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Feasibility of reducing the irradiation dose in regions of active neurogenesis for prophylactic cranial irradiation in patients with small-cell lung cancer

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Prophylactic cranial irradiation (PCI) is performed on patients with limited or extensive small-cell lung cancer to reduce incidence of brain metastases and prolong survival. PCI may induce neurocognitive impairment. Decreasing irradiation of neural stem cells (NSC) might reduce PCI-induced toxicity. We tested the feasibility of reducing irradiation doses to neural stem cell (NSC) regions while maintaining prescribed doses to the planned target volume (PTV).

Irradiation plans utilizing intensity-modulated radiotherapy (IMRT), helical TomoTherapy, and RapidArc for 10 consecutive lung cancer patients were evaluated. The dose distribution, dose-volume histograms, and dose homogeneity indexes were analyzed. Planned and actual dose distributions were compared by dosimetric analysis. Both helical tomotherapy and LINAC-based IMRT reduced the radiation dose to the NSC regions by approximately 45% while maintaining the full dose to the rest of brain. Measured dose distributions matched the planned dose distributions.

Protecting the regions of active neurogenesis is technically feasible. Whether reducing the dose by 35% to 45% is sufficient to reduce treatment toxicity, however, can only be addressed in a randomized study. Further reducing the dose within the NSC region might also significantly decrease the dosage to the PTV.

Key words: stem cells, brain, whole brain radiotherapy, neurocognitive impairment, IMRT, helical tomotherapy, SCLC

Prophylactic cranial irradiation (PCI) significantly improves both overall and disease-free survival and is considered a standard care for small-cell lung cancer (SCLC) patients with limited disease in remission after chemotherapy [1, 2]. PCI is also offered to patients with extensive disease to prolong survival and to reduce the incidence of brain metastases [3]. Nevertheless, the toxicity of this treatment remains an important concern, supported by evidence that whole brain irradiation (WBRT) and chemotherapy potentially induce neurocognitive impairment [4-6].

Brain tissue is very sensitive to reducing the dose per fraction, and reducing the dose from 3 Gy to 2 Gy may reduce the neurotoxicity of combined treatment. Further reduction of the dose per fraction (below 2 Gy) requires hyperfractionation (i.e., applying 2 daily irradiations) to maintain the radiotherapy intensity. On the other hand, hyperfractionation may lead to incomplete repair of radiation-induced damage.

The adult mammalian brain had long been thought to be an organ with no regenerative potential. More recent findings, however, indicate that regeneration is possible in specific regions of the brain that contain multipotent cells with proliferative potential. These cells are usually referred to as stem cells and are capable of differentiating into both glial and neural cells in the adult brain [7, 8]. Regions that contain stem cells are localized in the subventricular zone (SVZ) and subgranular zone (SGZ) [7, 9-11]. Neural stem cells (NSC) are prone to radiation-induced damage and studies performed in murine models demonstrated that neurogenesis is impaired by radiation doses as low as 2 Gy [12-14]. Because the damage severity is dose-dependent, a reduction of the dose delivered to regions of active neurogenesis could potentially reduce the damage to the brain rescue system and diminish irradiation-induced neurocognitive deficits.

In 2007, Barani et al. published the concept of minimizing the toxicity of WBRT by reducing the radiation dose in regions containing NSC [15]. In that study, only two techniques were compared: IMRT and two-field conformal radiotherapy (CRT) in two clinical settings: cerebral glioma and single brain metastasis [16].

We believe that NSC-protecting techniques are also of special interest in PCI in the absence of overt metastases or primary tumors. Treatment of patients with potential subclinical disease (micrometastases) or even without brain seeding at the time of PCI provides greater opportunity to apply NSC-protecting techniques without jeopardizing tumor control, such as in cases of overt metastases or primary brain tumors. Some of these patients may never experience brain seeding and become long-term survivors. For these patients, the issue of reducing the long-term treatment toxicity is of particular importance. Marsh et al. published a dosimetric study in which helical tomotherapy was used to reduce the dose in regions of active neurogenesis during WBRT [17].

Following the concept of Barani and Marsh, the aim of the present study was to test the feasibility of WBRT with a reduced dose in regions of active neurogenesis comparing helical tomotherapy to dynamic static field IMRT and Rapid Arc as the most advanced technologies utilized in radiotherapy. We report dosimetric studies in which we tested the performance of different IMRT techniques, and present revised treatment plans for the first 10 consecutive patients that were qualified for a phase I clinical study which aim is to assess the risk of brain seeding in the region of dose reduction (NSC) and possibility of protecting neurocognitive functions in these group of patients.

