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Volumetric Modulated Arc Therapy Craniospinal Re-Irradiation of Adulthood Medulloblastoma Leptomeningeal Disease

Kremena Petrova*, Lena Marinova, Zdravko Yankov and Dimka Nikolaeva

Department of Radiotherapy, Complex Oncology Center, Russe, Bulgaria.

***Correspondence:**
Kremena Petrova, Department of Radiotherapy, Complex Oncology Center, Russe, Bulgaria.

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ABSTRACT

For the first time in the English medical literature we present two adulthood clinical cases with medulloblastoma leptomeningeal disease (LMD) in which we have performed second craniospinal irradiation (re-CSI) using bias volumetric-modulated arc therapy (VMAT) technique.

In this article we present bias volumetric-modulated arc therapy (VMAT) technique for repeated CSI (re-CSI) in two patients with adulthood medulloblastoma leptomeningeal disease (LMD). In both clinical cases (case1/case2) with adulthood medulloblastoma LMD, re-CSI has been performed using the bias VMAT technique in the area of the spinal cord up to total dose (TD) - 24 Gy/32 Gy; cauda equina up to TD- 28 Gy/38 Gy; in the cerebellum up to TD- 24 Gy/28 Gy; both cerebral hemispheres up to TD- 26 Gy/32 Gy and the cerebral ventricles up to TD-30 Gy/38 Gy with daily dose (DD)-1.8 Gy (17/21fractions). We describe in detail the stages of dosimetry planning of this radiotherapy technique, presenting its advantages and disadvantages, the observed early radiation toxicity and the possible treatment outcome.

Volumetric-modulated radiotherapy with bias dose VMAT technique in adulthood medulloblastoma patients achieves improved dose homogeneity at the junction of the fields, increased compliance with the target volume and minimized dose to the organs at risk (OARs).

Keywords

Adulthood medulloblastoma, Medulloblastoma leptomeningeal disease, Volumetric-modulated arc therapy, Craniospinal irradiation, Dosimetry planning.

Introduction

Meduloblastoma (MB) is a rare disease in adolescents and young adults, diagnosed in 1% of all brain tumours [1,2]. MB behaves differently in adults than in children and is identified as a different biological and clinical entity [1]. The prognosis and survival are directly dependent on the volume of the surgery, the magnitude of the postoperative brain residue (> 1.5 cm^2), the infiltration of the IV ventricle and the pathohistological variant [3-5]. In adulthood medulloblastoma patients the five-year progression-free survival rate ranges from 45% to 75% depending on the risk class [6,7]. Re-irradiation is frequently undertaken for isolated brain relapses. A meta-analysis of brain re-irradiation found no cases of necrosis if the total dose was lower than 100 Gy (2 Gy/fraction; $\alpha:\beta = 2$ Gy) [2]. There is limited high-quality evidence to guide the optimal use of radiotherapy (RT) and re-iradiation for the treatment of adulthood medulloblastoma leptomeningeal disease (LMD). For the first time in the English medical literature we present two adulthood clinical cases with medulloblastoma leptomeningeal disease (LMD) in which we have performed second craniospinal irradiation (re-CSI) using bias volumetric-modulated arc therapy (VMAT) technique.

First clinical case

A 37-year-old woman with medulloblastoma in adulthood with subependymal, cerebellar and spinal leptomeningeal metastasis after 7 years from primary treatment is presented. Initially, subtotal tumor extirpation was performed, followed by postoperative

conventional fractionated craniospinal radiotherapy (CSRT) of a telegamotherapy device up to TD-36 Gy with cerebellar overdose/boost up to TD-54 Gy with DD-1,8 Gy. From 2012 to 2017, local tumor control (LTC) was reported on CT. In 2017, 2018 and 2019 three local recurrences were identified, which were surgically removed. After the operation of the third recurrence, she performed 6 courses Chemotherapy (Ch) with Etoposide and Carboplatin. MRI of the craniospinal axis showed diffuse subependymal ventricular metastasis combined with leptomeningeal in the cerebellum and the entire spinal axis (Figure 1). Complementary re-CSRT was performed using bias VMAT technique in the area of the spinal cord up to TD-24 Gy; cauda equina up to TD-28 Gy; in the cerebellum up to TD-24 Gy; both cerebral hemispheres up to TD-26 Gy and paraventricular up to TD-30 Gy with DD-1.8 Gy (17 fractions). Table 1 presents the summary biologically equivalent dose (BED) after the first and second CSRT in the separate areas of the brain and spinal axis. Three months after the completion of the re-CSRT, we conducted an MRT of the brain and cervical spinal cord, which reported lack of subependimal periventricular and leptomeningial metastases in the brain, cerebellum and cervical spinal axis (Figure 2).

Second clinical case

A 47-year-old man with adult medulloblastoma with intraventricular and spinal leptomeningeal metastases after 9 years of treatment is presented. Initially, maximal radical tumor extirpation was performed, followed by postoperative 3-D conformal CSRT at a linear accelerator with 6 MV up to TD-21.6 Gy with DD-1.8 Gy and boost in the tumor bed up to TD-27 Gy (total dose in the tumor bed up to TD-48.6 Gy). He has not had postoperative Ch. On MRI, supratentorially intraventricular leptomeningeal metastases combined with spinal in the cervical part of the myelon were visualized (Figure 3). Complementary re-CSRT was performed using bias VMAT technique in the area of the spinal cord up to TD-32 Gy; cauda equina up to TD-38 Gy; in the cerebellum up to TD-27 Gy; both cerebral hemispheres up to TD-32 Gy and paraventricular up to TD-38 Gy with DD-1.8 Gy (21 fractions). Table 2 presents the summary biologically equivalent dose (BED) after the first and second CSRT in the separate areas of the brain and spinal axis. The patient is currently undergoing final stage of second radiotherapy.

