Spectroscopic MRI may also be used to increase volume of the CTV based on disease identified by that specialized MRI.

NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma Christina I. Tsien, Stephanie L. Pugh, Adam P. Dicker, Jeffrey J. Raizer, Martha M. Matuszak, Enrico C. Lallana, Jiayi Huang, Ozer Algan, Nimisha Deb, Lorraine Portelance, John L. Villano, John T. Hamm, Kevin S. Oh, Arif N. Ali, Michelle M. Kim, Scott M. Lindhorst, and Minesh P. MehtaJournal of Clinical Oncology 2023 41:6, 1285-1295.

For base of skull tumors (large acoustic neuromas, glomus tumors, pituitary adenomas, meningiomas, sarcomas), The RTOG 0539 (cited below) as a guide fir contouring and dosing.

Rogers L, Zhang P, Vogelbaum MA, Perry A, Ashby LS, Modi JM, Alleman AM, Galvin J, Brachman D, Jenrette JM, De Groot J, Bovi JA, Werner-Wasik M, Knisely JPS, Mehta MP. Intermediate-risk meningioma: initial outcomes from NRG Oncology RTOG 0539. J Neurosurg. 2018 Jul;129(1):35-47. doi:

10.3171/2016.11. JNS161170. Epub 2017 Oct 6. Erratum in: J Neurosurg. 2018 Dec 1;129(6):1650. PMID: 28984517; PMCID: PMC5889346.

Treatment planning guidelines:

72 patients treated to brain or base-of-skull with IMPT technique were included in this study. Boost plans were excluded from the training set. For 66 of the patients, the prescription dose was 50 – 60Gy with 1.8-2 Gy per fraction. The remaining 6 patients had recurrent glioblastoma treated to 35 Gy with 3-3.5 Gy per fraction.

All cases used to train and validate this model were planned using head-first supine position using IMPT technique. The number and orientation of proton beams used varied from two to four depending upon each patient. Clinical IMPT plans used single-field optimization (SFO) with 2-3 coplanar fields. If plan quality was not adequate, multi-field optimization (MFO) and/or non-coplanar fields were also utilized. IMPT plans were generated using robust optimization to the clinical target volume (CTV) rather than planning target volume-based optimization. For robust optimization, ±3 mm setup uncertainties in all directions coupled with ±3.5% proton range uncertainty was used resulting in 12 uncertainty scenarios. Planners may create localized optimization helper structures to locally increase/decrease dose to cold/hot spots after initial optimization.

The following dose prescription and planning guidelines below were used for the cases to train and to validate the SCCC brain proton model.

CTV coverage:

1. If the CTV is prescribed to meet V100% > 95%
    - 100% of the prescription dose at least covers 95% CTV volume.
    - The maximum dose should be below 115% of the prescription dose.
    - CTV V95% of the worst-case scenario should be higher than 95% of the CTV volume.

2. If the CTV is prescribed to meet V95% > 95%
    - 95% of prescription dose cover at least 95% of target volume.
    - The maximum dose should be below 115% of the prescription dose.
    - CTV V90% of the worst-case scenario should be higher than 95% of the CTV volume.

Table 1: The following OAR constraints were commonly used for most cases for model training and validation. Note: the constraints can be adjusted based on physician's preference.

Structures	Dose-Volume Constraints
CTV	Dmax < 115%
Brainstem	Dmax < 54 Gy
Cochlea	Dmean < 45Gy
Hippocampus	Dmean < 45 Gy
Eye	Dmax < 45 Gy
Lens	Dmax < 7 Gy
Optic Nerve	Dmax < 54 Gy
Optic Chiasm	Dmax < 54 Gy
Pituitary	Dmax < 45 Gy
Skin	Dmax < 50 Gy
Lacrimal gland	Dmean < 20 Gy

Structure codes:

In order to ensure proper structure matching between cases and the structures defined in the model, the following structure code assignments are recommended:

Structure name example	**Structure name in model**	
CTV_High:	CTV_High	
CTV_Intermediate:	CTV_Intermediate	
Brain:	50801	
BrainStem:	79876	
Chiasm:	62045	
Cochlea:	60203 (Cochlea_L)	60202 (Cochlea_R)
Eye:	12515 (Eye_L)	12514 (Eye_R)
Hippocampus:	275024 (Hippocampus_L)	275022 (Hippocampus_R)
LacrimalGland:	59103 (LacrimalGland_L)	59102 (LacrimalGland_R)
Lens:	58243 (Lens_L)	58242 (Lens_R)
OpticNerve:	50878 (OpticNerve_L)	50875 (OpticNerve_R)
Pituitary:	13889	
Ring:	Ring	
Skin:	7163	
SpinalCord:	7647	

Optimization objectives and optimization settings:

In addition to the DVH estimates, the following optimization objectives will be generated when the model is applied to a new case.