Materials and methods

We used computed tomography (CT) and magnetic resonance imaging (MRI) data of patients with SCLC who received PCI as a part of a combined treatment. Each patient had full diagnostic MRI before treatment, including T1, T2 weighted images, perfusion-weighted images, and diffusion-weighted images. We used T1 3mm axial multiplanar reconstructed (MPR) MRI with gadolinium for treatment planning. CT and MRI data were fused with iPLAN 3.8 (BrainLab, Westchester, IL) using the automatic option. All organs at risk (OAR), including NSC compartments, and the planning target volume (PTV; brain) were contoured using the MRI data. The PTV was defined as the whole brain volume excluding the NSC compartments. This volume is similar to that proposed by Barani et al. [16] and contains regions thought to contain NSC with a 3 to 4-mm margin. The target volume for the reduced dose included a narrow 2-mm external wall strip of the lateral ventricle with a 4-mm margin in the medial and lateral directions (SVZ). This region at the end of temporal horn is joined to the hippocampus (SGZ). Thus, the target was slightly expanded at the region of the SGZ. This part was drawn manually based on the magnetic resonance images. An additional 3-mm margin was added automatically to optimize the IMRT algorithms, which allowed for more efficient reduction of the dose within the NSC compartments. The resulting structure included both lateral ventricles and hippocampi (Figure 1). Fused images and contours were transferred to the treatment planning systems. We used the HiArt 3.1.4.32 DQA Setup and Analysis Planning Station for TomoTherapy planning and Eclipse 8.6.14 (Varian Medical System, Palo Alto, CA) to prepare static field (SF) IMRT using sliding window technique and RapidArc plans using 2 non-coplanar arcs, 181° to 179° CW, 179° to 181° CCW, table +/- 20°. Helical TomoTherapy plans were prepared for a TomoTherapy treatment unit; all other plans were prepared for an LINAC Varian 23EX with Millenium 120 MLC. We used NSC as OAR and we defined NSC+3mm as PTV. Alternative radiotherapy plans were prepared for this research for 10 consecutive patients with Small Cell Lung Cancer after radio- and chemotherapy, which were qualified for phase I clinical study. Study had been accepted by Ethical Committee. All patients had been familiarized with the theoretical assumptions of the research and they signed informed consent.

Alternative radiotherapy plans were prepared for this study for 10 consecutive patients that qualified for PCI. We prepared three different plans for static field IMRT (using a 5, 7, and 9 field sliding window technique), three different plans for Rapid Arc using a two non-coplanar arc technique and different optimization parameters, and two plans for TomoTherapy. The best plans were selected for the dosimetric comparison study by the same physician.

All plans were prepared in an attempt to achieve a homogeneous dose distribution of 30 Gy with 2 Gy per faction (conventional PCI) in brain excluding the NSC regions. Other restrictions were established to protect OAR, such as the lenses, nasal cavity, and optic nerves. The most important restriction was to reduce the radiation dose to 17 to 20 Gy in the NSC compartments.

The plans were revised based on visual inspection of the isodose distribution, and comparison of the mean, modal, minimal, and maximal dose. We used T-Student Test for comparing statistical differences between plans. In case of dynamic techniques with intensity modulation, these parameters were not sufficient to compare plans and to choose the optimal plan. Dose distribution is usually not homogeneous throughout the PTV and various OAR sub-volumes receive different radiation doses. Consequently, a reliable plan comparison requires an analysis of dose volume histograms (DVH). We used the methods published by Gondi et al. [18]

The following treatment planning parameters were used to evaluate the treatment plans: Target Coverage (TC): TC describes the fraction of the target volume (V_T) receiving at least the prescription dose ($V_{T,presc}$) and is defined as TC = V_{Tpresc} / V_T For perfect coverage, TC equals 1.0 [18].

Homogeneity Index (HI): HI quantifies dose homogeneity in the target volumes, as recommended by the International Commission on Radiation Units and Measurements. The HI is defined as the greatest dose delivered to 2% of the target

