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Hippocampus, spare or not to spare? Normal Tissue Complication Probability considerations.

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Abstract

Purpose: The purpose of the study was to use the Lyman-Kutcher-Burman model to calculate and compare neurocognitive function (NCF) impairment in the two types of dose distributions in Volumetric Arc Whole-brain radiotherapy (VMAT WBRT).

Methods: The total dose prescribed to the Planning Target Volume (PTV) was 25 Gy and 30 Gy in 10 fractions. During the optimization of the Volumetric Arc Therapy Hippocampal-Avoidant WBRT (VMAT HA-WBRT) plan, the left and right hippocampus the $D_{100} < 9$ Gy, and the point dose $D_{max} < 16$ Gy were minimalized based on RTOG0933 criteria. As an alternative 59 plans for non-hippocampus sparing, 25 Gy, and 59 plans for 30 Gy VMAT WBRT plans were prepared. To calculate the probability of NCF impairment, the Lyman-Kutcher-Burman (LKB) normal tissue complication probability model was used.

Results: The probability of NCF impairment in the HA-WBRT VMAT was equal to 38%, and it was significantly lower compared to 90% in the 25 Gy WBRT VMAT and 97% in the 30 Gy WBRT VMAT ($p < 0.05$).

Conclusions: The probability of NCF impairment was 51-59 percentage points lower in VMAT HA-WBRT compared to VMAT WBRT plans. To achieve a 5% probability of NCF impairment, the D_{40} value should be reduced to a value of approximately 1 Gy. However, due to the complicated nature and types of NFC impairment, further analysis and strategies are needed to optimize dose distribution.

Keywords: hippocampus; NTCP; NCF impairment.

Introduction

Whole-brain irradiation exists in two variants determined by the patient's diagnosis. Whole-brain radiotherapy (WBRT) combined with a temozolomide, motexafin, or other radiosensitizer remains a treatment method in the incidence of multiple brain metastases (BM) or as prophylactic cranial irradiation (PCI) for small cell lung carcinoma (SCLC) patients.[1]

Due to early neurological complications such as cerebral edema resulting in headaches, somnolence, and vomiting, and late complications such as neurocognitive function (NCF) impairment resulting in severe dementia and memory loss as a result of the hippocampus irradiation,[2] WBRT irradiations are more often replaced by stereotactic radiosurgery (SRS) or stereotactic radiation therapy (SRT) in the case of single or multiple metastatic lesions.[3]

Static opposing beam, IMRT, and VMAT WBRT techniques in many studies have shown decreased cognitive function when the entire brain is irradiated.[4] A decrease in NCF is associated with radiation-induced damage of the hippocampus neural stem cell compartment.[3] Due to the low risk of metastases in the hippocampal area, it is possible to use hippocampal-sparing techniques.[5] Volumetric Arc Therapy Hippocampal-Avoidant WBRT (VMAT HA-WBRT) reduces neurocognitive toxicity compared to WBRT techniques.[6] Results of the prospective phase II RTOG0933 study showed no decline in the Hopkins Verbal Learning Test-Revised 4 (HVLT-R) test at two and four months compared to the WBRT patient group.[7] The HVLT-R is a list-based learning test consisting of 12 nouns, that assesses the number of words remembered and repeated by the patient before and after radiotherapy, that is able to evaluate memory dysfunction.[7]

From a clinical perspective, it is important to estimate radiotherapy side effects. Therefore, the use of radiobiological models that calculate normal tissue complications probability (NTCP) based on the physical dose distribution becomes essential.[8] Lyman Kutcher Burman Model (LKB)[9], and Relative Seriality (RS) [10] are biological dose metrics used to calculate the

Authors' contribution: A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

specific organ endpoint based on the dose volume histogram (DVH) or voxel of a structure.[8] Despite some simplifications, phenomenological radiobiological models are being used to assess the estimation of a specific organ complication or to compare treatment plans in depth for patient eligibility for photon beam therapy or proton therapy.[11]

The LKB model-based study aimed to calculate and compare the probability of NCF impairment in the two types of dose distributions. In this study, NFC impairment was estimated for the hippocampal-sparing VMAT HA-WBRT technique for total doses of 25 Gy and 30 Gy. The VMAT HA-WBRT technique was compared with the 25 Gy and 30 Gy non-hippocampal sparing VMAT WBRT technique in terms of NCF impairment.