Table 2: Final Optimization Objectives

Structure	Objective type	Relative volume (%)	Dose	Priority
CTV_High	Upper	0.0	100.0%	0
	Upper*	0.0	103.0%	180
	Lower*	99.5	99.0%	180
	Lower	99.9	100.0%	200
	Lower	95.0	100.0%	0
CTV_Intermediate	Upper	0.0	100.0%	0
	Upper	0.0	103.0%	180
	Lower	99.9	99.0%	180
	Lower	99.0	100.0%	200
Brain	Line (preferring target)	Generated	Generated	50
Brain-CTV	Line (preferring OAR)	Generated	Generated	50
BrainStem	Upper	0.0	48.000 Gy	100
	Upper	0.0	52.000 Gy	180
	Upper (fixed vol., generated dose)	0.0	Generated	79
	Line (preferring target)	Generated	Generated	50
Chiasm	Upper	0.0	48.000 Gy	100
	Upper	0.0	52.000 Gy	180
	Upper (fixed vol., generated dose)	0.0	Generated	79
	Line (preferring target)	Generated	Generated	50
Cochlea	Mean		30.000 Gy	50
	Mean		Generated	49
	Line (preferring target)	Generated	Generated	50

Structure	Objective type	Relative volume (%)	Dose	Priority
Eye	Upper	0.0	42.000 Gy	75
	Upper (fixed vol., generated dose)	0.0	Generated	49
	Line (preferring target)	Generated	Generated	50
Hippocampus	Upper	0.0	12.000 Gy	75
	Upper (fixed vol., generated dose)	0.0	Generated	99
	Line (preferring target)	Generated	Generated	50
LacrimalGland	Mean		10.000 Gy	50
	Line (preferring target)	Generated	Generated	50
Lens	Upper	0.0	5.000 Gy	50
	Upper (fixed vol., generated dose)	0.0	Generated	49
	Line (preferring target)	Generated	Generated	50
OpticNerve	Upper	0.0	52.000 Gy	200
	Upper	0.0	47.000 Gy	100
	Upper (fixed vol., generated dose)	0.0	Generated	99
	Line (preferring target	Generated	Generated	50
Pituitary	Upper	0.0	17.000 Gy	50
	Upper (fixed vol., generated dose)	0.0	Generated	49
	Line (preferring target)	Generated	Generated	50
Ring	Line (preferring target)	Generated	Generated	50
Skin	Line (preferring target)	Generated	Generated	50
SpinalCord	Upper	0.0	41.000 Gy	50
	Upper (fixed vol., generated dose)	0.0	Generated	99
	Line (preferring target)	Generated	Generated	50

*

Robust optimization was enabled for these objectives

Note: To emulate planners' tendency of reducing hotspots as a final step, the 'Continue Optimization' feature was used after initial KBP optimization with an additional 103% robust upper objective on the body at priority 500.

The Normal Tissue Objective (NTO) is set with the following parameters:

NTO Priority	60
Distance from Target Border	0.7cm
Start Dose	98.0%
End Dose	30.0%

Model Description and Training:

The training cases were extracted from the pool of already treated brain / base of skull cases on ProBeam at SCCC that satisfied the contouring and planning guidelines described above. The boost plans were excluded from the training. The SCCC RapidPlanPT brain model was created with the previous IMPT plans of the following number of cases (52 patients total) using RapidPlanPT (ver. 16.1).