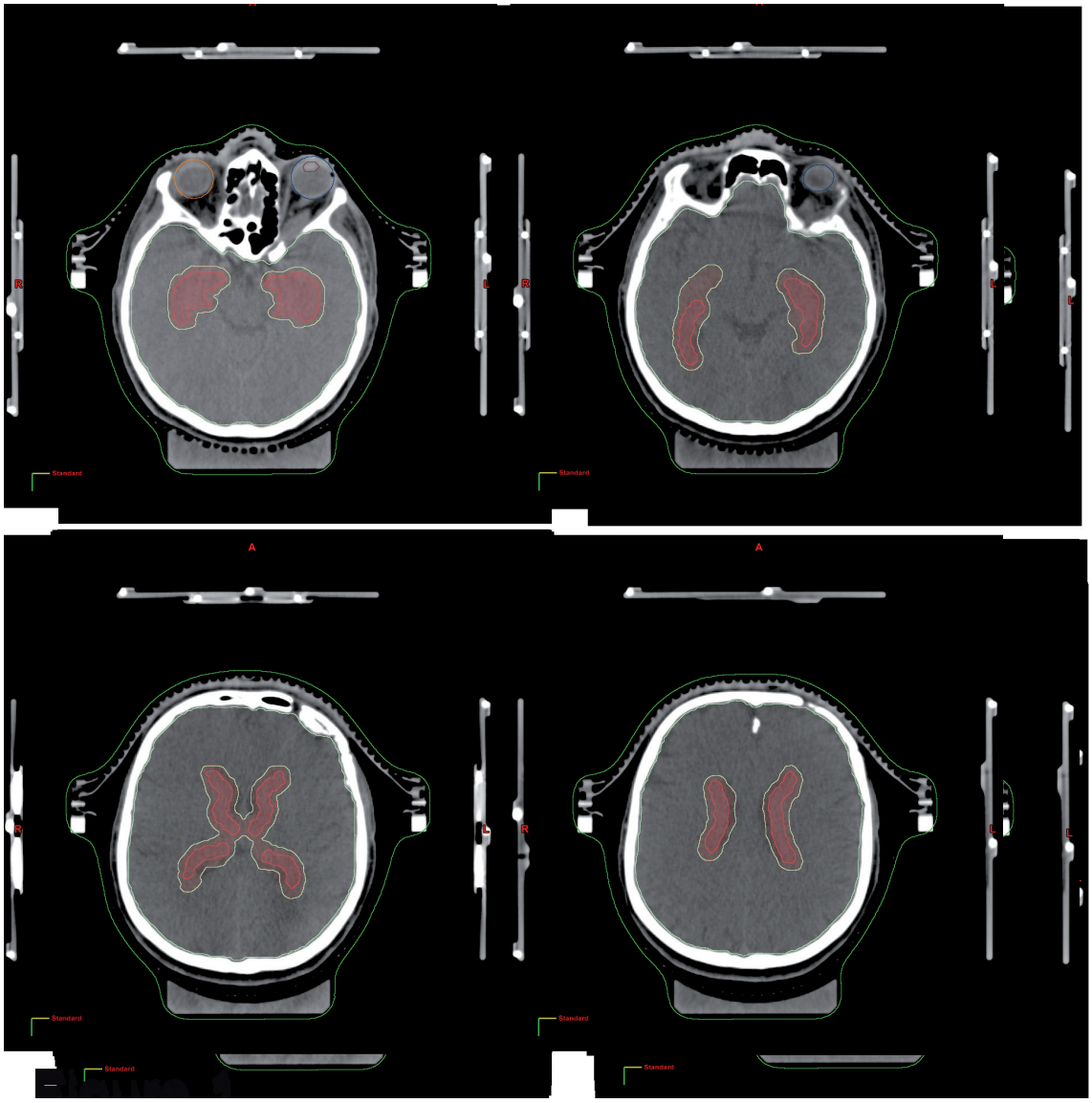

Figure1. The shape of the Neural Stem Cells Region (NSC) for a reduced irradiation dose after transfer of MRI data to CT (test patient). The PTV was defined as the whole brain volume excluding the NSC compartments. This volume contains regions thought to contain neural stem cells with a 4-mm margin. The volume for the reduced dose included a narrow 2-mm external wall strip of the lateral ventricle with a 4-mm margin in the medial and lateral directions (SVZ). This region at the end of temporal horn is joined to the hippocampus (SGZ).

volume (D2%) minus the dose delivered to 98% of the target volume (D98%) divided by the median dose (D_{median}) of the target volume: HI = ($D_{2\%} - D_{98\%}$)/ D_{median} [18]

Smaller values of HI correspond to more homogenous irradiation of the target volume. A value of 0 corresponds to absolute homogeneity of the dose within the target. We used T-Student Test for comparing statistical differences between TC and HI for different irradiation techniques.

Dynamic radiotherapy techniques like IMRT use non-uniform spatial modifications of the intensity of the beams across irradiated fields. Consequently, they require comparisons of measured and calculated dose distributions to assess the accuracy of dose delivery [19]. All IMRT plans were subject to the standard dose verifications procedures used in our institution for verification of the patient treatment plans. The dose verification methods used for the SF IMRT, RapidArc, and TomoTherapy plans are listed in Table I.