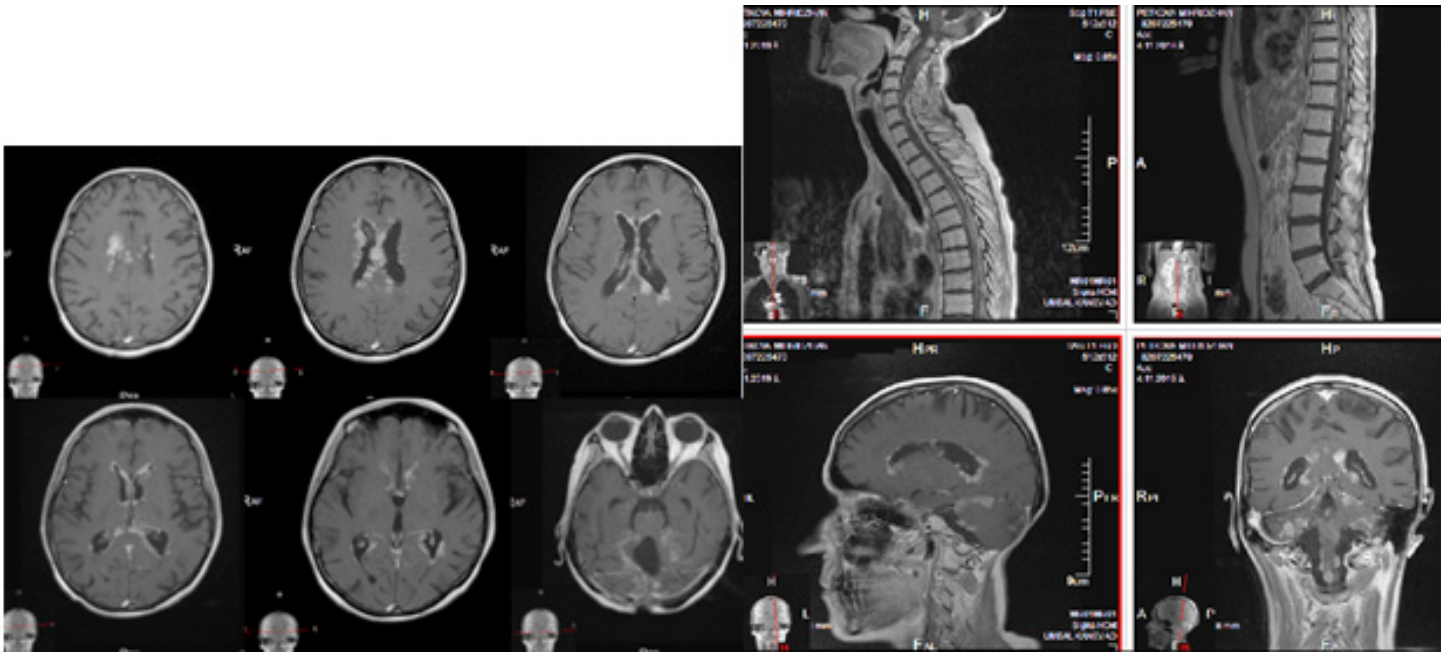


Figure 1: Case 1 - Head and Spine MRI – Leptomeningial spinal and cerebellar metastases combined with diffuse subependimal periventricular metastases.

Table 1: Summary biologically equivalent dose (BED) for the first clinical case after the first and second CSRT in the separate areas of the brain and spinal axis.

Target	D1 Gy	70% D1 (after 7 years) Gy	α/β Gy	D2 Gy	BED2 Gy	Total BED Gy
Cerebellum	54	37.8	3.3	24	23.1	60.9
Brain	36	25.2	3.3	26	25	50.2
Paraventricular	36	25.2	2	30	28.9	54.1
Spinal cord	36	25.2	2	24	22.8	48
Cauda equina	36	25.2	4	28	27.1	52.3

D1- total dose of the first CSRT; Gy- a unit for measuring radiation dose; D2- total dose of the second CSRT; α/β- ratio of two constants-linear and exponential in Gy.

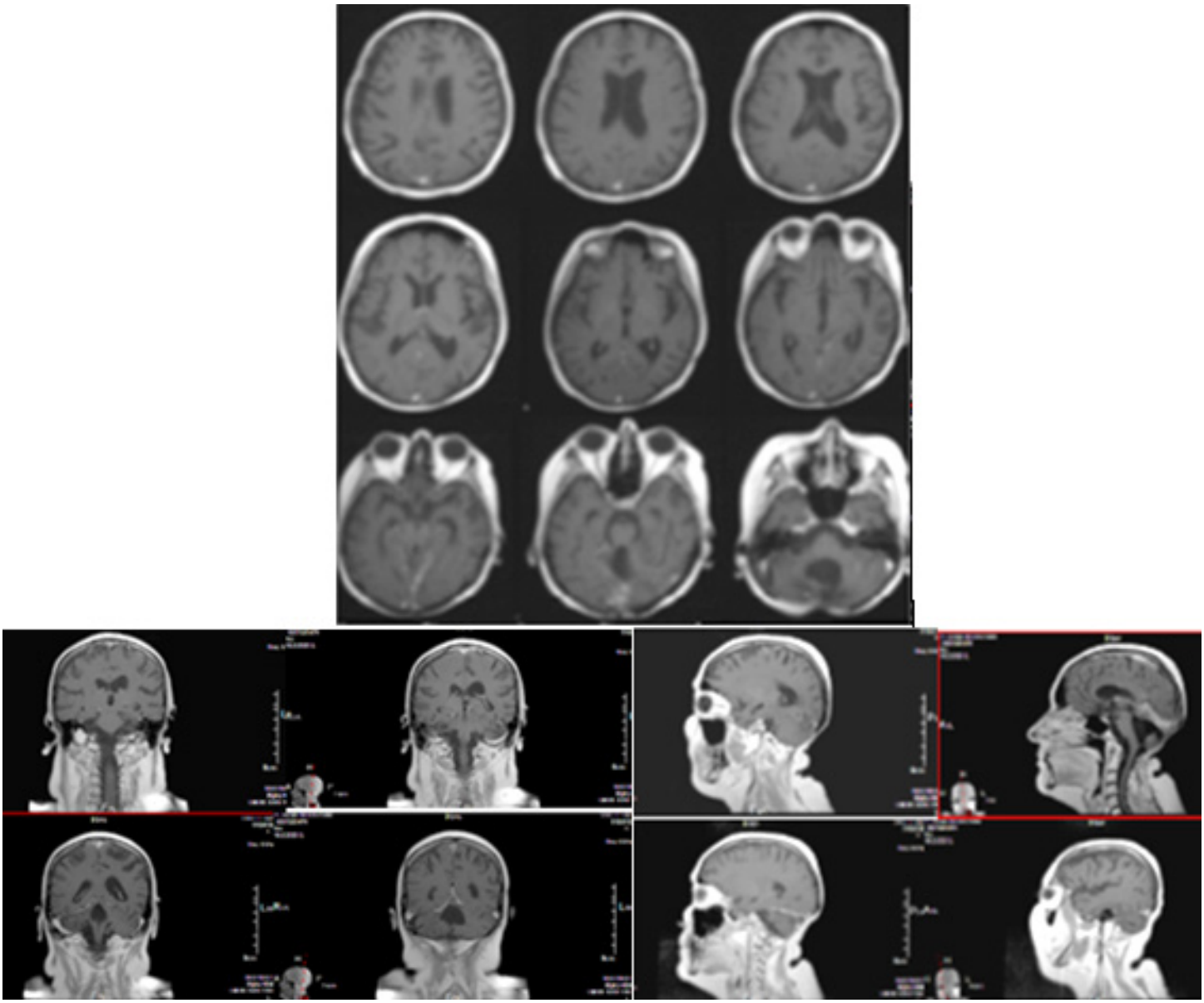


Figure 2: Case 1- MRT axial, frontal and sagittal images without metastases three months after the re-CSRT.

Table 2: Summary biologically equivalent dose (BED) for the second clinical case after the first and second CSRT in the separate areas of the brain and spinal axis.

Target	D1 Gy	56% D1 Gy (after 9 years)	α/β Gy	D2 Gy	BED2 Gy	Total BED Gy
Cerebellum	48.6	27.2	3.3	28	27	54.2
Brain	21,6	12.1	3.3	32	32.4	44.5
Paraventricular	21,6	12.1	2	38	37.8	50.1
Spinal cord	21,6	12.1	2	32	32.4	44.5
Cauda equina	21,6	12.1	4	38	37.8	50.1

D1- total dose of the first CSRT; Gy- a unit for measuring radiation dose; D2- total dose of the second CSRT; α/β- ratio of two constants-linear and exponential in Gy.