Dose Prescribed to CTV (Gy)	Number of patients
35	6
46, 60 Boost	2
50, 74 Boost	1
50.4	6
50.4, 59.4 Boost	4
54	10
54, 60 Boost	8
59.4	9
60	5
66	1

The dose distributions and geometric parameters were analyzed using the machine learning algorithm tools. After the completion of initial training, outliers were identified by visually comparing the estimated DVH range and the actual DVH curves. Cases where the actual DVH curve significantly deviated from the estimation DVH band were excluded from the model. As a result, 11 cases of brainstem, 9 cases of left optic nerve, 10 cases of right optic nerve and 6 cases of chiasm were excluded from the model. The number of cases included in the model were shown in the figure below. During development of the model, the user sets optimization objectives that act as a template for every model-generated plan. A subset of 20 IMPT plans from the training set was chosen to further tuning of the optimization objectives. These 20 cases were re-planned by using the initial

(first iteration) KBP model and then the model-generated and manual (clinical) plans were compared using DVH parameters. Aggregate differences between the manual (clinical) and KBP-model generated plans are used to iteratively adjust the optimization objectives. This recursive method was used until a paired t-test ($p<0.05$) showed no statistically significant differences between KBP model generated and manual plans and the optimization objectives were finalized (Table 2).

Structure	Trained	Matched	In-field
CTV_High	N/A	52	
CTV_Intermediate	N/A	9	
Brain	Yes	23	23
BrainStem	Yes	40	34
Chiasm	Yes	43	34
Cochlea_L	Yes	43	19
Cochlea_R	Yes	46	22
Eye_L	Yes	50	19
Eye_R	Yes	50	21
Hippocampus_L	Yes	23	20
Hippocampus_R	Yes	24	20
Lens_L	Yes	38	15
Lens_R	Yes	38	13
OpticNerve_L	Yes	41	25
OpticNerve_R	Yes	40	23
Pituitary	Yes	22	15
Ring	Yes	82	82
Skin	Yes	40	40
Brain-CTV	No	11	10
SpinalCord	No	12	6
LacrimalGland_L	No	15	10
LacrimalGland_R	No	16	8

Model Validation:

The SCCC Proton Brain model was validated by re-planning of an independent set of 20 cases which were not included in the KBP model library. The validation cases were as follows:

Dose Prescribed to CTV (Gy)	Number of patients
50.4	2
50.4, 54 Boost	1
50.4, 59.4 Boost	3
54	7

54, 59.4 Boost	2
54, 74 Boost	1
59.4	4

All validation cases were selected from our pool of previously treated brain / base of skull cases treated with IMPT on ProBeam. All plans met or exceeded the contouring and planning guidelines previously stated.

The purpose of the validation was to demonstrate that the model would produce plans comparable to expert plans with minimal user interference. Model performance was validated by re-planning 20 previously treated brain cases using the same beam angles and same technique (SFO/MFO) as the clinical plan. The DVHs produced by the model were compared against DVHs of an expert's plan that were deemed clinically acceptable for treatment at SCCC. The validation plans were first optimized using the model-generated objective list. For targets, robust optimization was enabled by employing ±3 mm setup uncertainties in all directions coupled with proton range uncertainties of ±3.5%. To emulate planners' tendency of reducing hotspots as a final step, the 'Continue Optimization' feature was used after initial KBP optimization with an additional 103% robust upper objective on the body at priority 500.

The Normal Tissue Objective (NTO) is set with the following parameters:

NTO Priority	60
Distance from Target Border	0.7cm
Start Dose	98.0%
End Dose	30.0%

All validation plans were normalized to the same level (V100 = 95%) as the clinical plans for comparison.

KBP plans were compared to manual expert plans in terms of max dose to the body, CTV coverage and OAR sparing of brainstem, cochlea, eye, hippocampus, lens, optic chiasm, optic nerves, and pituitary gland. Additionally, CTV min dose, CTV V105% and robustness in terms of worst-case scenario CTV V95% for the 12 uncertainty scenarios were compared. For the cochlea, mean dose was also analyzed. Aggregate differences were tested for significance using paired t-tests ($p<0.05$).

Please refer to Annexes A, B, and C for library validation and optimization results and example cases.