Material and Methods

Two techniques were compared: the VMAT hippocampal-sparing and the hippocampus non-sparing techniques, regardless of clinical qualification. Patients were positioned in the supine position, and the head was stabilized with a thermoplastic mask. Computed tomography (CT) scans for planning were made in a supine position with a 3 mm slice thickness, using a Siemens Somaton CT scanner. The total dose of 25 Gy and 30 Gy was prescribed as the mean dose to the PTV and delivered in 10 fractions. Hippocampi were contoured on rigid-fusion MRI images with CT for treatment planning. A Planning Risk Volume (PRV) structure was created by adding a 5 mm isotropic margin to the hippocampi. VMAT treatment plans were prepared in *Varian's Eclipse™ treatment* planning system version 16.1. Dose distribution was calculated using an Anisotropic Analytical Algorithm (AAA) version 16.1. VMAT HA-WBRT hippocampal-sparing clinical plans were prepared in noncoplanar 6 MV beam geometry using four superiorly and inferiorly split arcs and one table rotation partial arc (**Figure 1**). For the non-sparing technique, the same noncooplanar beam geometry was used. During the optimization of the VMAT HA-WBRT clinical plans, the RTOG 0933 criteria were used as guidelines.[7] In the the left and right hippocampus the 100% volume i.e. $D_{100} < 9$ Gy, and the point dose $D_{max} < 16$ Gy were optimized. VMAT HA-WBRT plans were compared with non-hippocampus-sparing VMAT WBRT plans. PTV volumes $D_{98} \geq$ 95% of the prescribed dose and $D_2 \leq 107\%$ of the prescribed dose were optimized parameters.

The left and right hippocampus dose-volume statistics, mean dose, D_X the dose to X% of the hippocampus volume, and point maximum dose were analyzed. Physical dose distribution statistics: D_{mean}, D_{100}, D_{50}, D_{40}, D_{20}, D_{10}, D_2, D_1, and D_{max} were converted into 2 Gy per fraction equivalent dose (EQD_2) assuming α/β ratio of 2 Gy.[12]

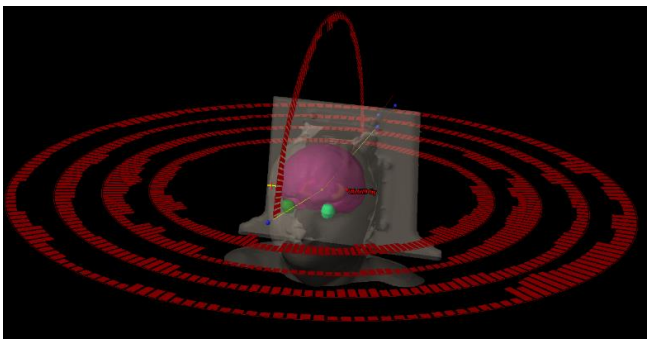

Figure 1a. VMAT HA-WBRT noncoplanar beam geometry.

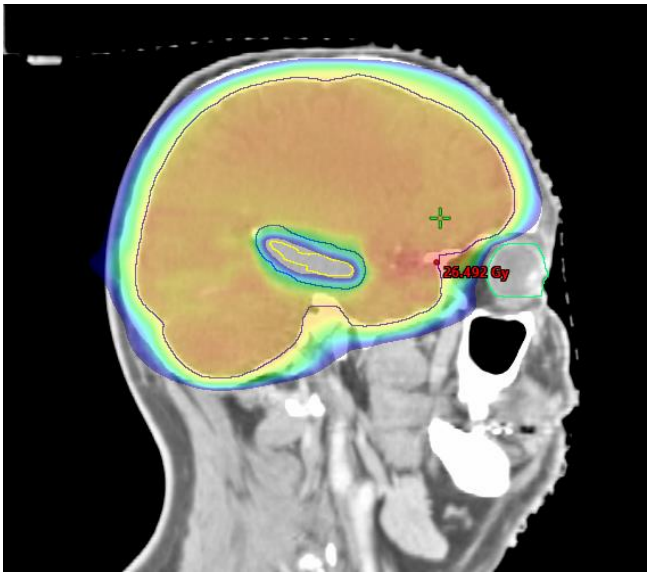

Figure 1b. Sagital slice with 14 Gy dose distribution in the VMAT HA-WBRT.