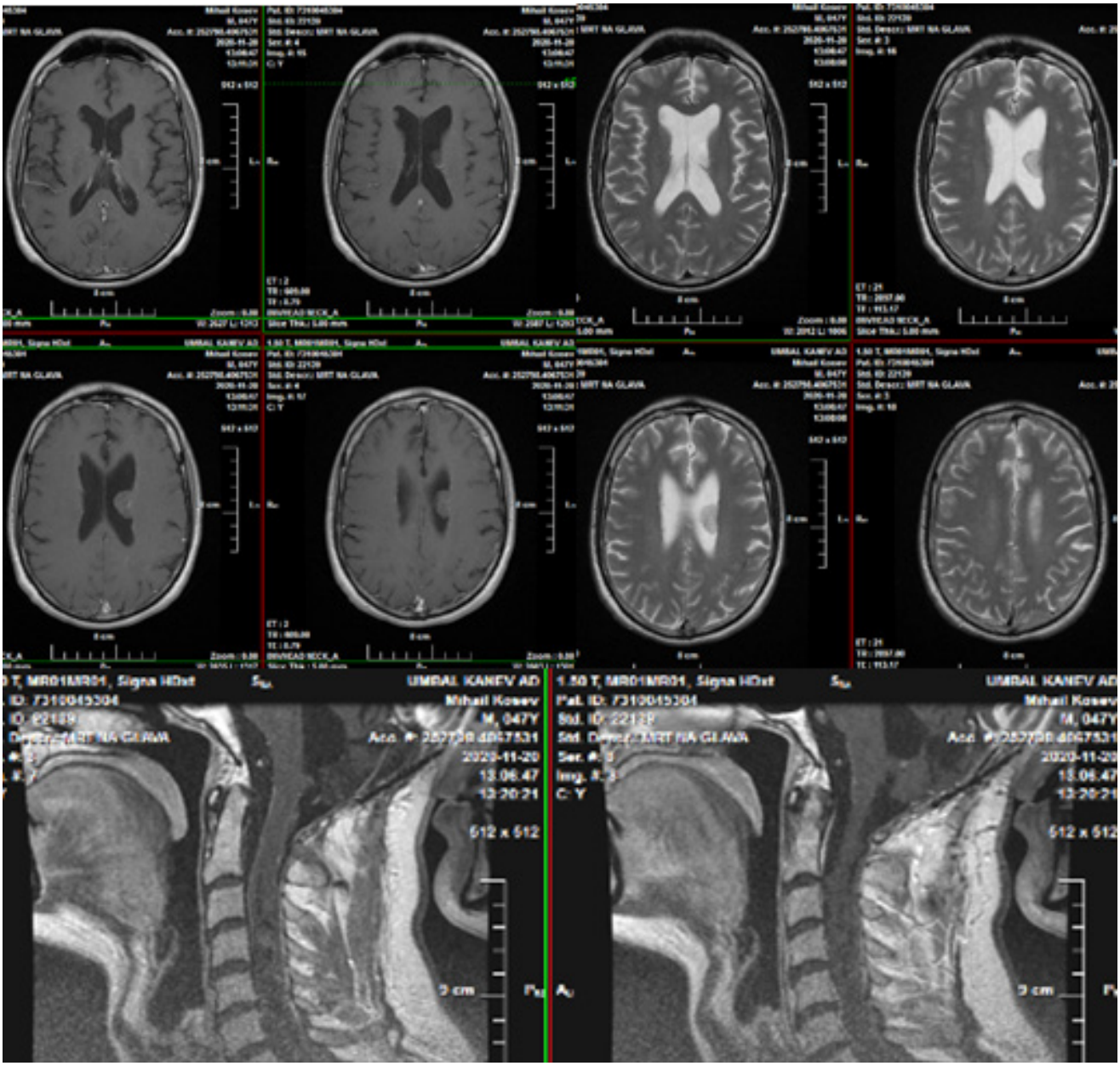


Figure 3: Case 2 - MRT axial and sagittal images with supratentorially intraventricular leptomeningeal metastases combined with spinal in the cervical part of the myelon.

Early radiation toxicity

In both patients, we have observed leukopenia and thrombocytopenia, which occurred in the second week of the radiotherapy course, which is an expected early hematogenous toxicity due to a large irradiated volume involving bone structures. In general, in the CSRT cases, due to irradiation of many bony structures (skull, spine and pelvic bones) thrombocytopenia manifests, which is treated with Dexamethasone (2 or 3 times 8 mg. /daily), Methylprednisolone 40 mg. /daily and Ecomer (3 times 2 caps./ daily). Early haematological toxicity does not disrupt the rhythm of craniospinal radiotherapy, as it can be overcome by corticosteroid drug therapy. Apart from the indicated haematological toxicity, we did not observe any other early radiation reactions from normal organs and structures.

Dosimetry planning

Anatomical targets and Clinical target volumes (CTVs)

In the first clinical case, the total planned target volume (PTV) range along the longitudinal axis is 68 cm and includes the following brain and spinal cord structures / anatomical targets : 1/ cerebral ventricles - with a supplementary dose of 30 Gy; 2/ the two cerebral hemispheres - with a supplementary dose of 27 Gy, including the cranial part of the brainstem (BS) with a maximum allowable dose of supplementation of 24 Gy; 3/ cerebellum - with a supplementary dose of 24 Gy, including the caudal part of the BS with a maximum allowable dose of supplementation of 24 Gy; 4 / spinal cord - with a supplementary dose of 24 Gy; 5 / cauda equina - with a supplement dose of 28 Gy. Five clinical target volumes (CTVs) are formed: CTV ventriculi; CTV cerebrum;

CTV cerebellum; CTV medula spinal and CTV spinal sacral. The critical brain structures are the following: the eyeballs, the optic nerves, the lens of the eye, the chiasm opticus and the brainstem. The replenishment dose in the individual target volumes and anatomical targets is calculated according to the alpha / beta model, estimating the residual doses after the determined elapsed time period from the first irradiation, provided that the maximum tolerable doses in the critical brain structures are not exceeded (Figure 4/A).

In the second clinical case, the total PTV range along the longitudinal axis is 81 cm and includes the following brain and spinal cord structures / anatomical targets: 1/ cerebral ventricles - with a supplementary dose of 38 Gy; 2 /the two cerebral hemispheres - with a refill dose of 32 Gy, including the cranial part of the BS with a maximum allowable refill dose of 28 Gy; 3/ cerebellum - with a supplementary dose of 28 Gy, including the caudal part of the BS with a maximum allowable dose of supplement 28 Gy; 4/ spinal cord - with a supplementary dose of 32 Gy; 5 /cauda equina - with a supplementary dose of 38 Gy. Here again five CTVs are formed: CTV ventriculi; CTV cerebrum; CTV cerebellum; CTV medula spinal and CTV spinal sacral. The critical brain structures are the following: the eyeballs, the optic nerves, the lens of the eye, the chiasm opticus and the brainstem. The replenishment dose in the individual target volumes and anatomical targets is calculated according to the alpha / beta model, estimating the residual doses after the determined elapsed time period after the first irradiation, provided that the maximum tolerable doses in the critical brain structures are not exceeded (Figure 4/B).

Determination of isocenters

In the first clinical case, the total PTV is divided into two volumes - cranial and caudal - with two isocenters selected in their midpoints and a junction between them approximately in the middle of the total volume along the longitudinal axis, which is necessary due to maximum size limitation of the field 40x40 cm2 at isocenter (Figure 4/A).

In the second clinical case, the longitudinal size of the total planned target volume is greater than 80 cm, that is why it is divided into three volumes - cranial, middle and caudal- with approximately equal longitudinal dimensions with three isocenters selected approximately in their midpoints (Figure 4/B). The number and coordinates of all selected isocenter points are consistent with both the volume of the targets and the physical ability to perform automatic positioning of the patient table.

For both clinical cases the dosimetry planning is carried out in three stages. For the first clinical case two dosimetry plans are made at the first and second stage and at the third stage - one dosimetry plan. For the second clinical case three dosimetry plans are made at the first and second stage and at the third stage - two dosimetry plans.

The preparation for dosimetry planning includes the creation of auxiliary structures for targets and critical organs, the inclusion of immobilization pads in the plan and the delineation of visible inhomogeneities.