Annex A

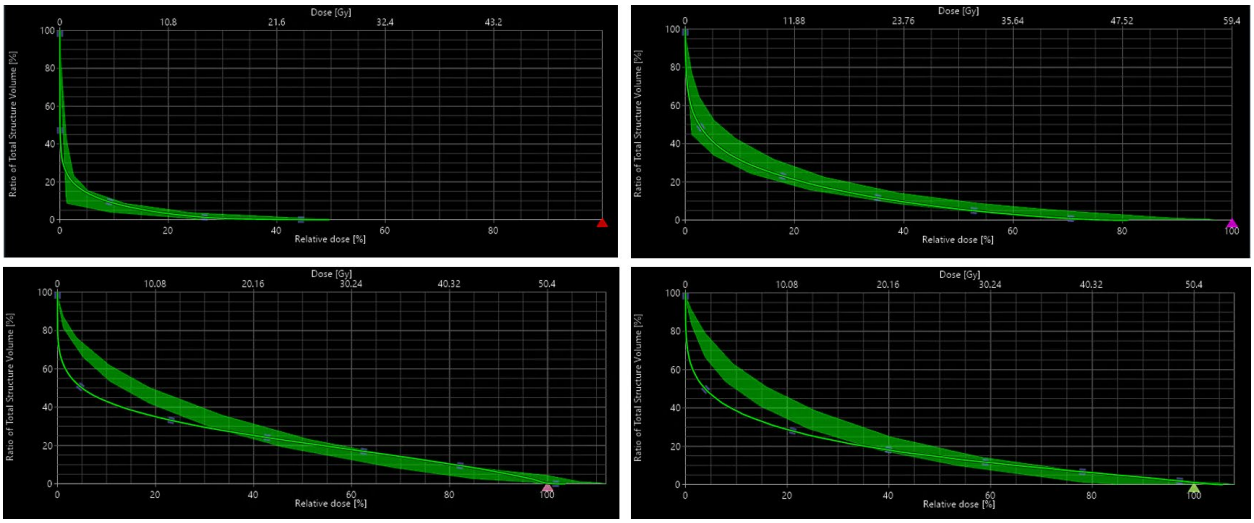

Figure A1: DVH estimate bands shown along with achieved DVHs for Brainstem. Triangles represent the prescription dose to the CTV. Dose is presented on the X-axis in % and the relative volume is on the Y-axis (%).

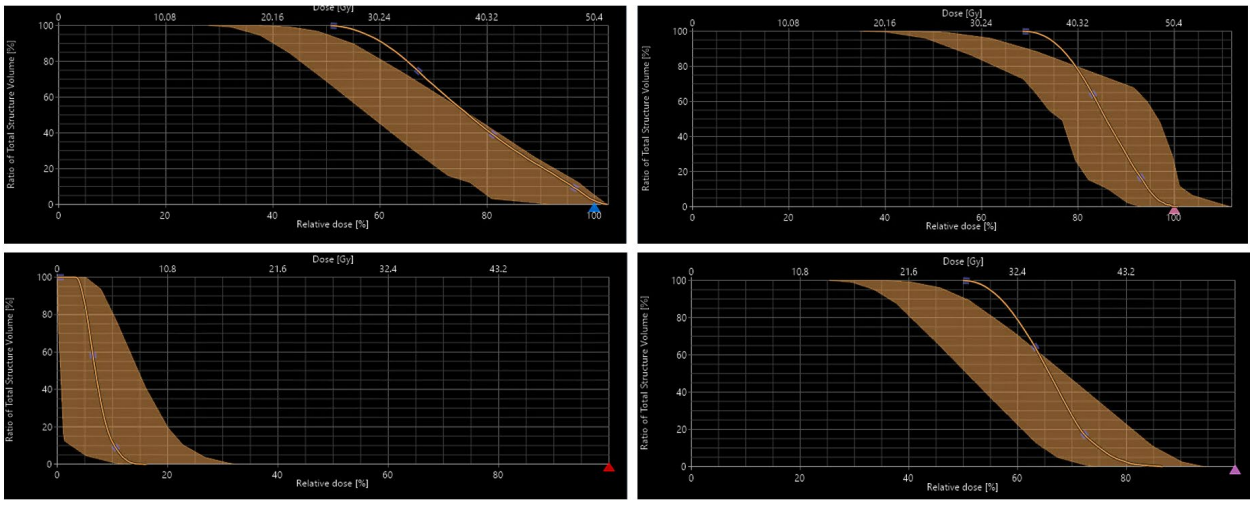

Figure A2: DVH estimate bands shown along with achieved DVHs for optic chiasm. Triangles represent the prescription dose to the CTV. Dose is presented on the X-axis in % and the relative volume is on the Y-axis (%).