To verify the concordance between the calculated and measured dose distribution, we used the Dose Distribution Evaluator based on the gamma function method. The gamma function takes into account the dose difference (DD=3%) and the distance to agreement parameters (DTA=2mm). A gamma

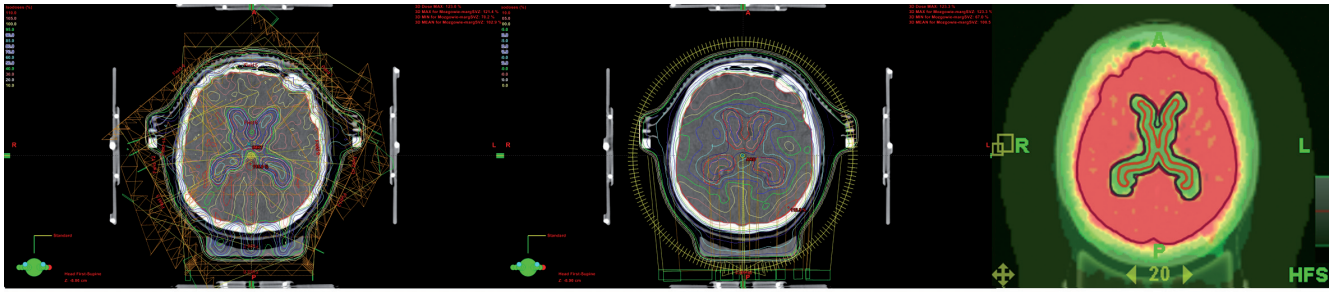

Figure 2. Dose distribution throughout the brain and Neural Stem Cells compartment. (test patient)
The region for a reduced irradiation dose is presented in red colour (RapidArc and IMRT) and in green colour (tomotherapy).
A – Static Field Intensity Modulated Radiotherapy (SF IMRT)
B – Rapid Arc
C – Helical TomoTherapy

function value below 1 indicates acceptable agreement between the two points of the map.

Results

Figure 2 shows the isodose distribution for different irradiation techniques. TomoTherapy and LINAC-based plans have isodoses resembling the shapes of the PTV and NSC regions. The statistics of the calculated radiotherapy plans is shown in Table II. It is difficult to assess the clinical relevance of mean, minimal, and maximal doses in cases of elective treatment with no observable tumor. All techniques enabled a dose reduction of approximately 17-20 Gy in the NCS compartment. Table III shows calculated doses to eyeballs and lenses. Mean doses to eyeballs and lenses were not significantly different between Tomotherapy plans and SF IMRT. Rapid Arc doses to lenses

Table 1. Methods of dose distribution verification according to irradiation technique.

Radiotherapy Technique	*TomoTherapy*	*RapidArc*	*SF IMRT*
Dosimetric method	1) *TomoTherapy Cheese Phantom* with Ionization Chamber – *Standard Imaging A1SL*; 2) Electrometer – *Standard Imaging, Model*: T*omoElectrometer*; 3) film dosimetry: *Kodak EDR2*	1) Phantom with single Ionization Chamber *WELLHOFER* 2) Fluence map analysis: Dosimetric phantom with matrix IBA; Software OmniPro. 3) Fluence map analysis with Electronic Portal Images Dosimetry (EPID)	1) Phantom with single Ionization Chamber *WELLHOFER* 2) Fluence map analysis

Table 2 Statistics from radiotherapy plans of 10 patients qualified for PCI

	Tomotherapy (Mean±SD)	SF IMRT (Mean±SD)	Rapid ARC (Mean±SD)
Min Dose NSC [Gy]	11.9±1.51	14.5±1.41	15.9±1.29
Min Dose NSC + 3mm [Gy]	13.3±1.45	14.4±1.46	16.2±1.11
Min Dose Brain – NSC [Gy]	19.6±1.86	14.7±1.44	16.7±1.77
Max Dose NSC [Gy]	25.0±1.07	29.4±1.72	27.6±2.31
Max Dose NSC + 3mm [Gy]	29.7±0.49	31.2±1.07	30.3±1.93
Max Dose Brain – NSC [Gy]	33.5±0.67	32.9±1.5	34.7±2.36
Mean Dose NSC [Gy]	17.6±0.79	17.6±0.86	19.0±1.53
Mean Dose NSC + 3mm [Gy]	22.1±0.64	19.6±1.16	20.5±2.07
Mean Dose Brain – NSC [Gy]	30.1±0.14	28.8±1.05	28.3±0.89
Median Dose NSC [Gy]	17.6±0.84	17.2±0.89	18.9±1.57
Median Dose NSC + 3mm [Gy]	22.2±0.69	18.9±1.29	20.1±1.86
Median Dose Brain – NSC [Gy]	30.2±0.17	29.6±1.08	29.4±1.0