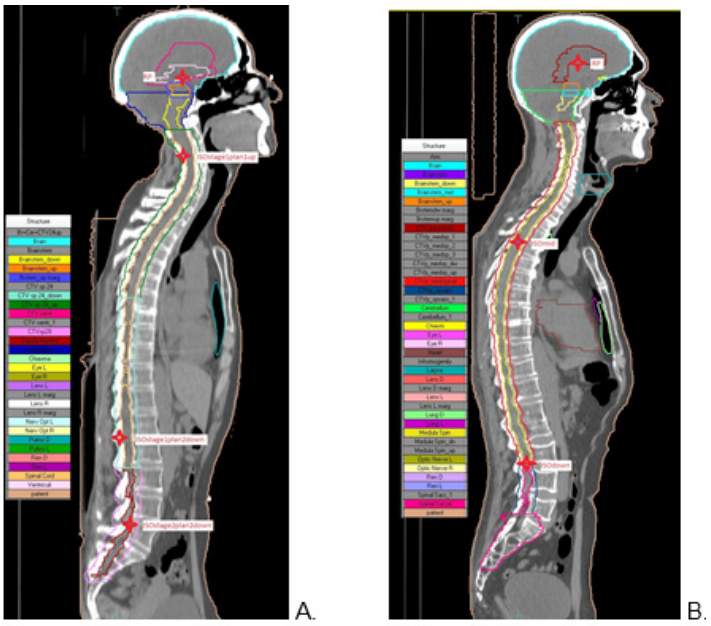
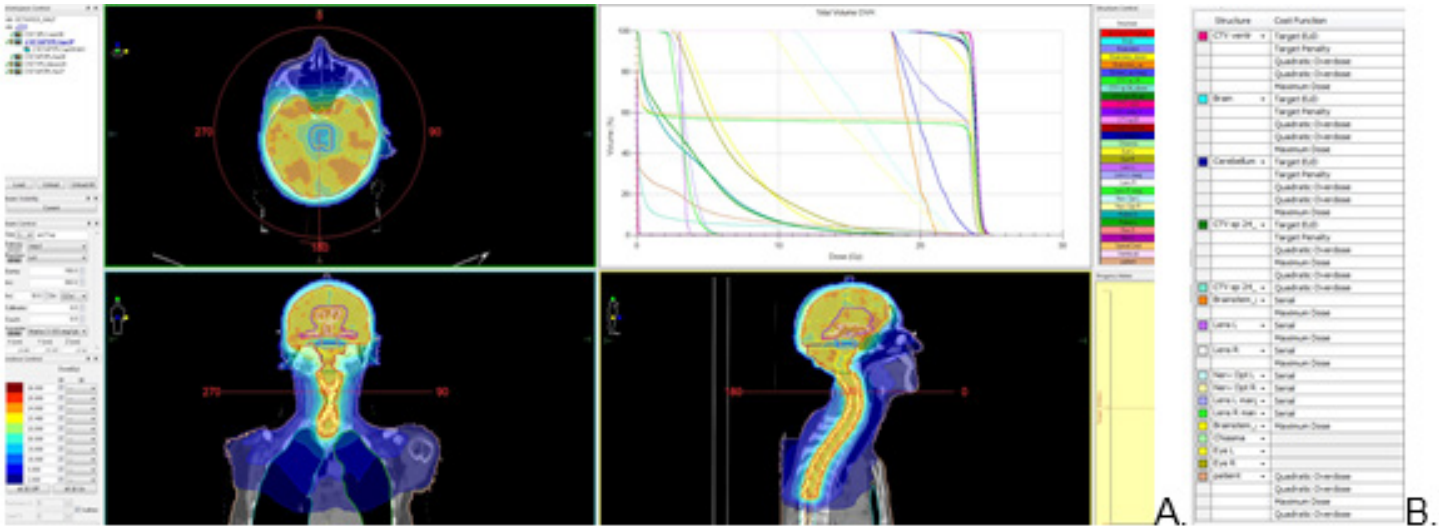


Figure 4: Planned target volumes, critical structures, reference points (RP) and selected isocenter points (ISO) for the first (A) and second (B) clinical case**.**

First stage of dosimetry planning

In the first clinical case, the cranial half of the total planned target volume includes the clinical target volumes: CTV ventriculi; CTV cerebrum; CTV cerebellum, including the Brainstem and the cranial half of the CTV medula spinal. At the first stage of dosimetry planning, a VMAT plan was created with two pairs of double full coplanar arcs with a zero and ninety degree collimator, respectively, for irradiation of the cranial targets up to a total dose of 23.4 Gy in 13 fractions of 1.8 Gy daily dose. In this plan, the brainstem is divided into cranial and caudal parts (Brainstem up and Brainstem down), with the division at the cerebellum-brain border. For the cranial part - Brainstem up, additional restrictions are imposed on the maximum dose not to exceed 20-21 Gy, due to a higher dose in this volume residual from the primary radiotherapy of the patient and in order to advance for an additional dose to a final total dose of 24 Gy of the target CTV cerebrum to a total dose of 27 Gy in the second stage of dosimetry planning (Figure 5). The first stage of dosimetry planning also includes the development of a bias VMAT plan with dose supplementation with two pairs of double full coplanar arcs with collimator zero and ninety degrees, respectively, to irradiate the caudal half of the total planned target volume to a total dose of 23.4 Gy in 13 fractions of 1.8 Gy daily dose. It includes the caudal half of the CTV medula spinal and the CTV spinal sacral (Table 3).

Dosimetry planning is realized in a similar way for the second clinical case with the difference that the total planned target volume is divided into three volumes - cranial, middle and caudal. The cranial target volume includes the targets CTV ventriculi, CTV



Structure	Volume [cm]	Min. Dose [Gy]	Max. Dose [Gy]	Mean Dose [Gy]	Cold Ref. [Gy]	Volume < [%]	Hot Ref. [Gy]	Volume > [%]	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
CTV ventr	193.992	21.444	25.038	23.964			**23.400**	98.51	100.00	no	1.04	0.00
Brain	995.295	17.216	25.128	23.720			**23.400**	88.93	100.00	no	1.05	0.00
Cerebellum	188.121	14.489	25.136	23.805			**23.400**	88.88	100.00	no	1.07	0.00
CTV sp 24_up	143.298	21.208	24.998	23.817			**23.400**	91.87	100.00	no	1.04	0.00
CTV sp 24_down	121.533	0.000	24.102	1.116					100.00	no	868.67	0.19
Brainstem_up	6.213	17.850	21.276	19.307					100.00	no	1.15	0.03
Lens L	0.156	2.971	3.716	3.283					100.00	no	1.17	0.00
Lens R	0.147	2.709	3.379	2.997					100.00	no	1.18	0.00
Nerv Opt L	0.360	11.066	22.215	16.648					100.00	no	1.82	0.18
Nerv Opt R	0.474	9.227	22.132	15.200					100.00	no	2.14	0.14
Brainstem_down	13.257	20.770	24.470	23.364					100.00	no	1.10	0.00
patient(Unsp.Tiss.)	26792.661	0.000	25.002	1.893					99.83	no	1934.54	0.00
Chiasma	0.303	22.807	24.296	23.765					100.00	no	1.04	1.00

Figure 5: First plan"11"-first clinical case-dose distribution and DVH (A), cost functions (B), DVH statistics (C).