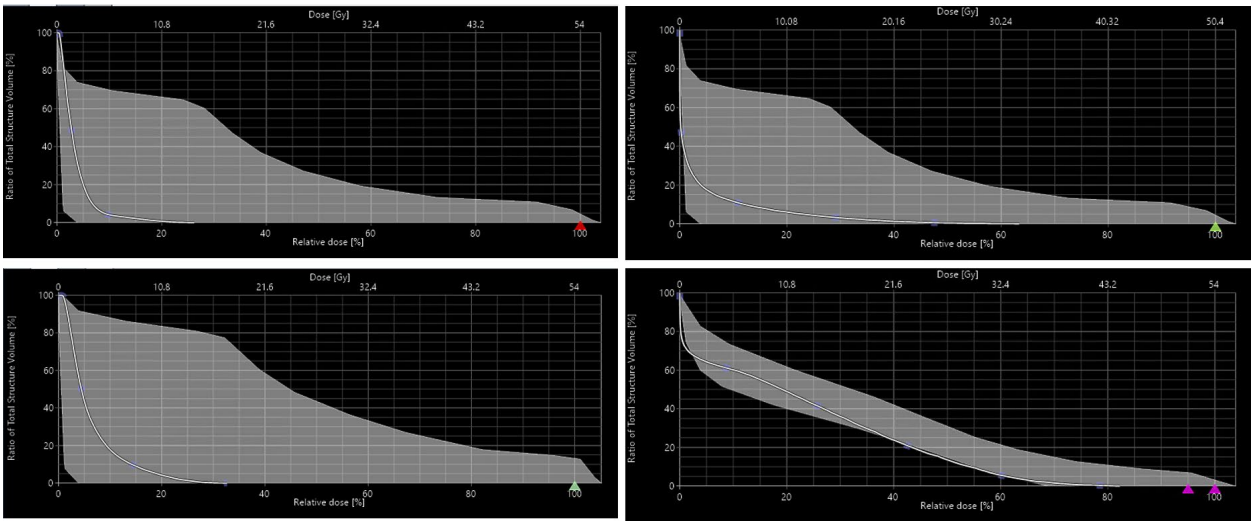

Figure A3: DVH estimate bands shown along with achieved DVHs for hippocampus. Triangles represent the prescription dose to the CTV. Dose is presented on the X-axis in % and the relative volume is on the Y-axis (%).

Annex B

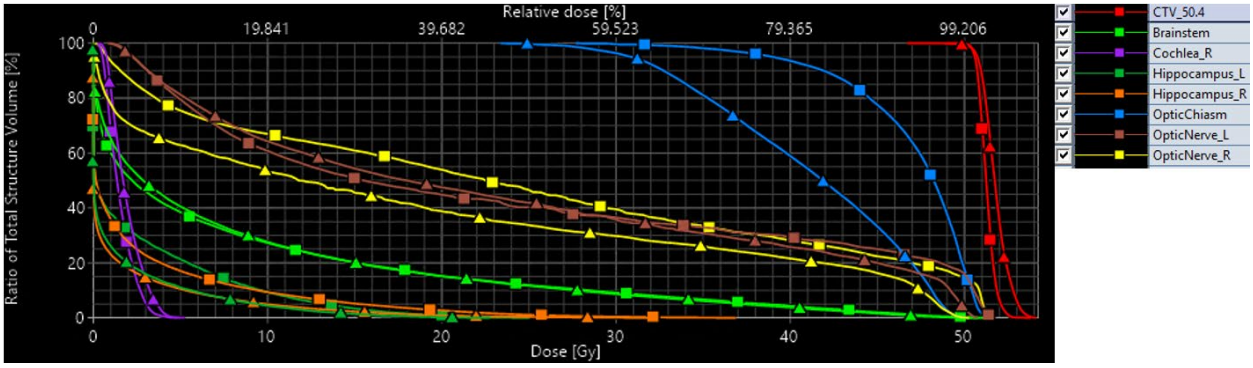

Figure B1: Model validation DVH comparison results for an example case: DVHs produced by the model-based library (triangles) and the corresponding expert plan (squares). Dose is presented on the X-axis in Gy and the relative volume is on the Y-axis (%)

Annex C

Table C1: Overview of dosimetric parameters for 20 validation patients. Table lists mean dose and standard deviation across 20 patients for clinical manual reference plans, model-created plans, difference in mean values and p-values from paired t-test. Significant values highlighted in red. Note: for structures receiving Dmax < 2 Gy were excluded from the analysis.