Table 3 Doses calculated to eyeballs and lenses

		Eyeball left		Eyeball Right		Lens Left		Lens Right	
		Max. Dose	Mean Dose	Max. Dose	Mean Dose	Max. Dose	Mean Dose	Max. Dose	Mean Dose
Tomotherapy	Mean	9.22	4.51	9.37	4.61	3.93	3.06	3.31	2.76
RapidArc	SD	1.66	0.84	1.30	0.89	1.96	1.00	1.73	1.51
	Mean	17.68	9.0	18.86	9.15	6.07	5.13	6.46	5.34
IMRT	SD	3.45	2.32	3.25	2.42	2.07	1.69	2.36	2.01
	Mean	18.57	5.18	17.69	5.26	3.95	3.37	3.81	3.24
	SD	4.70	0.96	3.06	1.03	1.08	1.04	0.85	0.90

Table 4 Target Coverage and Homogeneity Indexes for 10 patients

Patient	Target Coverage			Homogeneity Index		
	HT	RapidArc	IMRT	HT	RapidArc	IMRT
1	0,75	0,7	0,3	0,13	0,4	0,27
2	0,8	0,05	0,25	0,13	0,22	0,38
3	0,8	0,4	0,3	0,13	0,55	0,29
4	0,6	0,55	0,3	0,17	0,45	0,42
5	0,75	0,4	0,4	0,16	0,44	0,44
6	0,8	0,3	0,4	0,16	0,44	0,35
7	0,75	0,39	0,4	0,13	0,41	0,47
8	0,7	0,4	0,3	0,09	0,4	0,39
9	0,8	0,59	0,38	0,16	0,37	0,27
10	0,7	0,62	0,5	0,16	0,42	0,5
Mean	0,745	0,44	0,353	0,142	0,41	0,378
SD	0,06	0,18	0,07	0,02	0,08	0,08

and eyes were statistically significantly higher ($p<0.001$) than doses calculated for helical tomotherapy and SF IMRT but still within acceptable limits.

Table IV shows target coverage and HI for IMRT, Rapid Arc, and ThomoTherapy. There were no statistically significant differences between TC and HI between SF IMRT and Rapid Arc. Both LINAC-based techniques were inferior to TomoTherapy. TC was significantly higher (Student-t test $p<0.0001$) for TomoTherapy than for Rapid Arc and SF IMRT. The homeogeneity of the Thomotherapy plans was significantly better than that for the LINAC-based plans. Figures 3,4,5 present example cumulative dose volume histograms for the test patient. The region of dose reduction (NSC) is a complicated – "croissant" like shape and it is localized in the central volume of PTV (Brain), what may explain the lower efficiency of RapidArc and SF IMRT which are limited by static fields (IMRT) and non-coplanar arcs (RapidArc) in creation of dose distribution. For Helical Tomotherapy the radiation is delivered slice-by-slice. Thus each plane of PTV is treated by software individually, what differs this method from SF IMRT and RapidArc in which the entire tumor volume is irradiated at one time and it is treated as one solid. This results in higher degree of modulation for Tomotherapy plans and better dose homogeneity.

Dosimetric analysis indicated that the measured values were within the allowed tolerance (+/- 5% of the planned dose) in all cases.

Discussion

The brain is the primary site of failure in 15% to 45% of SCLC patients, and in autopsy studies this level increases to 65% [20, 21]. The introduction of PCI has dramatically reduced the incidence of brain metastases by 25% (58.6% vs. 33.3% in 3 years) [22]. This success has been achieved, however, at the cost of a reduced quality of life and impaired cognitive abilities due to WBRT. The influence of WBRT on neurocognitive functions remains under debate, and there continues to be new evidence concerning the damaging effects of chemotherapy on the brain and chemotherapy-induced neurocognitive impairment, often referred to as "chemobrain" [23, 24] . This term, however, suggests that the neurocognitive dysfunction is due solely to the toxic effects of chemotherapy, whereas the disease itself may contribute to the observed impairment, so the term "chemobrain" is imprecise and should not be used [25]. Observations suggesting that chemotherapy has harmful effects are supported by research on neurocognitive abilities in patients after chemotherapy for SCLC showing reduced baseline (as-