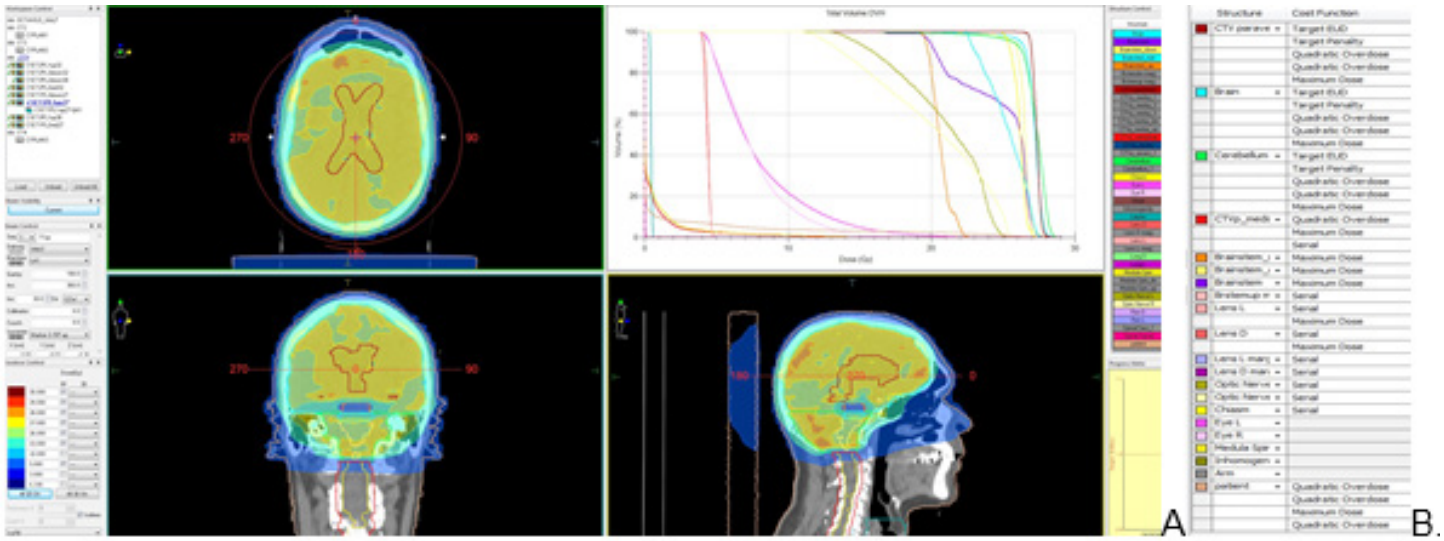
Table 3: Stages of dosimetry planning for the first clinical case.

Stage	Plan	ISO	ARCS	Fractions	DD, Gy	TD, Gy	Target	OARs	MUs
I	11	ISO stage1plan1 up	11up 12up	13	1,8	23,4	CTVventriculi, CTVcerebrum, CTVcerebellum, CTVmedspinal	Brainstem, Lens, Eyes, Optic nerves, Chiasma	754
	12	ISO stage1plan2 down	11down 12down	13	1,8	23,4	CTVmedspinal, CTVspinalsacral	Lungs, Kidneys,	580
II	21	RP	21up	2	1,8	3,6	CTVventriculi, CTVcerebrum	Brainstem, Lens, Eyes, Optic nerves, Chiasma	846
	22	ISO stage2plan2 down	21down 22down	3	1,8	5,4	CTVspinalsacral	Kidneys	515
III	31	RP	31up	2	1,8	3,6	CTVventriculi	Brainstem, Lens, Eyes, Optic nerves, Chiasma	883

cerebrum, CTV cerebellum, including the Brainstem and at the first stage a total dose of 27 Gy in 15 fractions of 1.8 Gy daily dose is delivered except for the cranial part of Brainstem - Brainstem up, for which additional restrictions are imposed on the maximum dose not to exceed 22-23 Gy. Similarly, this is necessary due to the higher dose residual in this volume from the primary radiotherapy of the patient and in order to advance for an additional dose to a final total dose of 28 Gy when supplementing the target CTV cerebrum to a total dose of 32 Gy at the second stage of dosimetry planning (Figure 6).

The median target volume includes the cranial portion of the CTV medula spinal. The caudal target volume includes the targets caudal portion of the CTV medula spinal and CTV spinal sacral. For the middle and caudal target volumes, two consecutive dose-complementary bias VMAT plans were developed analogously, each with two pairs of double full coplanar arcs with a zero and ninety degree collimator, respectively, and a total dose of 27 Gy in 15 fractions of 1.8 Gy daily dose (Table 4).

In all bias VMAT plans, in the first stage of dosimetry planning, the doses for targets and critical organs are summed with the corresponding doses from their respective base plan, which allows better control of the joints. In the Monaco 3.11 planning system, this is achieved by checking the corresponding box of the "Bias Dose" column in the prescription of the corresponding cost function. Restrictions on the 'patient's body' are left more free in the bias plan due to the effect of the baseline doses.



Structure	Volume (cm)	Min. Dos...	Max. Dose (Gy)	Mean Dose (Gy)	Cold Ref. ...	Volume < (%)	Hot Ref. (Gy)	Volume ...	% in Volume	Is in SS	Heter...	Conformit...
CTV paraventri	97.776	24.503	28.608	27.331	**26.000**	0.13	**27.000**	89.44	100.00	no	1.03	0.00
Brain	1290.940	16.644	29.119	27.123	**26.000**	3.73	**27.000**	70.15	100.00	no	1.06	0.98
Cerebellum	223.660	16.087	28.989	27.182	**26.000**	6.28	**27.000**	70.00	100.00	no	1.10	0.96
CTVp_medspinal	304.752	0.000	14.494	0.507					100.00	no	390.69	0.00
Brainstem_up	5.546	19.139	22.808	20.608	**21.000**	74.71	**22.000**	4.75	100.00	no	1.12	0.12
Brainstem_down	12.266	21.789	28.055	26.441	**26.000**	9.12	**27.000**	7.79	100.00	no	1.05	0.00
Brainstem	23.308	16.556	28.055	24.668	**26.000**	43.55	**27.000**	6.79	100.00	no	1.36	0.00
Lens L	0.328	4.064	4.820	4.434					100.00	no	1.12	0.03
Lens D	0.226	3.922	4.774	4.369					100.00	no	1.15	0.03
Optic Nerve L	0.638	12.944	25.296	20.839					100.00	no	1.66	0.01
Optic Nerve R	0.820	11.036	25.702	20.030					100.00	no	1.99	0.11
Chiasm	1.178	24.793	27.361	26.152					100.00	no	1.06	0.02
patient(Unsp.Tiss.)	39729.568	0.000	28.717	1.071					99.84	no	1172.51	0.00
Medula Spin	105.726	0.000	14.360	0.591					100.00	no	460.47	

Figure 6: First plan "11"-second clinical case-dose distribution and DVH (A), cost functions (B), DVH statistics (C).

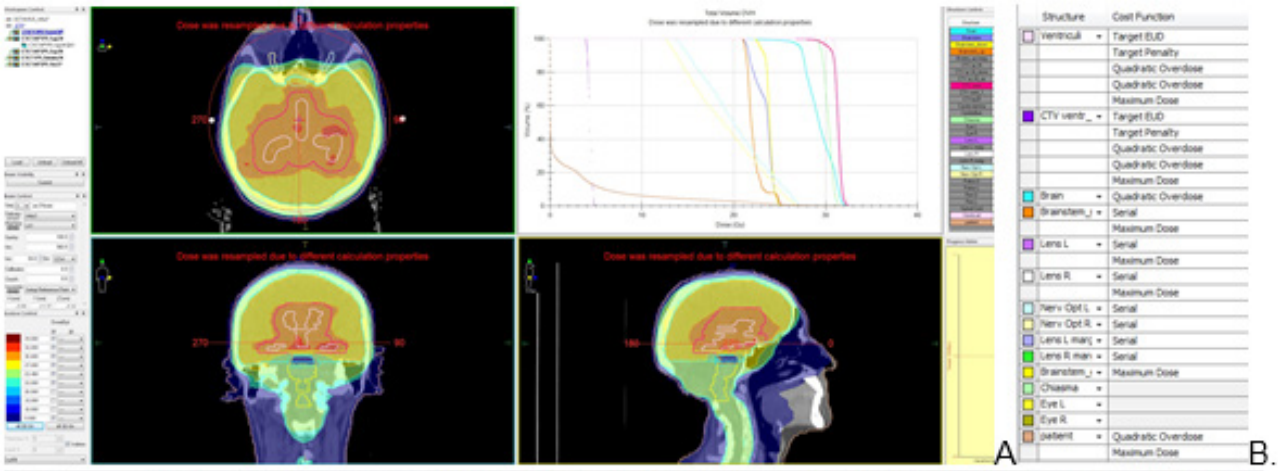
Table 4: Stages of dosimetry planning for the second clinical case.