	N	Clinical	Validation	Validation - Clinical	P-value
CTV Dmax (%)	20	108.3 ± 1.88	109.01 ± 2.02	0.71 ± 2.85	0.28
CTV V105% (%)	20	7.09 ± 8.39	3.29 ± 3.92	-3.8 ± 8.96	0.07
CTV Dmin (%)	20	85.17 ± 13.33	79.92 ± 15.06	-5.24 ± 13.66	0.1
CTV V95 (worst case) (%)	20	97.05 ± 3.27	97.86 ± 2.31	0.81 ± 1.7	0.04
Brainstem Dmax (Gy)	16	46.2 ± 12.08	48.3 ± 12.76	2.09 ± 6.72	0.23
Cochlea Lt Dmax (Gy)	8	20.65 ± 19.42	18.02 ± 17.71	-2.63 ± 4.08	0.11
Cochlea Lt Dmean 40Gy (Gy)	8	14.68 ± 15.6	11.68 ± 13.31	-3 ± 4.57	0.11
Cochlea Rt Dmax (Gy)	6	17.78 ± 17.23	19.72 ± 19.09	1.94 ± 4.86	0.37
Cochlea Rt Dmean<40Gy (Gy)	6	12.12 ± 14.96	13.44 ± 15.74	1.32 ± 6.07	0.62
Hippocampus Lt Dmax (Gy)	14	24.49 ± 20.81	22.91 ± 18.64	-1.58 ± 5.65	0.31
Hippocampus Lt Dmean (Gy)	14	8.45 ± 12.13	5.23 ± 7.45	-3.23 ± 5.22	0.01
Hippocampus Rt Dmax (Gy)	11	26.51 ± 19.68	21.97 ± 17.94	-4.55 ± 2.8	<0.01
Hippocampus Rt Dmean (Gy)	11	9.57 ± 14.98	5.19 ± 7.45	-4.38 ± 8.01	0.1
Eye Lt Dmax<45 Gy (Gy)	13	16.05 ± 15.3	14.75 ± 15.66	-1.3 ± 2.64	0.1
Eye Rt Dmax<45Gy (Gy)	9	17.78 ± 11.9	16.98 ± 12.17	-0.8 ± 1.36	0.1
Lens Lt Dmax (Gy)	5	5.14 ± 2.26	4.51 ± 2.64	-0.63 ± 2.62	0.61
Lens Rt Dmax (Gy)	6	2.87 ± 1.66	2.75 ± 1.2	-0.12 ± 1.45	0.84
Optic Chiasm Dmax<50Gy (Gy)	16	37.06 ± 18.78	37.68 ± 19.47	0.62 ± 6.59	0.71
Optic Nerve Lt Dmax<50Gy (Gy)	15	37.19 ± 19.4	37.26 ± 20.49	0.07 ± 5.9	0.96
Optic Nerve Rt Dmax<50Gy (Gy)	14	31.35 ± 20.57	29.87 ± 18.77	-1.48 ± 6.03	0.37
Pituitary Dmax (Gy)	9	23.86 ± 14.68	19.71 ± 13.7	-4.15 ± 6.14	0.08
Skin Dmax (Gy)	17	39.63 ± 15.29	40.81 ± 12.76	1.18 ± 4.82	0.33