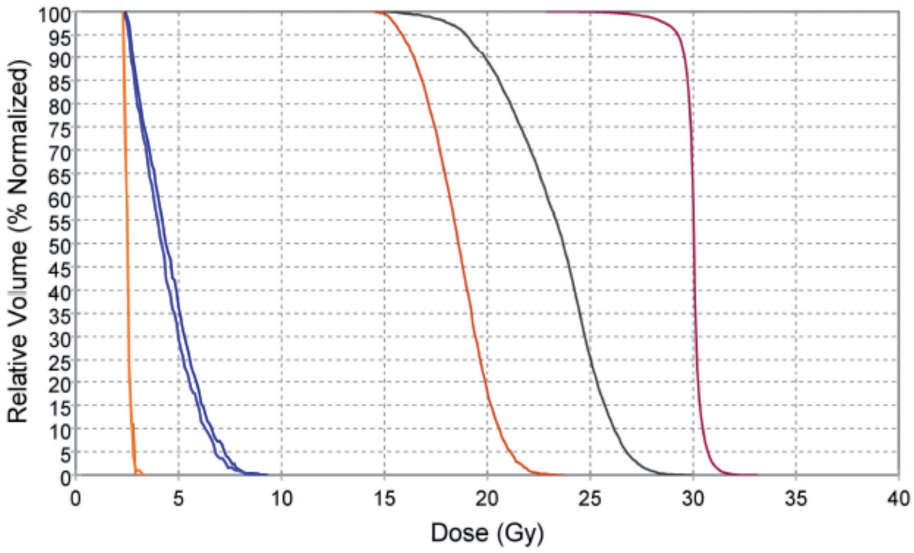

Figure 3. Tomotherapy
Cumulative Dose Volume Histogram – *test patient.*
Brain – Neural Stem Cells Compartment (Dark Red), Neural Stem Cells Compartment + 4mm (Gray), Neural Stem Cells Compartment (Dark Orange), EyeBall Left (Light Blue), EyeBall Right (Dark Blue), Lens Right (Light Orange) Lens Right (Brown).

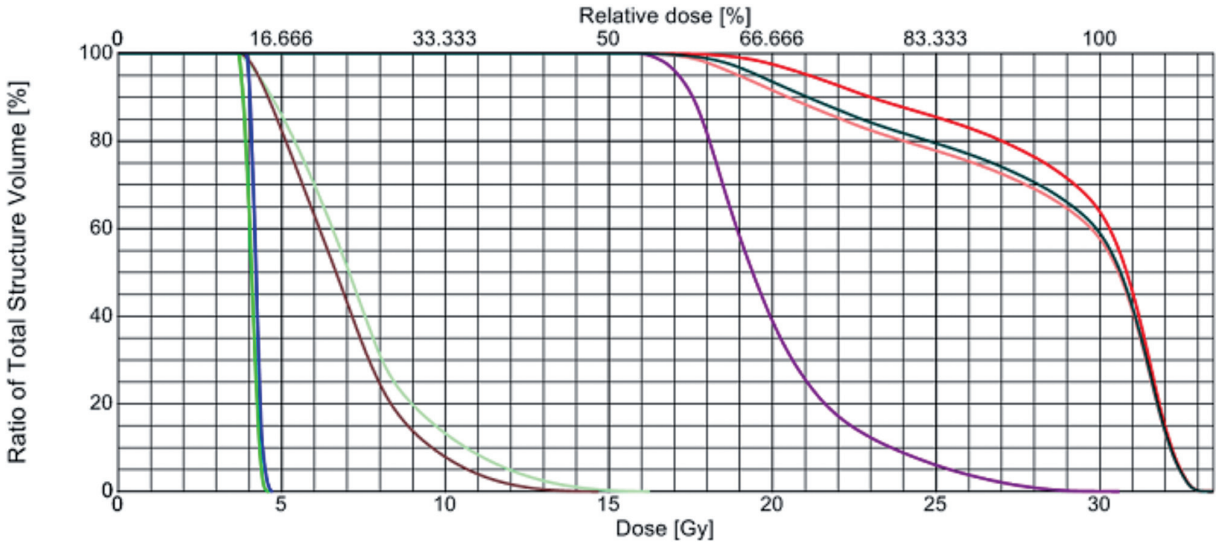

Figure 4. RapidArc
Cumulative Dose Volume Histogram – ***test patient.***
Brain – Neural Stem Cells Compartment with marg (Red), Brain – Neural Stem Cells Compartment (Dark Blue), Brain (Orange), Neural Stem Cells Compartment + 4mm (Purple), EyeBall Right (Brown), EyeBall Left (Light Green), Lens Left (Blue), Lens Right (Dark Green).