Stage	Plan	ISO	ARCS	Fractions	DD, Gy	TD, Gy	Target	OARs	MUs
I	11	RP	11up 12up	15	1,8	27	CTVventriculi, CTVcerebrum, CTVcerebellum	Brainstem, Lens, Eyes, Optic nerves, Chiasma,	530
	12	ISOmid	11mid 12mid	15	1,8	27	CTVmedspinal	Lungs, Laryngis, Heart	489
	13	ISOdown	11down 12down	15	1,8	27	CTVmedspinal, CTVspinalsacral	Kidneys	673
II	21	RP	21up 22up	3	1,8	32,4	CTVventriculi, CTVcerebrum	Brainstem, Lens, Eyes Optic nerves, Chiasma,	1489
	22	ISOmid	21mid 22mid	3	1,8	32,4	CTVmedspinal	Lungs, Laryngis, Heart	1160
	23	ISOdown	21down 22down	3	1,8	32,4	CTVmedspinal, CTVspinalsacral	Kidneys	3050
III	31	RP	31up 32up	3	1,8	37,8	CTVventriculi	Brainstem, Lens, Eyes Optic nerves, Chiasma	1265
	32	ISOdown	31down 32down	3	1,8	37,8	CTVspinalsacral	Kidneys	1803

Complementation to a final total dose in the planned target volumes is achieved at the second and third stages of dosimetry planning in both clinical cases with bias VMAT plans based on the respective base plan (Table 3 and 4).

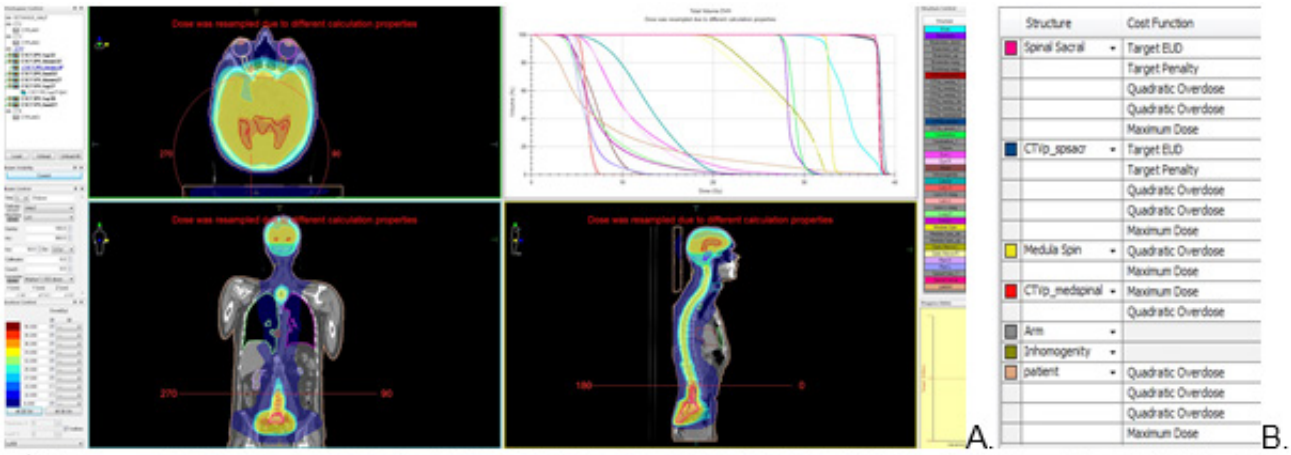
For the first clinical case, this was achieved without summing the doses separately for the cranial targets - CTV cerebrum up to 27 Gy and CTV ventriculi up to 30.6 Gy - with two more consecutive bias VMAT plans and for the caudal target - CTV spinal sacral - up to 28.8 Gy with another bias VMAT plan. In the Monaco 3.11 planning system, this is done by unchecking the corresponding box of the "Bias Dose" column in the prescription of the corresponding cost function. Restrictions on the "patient's body" are left more free in the bias plan due to the influence of the doses from the base plan (Figure 7).

For the second clinical case, this was achieved by summing the doses with five more consecutive bias VMAT plans to a final dose for the respective targets CTV ventriculi up to 37.8 Gy, CTV cerebrum up to 32.4 Gy, CTV medula spinal up to 32.4 Gy,



Structure	Volume (cm)	Min. Dose (Gy)	Max. Dose (Gy)	Mean Dose (Gy)	Cold Ref. (Gy)	Volume < (%)	Hot Ref. (Gy)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
Ventriculi	41.607	30.314	32.717	31.529			**30.600**	99.85	100.00	no	1.03	1.00
Brain	995.295	20.909	32.815	29.346			**27.000**	96.39	100.00	no	1.16	1.00
Brainstem_up	6.213	20.909	25.436	22.195			**25.000**	2.30	100.00	no	1.17	0.08
Lens L	0.156	3.916	4.882	4.337					100.00	no	1.18	0.00
Lens R	0.147	3.774	4.748	4.311					100.00	no	1.19	0.00
Nerv Opt L	0.360	13.562	27.169	20.156					100.00	no	1.83	0.14
Nerv Opt R	0.474	12.597	26.842	19.059					100.00	no	1.95	0.10
Brainstem_down	13.257	22.153	25.180	23.898			**23.400**	89.59	100.00	no	1.08	0.00
patient(Unsp.Tiss.)	26792.661	0.000	31.225	2.003					99.83	no	2012.40	0.15
Brainstem	19.464	20.909	25.436	23.354			**23.400**	63.87	100.00	no	1.15	
Cerebellum	188.121	14.811	28.364	24.779			**23.400**	96.34	100.00	no	1.15	
Chiasma	0.303	28.990	31.353	30.299					100.00	no	1.06	
CTV ventr	193.992	26.212	32.815	31.286			**30.600**	93.35	100.00	no	1.05	
Eye L	8.799	3.739	21.889	8.857					100.00	no	3.41	
Eye R	10.371	2.767	23.609	9.134					100.00	no	4.09	

Figure 7: Last plan"31"-first clinical case-dose distribution and DVH (A), cost functions (B), DVH statistics (C).



Structure	Volume (cm)	Min. Dose (Gy)	Max. Dose (Gy)	Mean Dose (Gy)	Cold Ref. (Gy)	Volume < (%)	Hot Ref. (Gy)	Volume > (%)	% in Volume	Is in SS	Heterogeneity Index	Conformity Index
Spinal Sacral	436.194	34.350	39.510	38.222			**38.000**	91.36	100.00	no	1.02	0.00
CTVip_spsacr	56.006	34.350	39.574	38.445			**38.000**	93.22	100.00	no	1.03	0.00
Medula Spin	105.352	31.098	34.693	32.867			**32.000**	99.69	100.00	no	1.03	0.00
CTVip_medspinal	306.532	27.836	35.481	32.660			**32.000**	94.43	100.00	no	1.04	0.00
patient(Unsp.Tiss.)	39751.388	0.099	39.393	8.968					99.51	no	21.23	0.00
Brain	1290.502	26.189	39.160	34.711			**32.000**	95.39	100.00	no	1.19	
Brainstem	23.318	27.210	31.893	28.449			**27.000**	100.00	100.00	no	1.09	
Cerebellum	222.850	26.244	31.893	28.940			**27.000**	99.73	100.00	no	1.08	
Chiasm	1.196	32.457	35.398	34.097					100.00	no	1.06	
CTV paraventri	97.374	32.771	39.160	38.229			**38.000**	90.34	100.00	no	1.02	
Eye L	10.826	4.295	29.543	11.358					100.00	no	3.49	
Eye R	9.726	3.966	24.317	10.840					100.00	no	3.15	
Heart	368.622	2.832	14.623	7.184					100.00	no	2.49	
Larynx	41.910	3.158	22.481	13.032					100.00	no	2.65	
Lens D	0.228	4.774	7.426	6.089					100.00	no	1.32	
Lens L	0.336	5.075	7.646	6.212					100.00	no	1.33	
Lung D	2121.068	2.069	27.402	7.762					100.00	no	4.23	
Lung L	1965.468	2.220	26.333	7.616					100.00	no	3.73	
Optic Nerve L	0.636	18.319	32.778	27.527					100.00	no	1.55	
Optic Nerve R	0.826	17.392	32.720	26.918					100.00	no	1.66	
Ren D	137.250	4.430	13.796	6.440					100.00	no	2.03	
Ren L	140.132	3.750	13.922	6.083					100.00	no	2.35	

Figure 8: Last plan "32"-second clinical case-dose distribution and DVH (A), cost functions (B), DVH statistics (C).

and CTV spinal sacral to 37.8 Gy. In the Monaco 3.11 planning system, this is done by checking the corresponding box of the "Bias Dose" column in the prescription of the corresponding cost function. Restrictions on the "patient's body" are left more free in the bias plan due to the influence of the doses from the baseline plan (Figure 8).