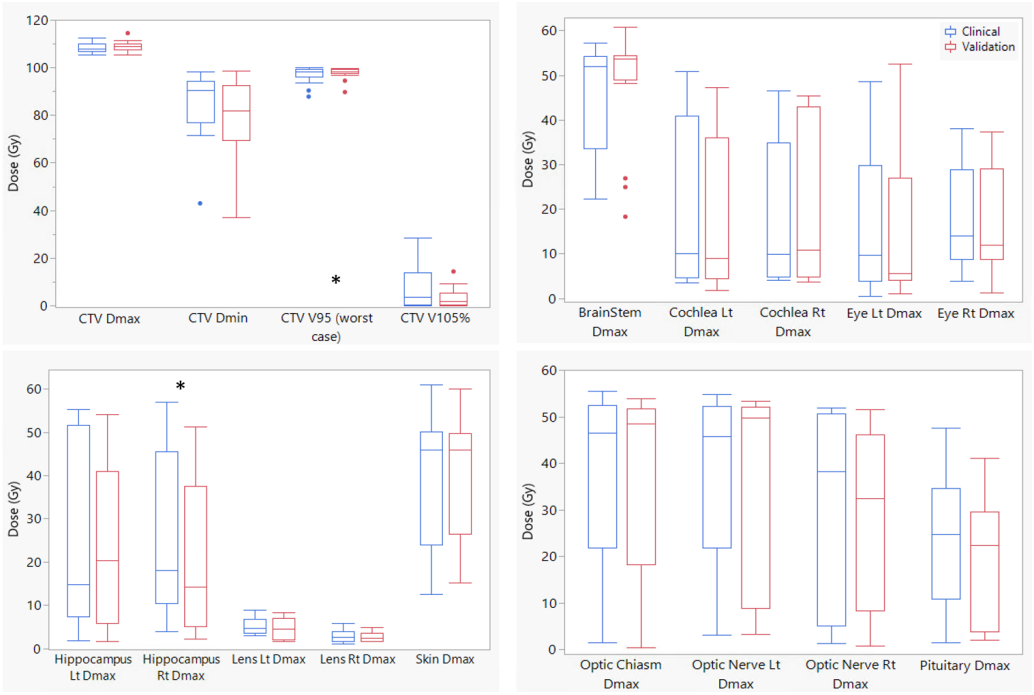

Figure C1: Boxplots of dosimetric parameters for the target and organs-at-risk, with the blue box representing the clinical manual plans and red boxes showing model-generated plans. Boxes represent 2nd and 3rd quartiles, whiskers denote data range within 1.5 interquartile range, outliers shown as crosses. Asterisk highlights significance ($p<0.05$).

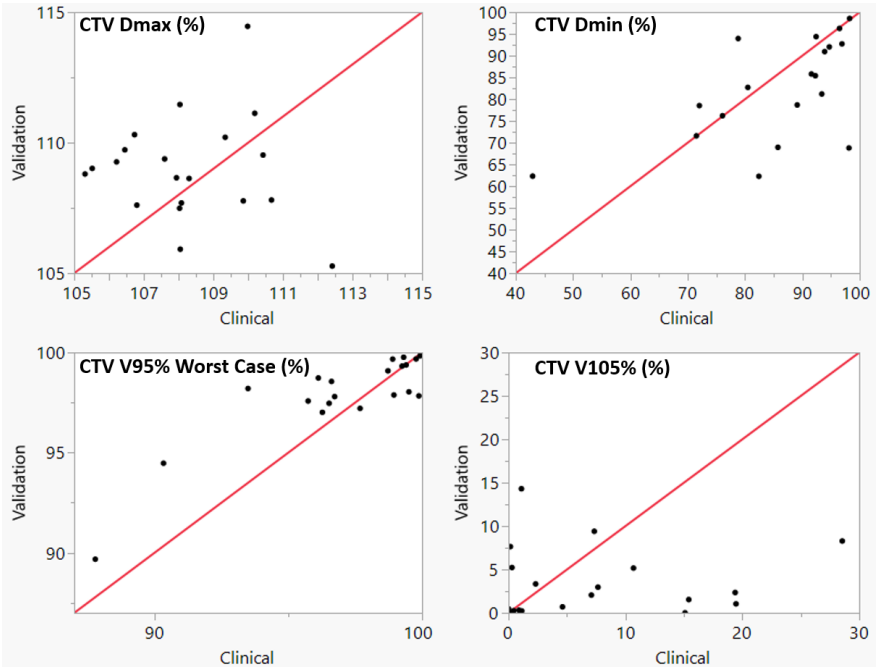

Figure C2: CTV parameters where each point is one plan with the x-coordinate being the manual plan and the y-coordinate the KBP value. Points above the equality line thus indicate a higher value of the model-generated (validation) plan compared to the clinical plan and vice versa.