sessed prior to radiotherapy) scores in neurocognitive tests in a significant number of examined patients. In most published studies, the numbers range between 15% and 70%, but some authors claim that baseline memory and cognitive abilities are significantly impaired in virtually all chemotherapy-exposed patients [4, 5, 26]. On the other hand, there is increasing evidence of the detrimental effects of WBRT. Previous studies aimed at elucidating the severity of cognitive impairment after WBRT have often lacked adequate baseline assays or sufficient follow-up to evaluate the impairment of cognitive function and memory that could be due solely to radiation effects [24]. More recent studies, however, have demonstrated that the influence of ionizing radiation on cognitive functions in the brain cannot be neglected. Chang et al., in a randomized

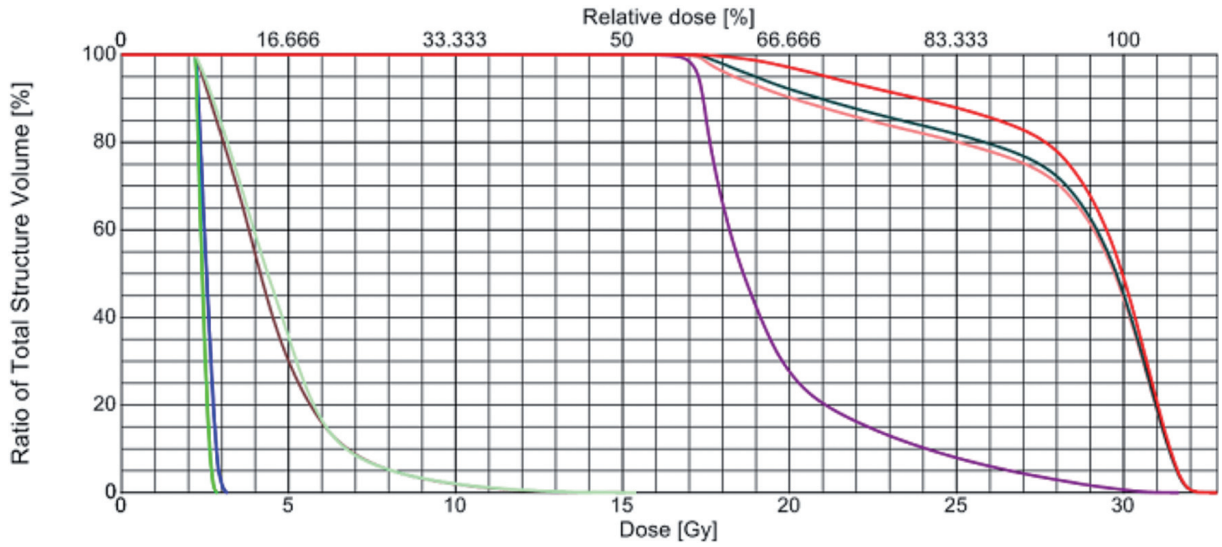

Figure 5. IMRT
Cumulative Dose Volume Histogram – *test patient.*
Brain – Neural Stem Cells Compartment with marg (Red), Brain – Neural Stem Cells Compartment (Dark Blue), Brain (Orange), Neural Stem Cells Compartment + 4mm (Purple), EyeBall Right (Brown), EyeBall Left (Light Green), Lens Left (Blue), Lens Right (Dark Green).

study designed to assess quality of life and memory impairment in patients with 1 to 3 brain metastases, demonstrated that WBRT significantly reduces memory and learning abilities and that this effect cannot be attributed to the development of new brain metastases [6]. Moreover, Li et al. showed that neurocognitive deterioration precedes a decline in the quality of life in patients after WBRT [27]. This evidence along with other studies revealing the damaging effects of WBRT indicate the need for developing a "golden middle" between the curative effects of this treatment and the damage it causes. Marsh et al. proposed that pilot studies employing NCS sparing during PCI would be appropriate [28].

Dynamic, highly-conformal radiotherapy techniques have the potential to reduce the radiation dose to OAR situated in close proximity to the PTV, while maintaining the planned dose distribution in the PTV. Application of IMRT theoretically allows for the delivery of a lower dose to the central region of an irradiated volume than to its periphery, which is the rationale for using it in, for example, radiotherapy of brain tumors surrounding elements of the optic pathway or brainstem. This capability was confirmed in our study. Both TomoTherapy, and LINAC-based IMRT were effective for reducing the radiation dose in the NSC zones with a satisfactory dose distribution in the remaining areas of the brain. Dose homogeneity is better for helical tomotherapy when compared to LINAC-based techniques but the practical and biological implications of better target coverage and better dose homogeneity remain unclear.