It has been found that the second planning strategy allows much better control of junctions and hotspots inside and outside the targets. In addition, in the second planning strategy, the last planned bias plan presents eventually the sum of the doses for all targets and critical organs, which allows a clearer picture of the total radiation doses (Figure 8).

Dosimetry planning evaluation

Normalization of the plans

Plans for both cases are normalized so that at least 95% of CTV is covered by at least 95% of prescription dose. Evaluation of all plans is performed by DVH analysis of the target volumes and relevant OARs. For the CTVs, the dosimetric parameters analyzed include mean dose (Dmean), maximum dose (Dmax), $D_{2\%,}$ $D_{50\%,}$ $D_{95\%,}$ $D_{98\%}$ and $V_{95\%}$ wherein $Dx_{\%}$ was defined as the dose received in x% of the volume and $Vy_{\%}$ is the volume of CTV in cm3 receiving at least y% of the prescribed dose (Table 5 and 6).

Assessment of the requirements for dose coverage of the targets - for clinically acceptable coverage is assumed that 95% of the prescribed dose covers at least 95% of the volume of the clinical target volume, which is achieved for all targets in both cases (Table 5 and 6). The requirement is that the maximum dose in volume does not exceed 107% of the prescribed dose, which is not achieved only for minor volumes of CTV cerebrum and CTV cerebellum for both cases as those are in the vicinity of a higher dose targets (Table 5 and 6).

Evaluation of the conformity

Conformity of the prescription dose to the CTVs is expressed by the conformity index (CI), which represents the volume of the CTV receiving more than 95% of the prescribed dose divided by the volume of the CTV i.e., $CI=V_{95\%}/VCTV$. It provides information regarding the degree the prescribed isodose volume conforms to the shape and size of the target volume(s) (Table 5 and 6).

Evaluation of the homogeneity

The homogeneity index (HI) of the CTVs is defined as the ratio of the difference of D2% and D98% to D50% i.e., $HI=(D_{2\%}–D_{98\%})/D_{50\%}$ for the CTV, where D2%, D50%, and D98% correspond to the dose delivered to 2%, 50%, and 98% of the CTV, respectively. It provides information regarding the dose uniformity within the target volume(s). This is an estimate for optimizing the dose coverage. Better homogeneity means that the prescribed dose for the respective target will be delivered at the lowest possible maximum value in the irradiated volume (Table 5 and 6).

Evaluation of the dose in the critical organs

For the relevant OARs, the mean and maximum doses for each organ are reported for dosimetric comparison for both cases (Table 7). The data analysis has shown, that the dose constraints for all critical OAR have been maintained, taking into account the doses, received in the same organs after the primary radiotherapy for both cases.

In both cases, the better homogeneity and conformity of the CTV coverage, the better sparing of OARS and the better control of subdosing or overdosing of the junction area between targets were observed. However, this is at the expense of a higher integral dose and larger body volumes covered by low doses compared to a similar 3DCRT plan. The results show that in the first clinical case 10% of the highest prescribed dose (30.6 Gy) - covers up to 60% of the patient's body, and in the second clinical case 10% of the highest prescribed dose (37.8 Gy) - covers up to 70% of the patient's body.

Delivery time and monitor units (MUs) estimation

Craniospinal re-irradiation (re-CSI) for the presented clinical cases is realized with multiple, compound treatment plans in each stage and it is important that the patient is able to maintain the treatment position for a longer time. For the first clinical case plans for stage 1 were delivered for less than 25 minutes (2 plans with Cone-beam CT (CBCT); plans for stage 2 – for less than 20 minutes (2 plans with CBCT); stage 3 - less than 10 minutes (1 plans with CBCT). For the second clinical case: stage 1 - less than 40 minutes (3 plans with CBCT); stage 2 - less than 45 minutes (3 plans with CBCT); stage 3 - less than 30 minutes (2 plans with CBCT). The delivered monitor units ranged from 500 to 900 MUs in the plans for the

Table 5: The dosimetric parameters of the CTVs analyzed for the first case: mean dose (Dmean), maximum dose (Dmax), $D_{2\%,}$ $D_{50\%,}$ $D_{95\%,}$ $D_{98\%}$ and $V_{95\%,}$ wherein $Dx_{\%}$ is defined as the dose received in x% of the volume and $Vy_{\%}$ is the volume of CTV in cm3 receiving at least y% of the prescribed dose.

CASE 1	PCD, Gy	95% of PCD, Gy	107% of PCD, Gy	VCTV, cm3	$V_{95\%,}$ cm3	$D_{98\%,}$ Gy	$D_{95\%,}$ Gy	$D_{50\%,}$ Gy	$D_{2\%,}$ Gy	$D_{mean,}$ Gy	$D_{max,}$ Gy	HI	CI
CTV ventriculi	30.6	29	32.7	41.6	41.6	30.9	31.1	31.5	32.3	31.5	32.7	0.04	1
CTV cerebrum	27	25.7	28.9	801.3	787.7	26	27.1	28.9	31.3	28.9	32.1	0.18	0.983
CTV cerebellum	23.4	22.2	25	188.1	186.4	22.9	23.6	24.5	27.4	24.8	28.3	0.18	0.992
CTV medula spinal	23.4	22.2	25	265.3	264.2	23.1	23.3	23.9	24.5	24	29	0.06	0.996
CTV spinal sacral	28.8	27.4	30.8	138.7	138.5	28.3	28.5	29.3	30.2	29.3	30.8	0.06	0.999

PCD-prescribed complementary dose; VCTV – volume of CTV;
$HI= (D_{2\%}–D_{98\%})/D_{50\%}$ – Homogeneity index; $CI= V_{95\%}/VCTV$ – Conformity index;

Table 6: The dosimetric parameters of the CTVs analyzed for the second case: mean dose (Dmean), maximum dose (Dmax), $D_{2\%}$, $D_{50\%}$, $D_{95\%}$, $D_{98\%}$ and $V_{95\%}$, wherein $Dx_{\%}$ is defined as the dose received in x% of the volume and $Vy_{\%}$ is the volume of CTV in cm3 receiving at least y% of the prescribed dose.

CASE 2	PCD, Gy	95% of PCD, Gy	107% of PCD, Gy	VCTV, cm3	$V_{95\%}$, cm3	$D_{98\%}$, Gy	$D_{95\%}$, Gy	$D_{50\%}$, Gy	$D_{2\%}$, Gy	D_{mean}, Gy	D_{max}, Gy	HI	CI
CTV ventriculi	37.8	35.9	40.4	97.4	96.4	37.1	37.8	38.3	38.7	38.2	39.2	0.04	0.989
CTV cerebrum	32.4	30.8	34.7	1193	1172.2	30.9	32	34.5	37.9	34.4	39.1	0.2	0.983
CTV cerebellum	27	25.6	28.9	222.8	222.8	27.6	27.9	28.9	30.5	28.9	31.8	0.1	1
CTV medula spinal	32.4	30.8	34.7	105.3	105.3	32.3	32.4	32.8	33.6	32.9	34.6	0.04	1
CTV spinal sacral	37.8	35.9	40.4	436.2	435.7	37.8	37.9	38.2	38.6	38.2	39.5	0.02	0.999

PCD-prescribed complementary dose; VCTV – volume of CTV;
HI= $(D_{2\%}–D_{98\%})/D_{50\%}$ – Homogeneity index; CI= $V_{95\%}$/VCTV – Conformity index;

Table 7: Mean and maximum doses for each organ at risk (OAR) for both cases.