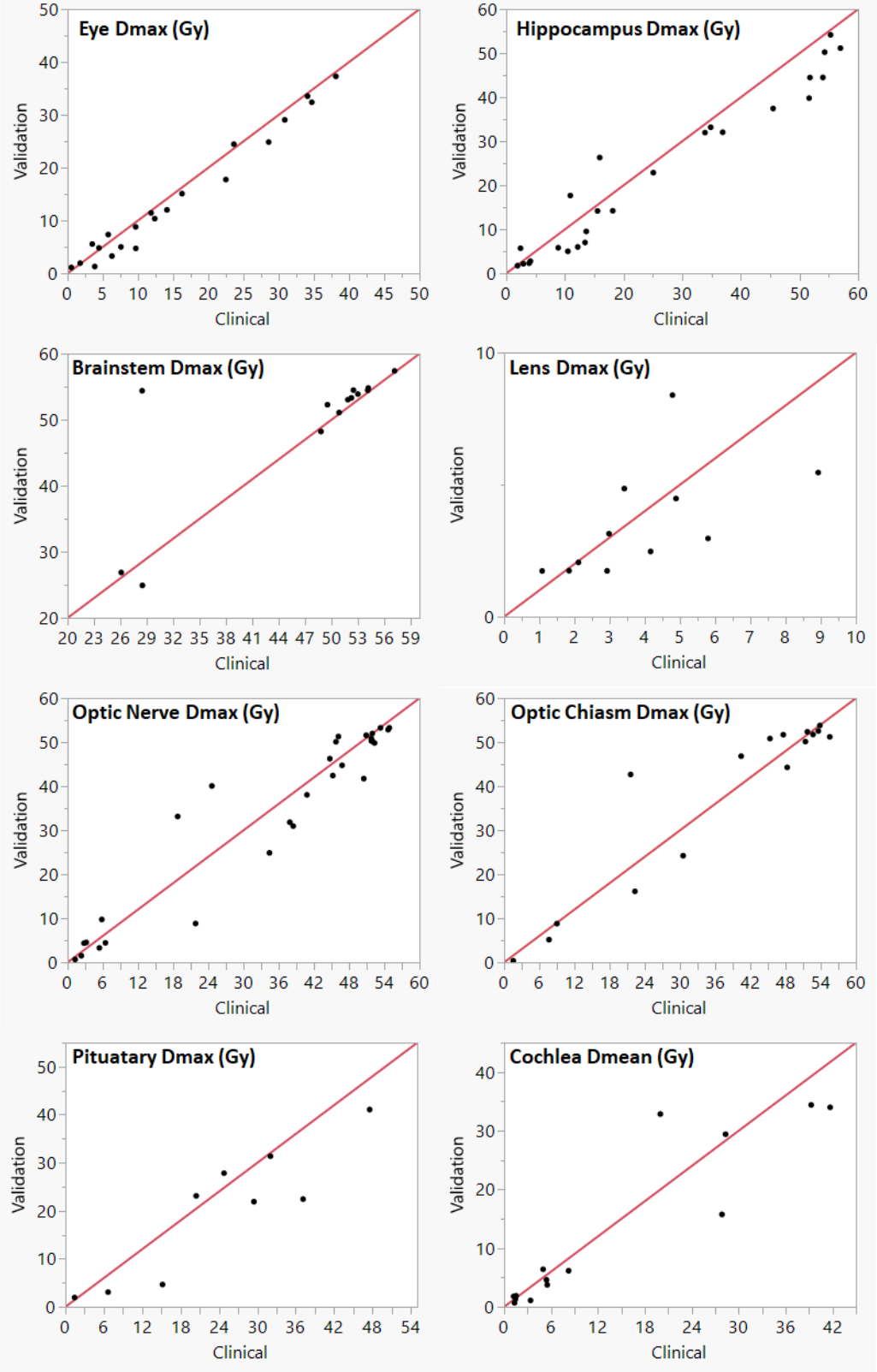

Figure C3: OAR parameters where each point is one patient with the x-coordinate being the clinical plan value and the y coordinate the model-generated (validation) plan value.