The present study has some limitations associated with defining the OAR and the concept of partial protection of the brain. Currently, *in vivo* imaging studies are not able to show the true location of the sites of active neurogenesis or migration paths of pluripotent cells in the living brain. Therefore, only a clinical study to compare cognitive testing results after PCI using the standard technique of homogenous dose distribution and highly conformal irradiation with dose reduction to the NSC compartment might test the hypothesis that limiting the dose to anatomically-defined sites of active neurogenesis will reduce cognitive deficits after PCI. Partial sparing of the brain volume has the potential to deliver a suboptimal radiation dose to some parts of the brain. The theoretical risk of an increased incidence of metastases in the regions receiving a reduced dose cannot be ignored, but the volume of the NSC compartment is relatively low and constitutes only about 7% of the whole brain volume. Moreover, the dose of 15 to 20 Gy delivered to the NSC region is within the range of doses that may abrogate subclinical disease [29].

We are not the first to test the possibility of a dose reduction in regions of active neurogenesis. We followed the work of Barani et al. [16] and reduced the dose to both the SVZ and SGZ regions. This is not, however, the only approach. Excellent papers have been published by a group from the University of Wisconsin in which a reduced dose was applied only to the hippocampal region containing the SGZ [18, 30-33]. Their rationale was based on the assumption that only the SGZ is important for human cognitive function and the SVZ is related to olfactory function. This is certainly the case for rodents, but human cognitive function is far more complex. Most studies describing migration of neuronal progenitors refer to studies

in rodents. Adult human SVZ is now accepted to be an NSC reservoir, and stem cell migration towards the olfactory bulb in humans remains controversial [34, 35]. It has been proposed that the pattern of cell proliferation and migration in the adult human brain is likely tailored to meet the demands of cell replacement that are required to maintain our unique cognitive functions [36]. We do not want to imply that decreasing the dose to only the hippocampal region is inferior to the Barani approach. The authors of this concept have published very valuable dosimetric studies and important studies regarding the spatial distribution of metastases in brain. Metastases of different origins and histology, including SCLC, are located mainly in the peripheral regions of the brain hemispheres and in the cerebellum [33]. The Radiation Therapy Oncology Group has launched a phase II trial, RTOG 0933, to compare IMRT WBRT that avoids the hippocampal region to conventional techniques. RTOG 0933 is a phase II clinical trial that aims to test the hypothesis that avoiding the hippocampus during WBRT (HA-WBRT) in patients with brain metastases may delay or reduce the onset, frequency, or severity of neurocognitive function decline, without compromising intracranial disease control [33]. Avoiding the hippocampal region is perhaps the only solution in patients with brain metastases, but human cognitive function is complex and involves more than just the hippocampal region. Other important brain structures, such as the striatum and amygdala, are also important for learning [37]. Our approach is to reduce the irradiation dose in all regions of active neurogenesis in the brain, including the SVZ. The same concept was proposed by Marsh et al., in which they used an approach similar to ours, reducing the dose to 11 to 12 Gy in the NSC region [17].

To test the safety of the proposed treatment, we have begun a phase I study. Data shown in current study are taken from the first 10 patients irradiated in this trial. Currently, we have irradiated 23 patients who are being followed by MRI at 3, 6, 12, and 18 months after IMRT PCI. The endpoint will be the number of brain metastases, especially in the regions that received a reduced irradiation dose. We have not observed the increased risk of brain seeding in in the region of reduced dose so far. All patients are tested using specific cognitive tests conducted by qualified clinical psychologists. We hope that psychologic testing prepared specially for the Polish population will facilitate the detection of differences in future planned randomized trials. We are using LINAC-based IMRT in our trial. After completion of the phase I study, we would like to cooperate with other institutions that have access to TomoTherapy.

In conclusion, protecting the regions of active neurogenesis in the brain during irradiation is technically feasible. Whether reducing the dose by approximately 30% to 50% is sufficient to reduce treatment toxicity, however, is a question that can only be addressed with prospective clinical trials. It is possible to reduce the dose even further, but this may result in a significant underdosage of the PTV. This issue must also be addressed in a randomized study aimed at detecting the benefit with regard to neurocognitive function after WBRT and the incidence of metastases with conventional and NSC-sparing arms, perhaps with two dose limits for the NSC compartment.

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