OAR	CASE 1		CASE 2	
	Dmean	Dmax	Dmean	Dmax
Left Lens	4.3	4.9	6.1	7.4
Right Lens	4.3	4.7	6.2	7.6
Optic chiasm	30.3	31.3	34.1	35.4
Left optic nerve	20.2	27.2	27.5	32.8
Right optic nerve	19.1	26.8	26.9	32.7
Left eye	8.8	21.9	11.4	29.5
Right eye	9.1	23.6	10.8	24.3
Brainstem	23.3	25.4	28.4	31.9
Left kidney	9.1	18.6	6.1	13.8
Right kidney	8.1	17.5	6.4	13.8

first case, but were much higher in the plans for the second case ranging from 500 to 3000 MUs (Table 3 and 4).

Discussion

Almost all clinically significant metastases from the medulloblastoma are located in the leptomeningial area, clinging to the soft brain sheath under the arachnoid membrane and are poured from the cerebrospinal fluid [8]. The metastasis model is limited to leptomeningial space, based on assumptions and poorly maintained empirical evidence that MB spread by direct distribution in the cerebrospinal fluid of tumor cells of the primary MB. Subsequently, tumor cells are implanted and grow on the surface of the soft brain matter [9].

Craniospinal irradiation (CSI) is a major part of the complex treatment of MB in children and adults. This is a complex radiotherapy technique in which the accuracy of the radiation fields location and the choice of radiation source and energy can play an important role in determining success or failure [10]. In planning CSI by supine technique, beam geometry and field matching have to be carefully considered. Careful positioning of the patient and optimal placement of the junction is important to avoid over or under dosage, and immobilization is essential to ensure reproducibility of treatment during fractions [11].

For optimal dose distribution, high-tech radiotherapy (RT) is applied with a number of radiation techniques such as two-dimensional (2D) RT, three-dimensional (3D) conformal RT, intensity-modulated RT (IMRT), volumetric-modulated arc therapy (VMAT) technique [12-14]. The main goal of RT in pediatric and adulthood medulloblastoma is improved dose homogeneity at the field junction (s), increased target volume conformity, and minimized dose to the organs at risk (OARs) [11,12,15]. The IMRT technique achieves sparing of risky organs without a significant increase in the integrated dose [15]. IMRT with daily intrafractionally modulated junction results in a superior target coverage and junction homogeneity compared with 3DCRT. A significant dose reduction can be obtained for acute as well as late-reacting tissues [11,12]. A VMAT technique significantly reduces OAR dose, potentially leading to lower late organ toxicity. However, this is achieved at the expense of increased low-dose volumes, which is inherent to the technique, carrying a potentially increased risk of secondary malignancies [14]. IMRT and VMAT provide highly conformal target radiation doses, but also expose large volumes of healthy tissue to low-dose radiation [16].

Re-irradiation of brain tumors is attracting increasing interest. In fact, a greater understanding of brain tolerance to radiation, developments in tumor imaging and advances in radiotherapy planning and delivery techniques now make possible the achievement of better target definition and highly conformal treatments [2]. A meta-analysis of LMD survival in adulthood with primary brain tumours following different types of treatments was performed - whole brain radiotherapy (WBRT), craniospinal irradiation (CSI), focal brain RT (FBRT), fractionated or stereotactic radiosurgery (SRS), focal spine radiotherapy (FSRT),

intrathecal chemotherapy (ITCh), intraventricular radioisotope, systemic chemotherapy (SC) and best supportive care (BSC) [17]. The median overall survival (OS) from the diagnosis of LMD ranged from 2.8 to 10.2 months. The studies indicated that patients treated with a combination of SC+RT had significantly prolonged survival compared to either therapy alone or BSC [17]. When the time interval between re-irradiation is not less than six months and the dose for each course is <98Gy BED, in humans there is evidence that the risk of myelopathy is low at radiation doses up to a mean cumulative BED of 135Gy (α: β = 2 Gy for the cervical and thoracic cord and 4 Gy for the lumbar cord). The summary biologically equivalent TD are consistent with the tolerant radiation doses of the spinal cord and the central brain structures [18]. Data exist concerning the re-irradiation of brain tumors to a median cumulative BED_2 (biological equivalent dose in 2Gy fractions) of 200Gy, with at least one year between the two treatments; long-term complications related to the retreatment were seen in patients with a BED_2>204Gy (α:β = 2 Gy) [19]. In the presented two clinical cases, given the unfavorable prognosis, young age and relatively good general condition, we decided that re-CSI is the last treatment strategy that should help them after strict determination of biologically equivalent additional doses in brain structures and spinal cord (Table 1 and 2).

Volumetric-modulated arc radiotherapy with bias VMAT technique in patients with adulthood medulloblastoma achieves improved dose homogeneity at the junction of the fields, increased compliance with the target volume and minimized dose to the organs at risk (OARs). These radiotherapeutic advantages are achieved at the expense of increased volumes of low doses, which is inherent in the technique, carrying a potentially increased risk of secondary malignancies. This fact is especially important in childhood, but not in adulthood, where re-irradiation is the only local treatment alternative. For the first clinical case, it is possible to compare the results of the re-irradiation planning with those of the primary 3-D dosimetry planning performed in the same volumes. It was created with the planning system PlanW 2000 for irradiation with cobalt machine Terabalt-80 ACS (TB-80) with a rectangular asymmetric collimator and SSD = 80 cm. The dosimetry planning for re-irradiation is in the same target volumes was performed with bias VMAT technique using Monaco 3.11 planning system for irradiation with linear accelerator Elekta Synergy with dynamic multileaf collimator Agility with 160 leafs and SSD = 100 cm. This comparison has shown the huge advantage for more homogeneous and conformal dose distribution, much better control of junctions and hotspots in targets and critical organs, easier positioning and examination of the patient when irradiated with a linear accelerator with bias VMAT technique (Table 5 and 6). Those advantages come at the expense of higher integrated dose and a larger volume, covered by low doses. The second planning strategy for the second clinical case with bias VMAT technique by summing the doses with consecutive bias VMAT plans has been found to allow much better control of junctions between targets and hotspots inside and outside targets compared to the planning strategy for the first clinical case. In addition, in the second planning strategy, the last bias plan presents the sum of the doses for all targets and critical organs, which allows a clearer picture of the total radiation doses (Figure 7 and 8).

Conclusion

Meduloblastoma in adulthood is a rare oncological disease. Leptomeningeal disease (LMD) is a rare cancer complication in which malignant cells infiltrate the layers of the central nervous system (CNS). Regardless of systemic and local control of the primary disease, prognosis in the setting of LMD is very poor. There is limited high-quality evidence to guide the optimal use of radiotherapy and re-iradiation for the treatment of LMD in adulthood meduloblastoma. For the first time in the English medical literature we present two adulthood clinical cases with medulloblastoma leptomeningeal disease (LMD) in which we have performed second craniospinal irradiation (re-CSI) using bias volumetric-modulated arc therapy (VMAT) technique. Volumetric-modulated radiotherapy with bias dose VMAT technique in patients with adulthood medulloblastoma achieves improved dose homogeneity at the junction of the field, increased compliance with the target volume and minimized dose to the organs at risk (OARs).

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