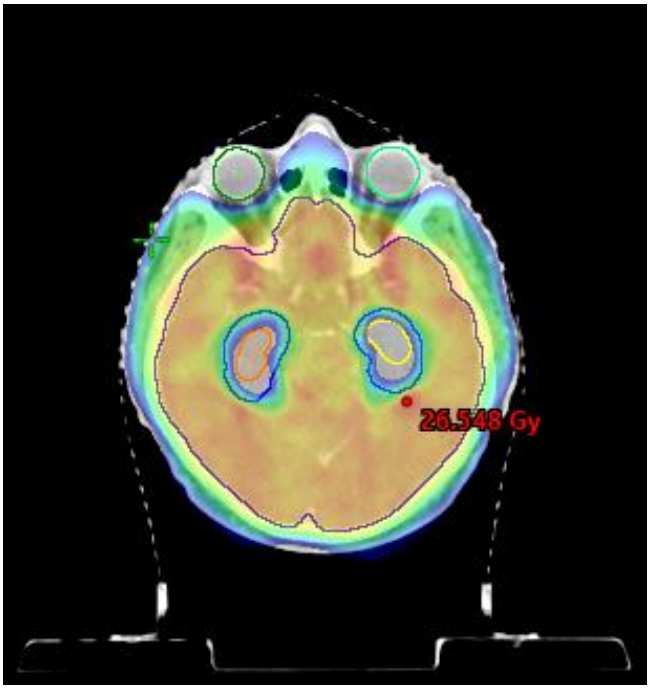

Figure 1c. Horizontal slice with 14 Gy dose distribution in the VMAT HA-WBRT.

The NCF impairment was defined as impairment in Wechsler Memory Scale-III Word Lists (WMS-WL) Delayed Recall at 18 months. WMS-WL is a subtest of the Wechsler Memory Scale III that evaluates verbal memory ability based on free recall of lists of words.[13] To calculate the probability of NCF impairment, based on hippocampus DVH, the Lyman-Kutcher-Burman normal tissue complication probability model was used:[8]

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{\frac{x^2}{2}}\,dx\ ,\ t = \frac{D_{eff}-TD_{50}}{m\cdot TD_{50}} \qquad \text{Eq. 1}$$

D_{eff} (EQD_2 D_{40}) is the dose that, if delivered uniformly to the whole volume, will lead to the same NTCP as a non-uniform dose distribution, TD_{50} is the uniform dose delivered to the whole organ that results in a 50% risk of complications, *m* is a measure of the slope of the sigmoidal curve.

To calculate NCF impairment, the parameters used in the LKB model were TD_{50} = 14.88 Gy, m = 0.54.[12] As an effective dose D_{eff} in **Equation 1**, the D_{40} EQD_2 of the hippocampus was used.

VMAT HA-WBRT and VMAT WBRT plans were compared in terms of NCF impairment. Statistical analysis of the data and plots was performed in the Python programming language using the Numpy and Pandas library. To compare the VMAT HA-WBRT and the VMAT WBRT plans the Wilcoxon signed-rank test was used. A p-value $p < 0.05$ was considered statistically significant.

The Kolmogorov-Smirnov test was used to test the normality distribution of the data. The Kolmogorov-Smirnov test yielded a $p < 0.05$ value. Due to the lack of normal distribution of the data the correlation between NTCP and dose distribution statistics was expressed in Spearman's correlation coefficient (r_S). Qualitatively, the interpretation of the Spearman coefficients is as follows: $r_S = 0 \leq 0.19$ very weak correlation, $r_S = 0.20 \leq 0.39$ weak correlation, $r_S = 0.40 \leq 0.59$ moderate correlation, $r_S = 0.60 \leq 0.79$ strong correlation, $r_S = 0.80 \leq 1$ very strong correlation, $r_S = 1$ monotonic correlation.

Results

Table 1 summarizes the hippocampal physical dose distribution parameters and the hippocampal EQD_2 dose distribution parameters in the VMAT HA-WBRT technique. The mean value of D_{40} was 12.6 Gy for the left hippocampus and 12.5 Gy for the right hippocampus (p = 0.76). The mean value of the D_{40} EQD_2 parameter was 10.3 Gy for the left hippocampus and 10.2 Gy for the right hippocampus (p = 0.75). In the 25 Gy VMAT WBRT plans, the mean D_{40} EQD_2 value was 28.3 Gy (0.5 Gy) for the left hippocampus and 28.4 Gy (0.4 Gy) for the right hippocampus. In the 30 Gy VMAT WBRT plans, the mean EQD_2 D_{40} value was 37.8 Gy (1.3 Gy) for the left hippocampus and the right hippocampus.

Table 2 presents the results of calculated NTCP values in the VMAT HA-WBRT and VMAT WBRT techniques. The mean value of NCF impairment in the VMAT HA - WBRT plans was 38.7% in the left and 38.4% in the right hippocampus (p = 0.5). The probability of NCF impairment was 89.9% and 90% in the 25 Gy VMAT WBRT and 97.1% in the 30 Gy VMAT WBRT.

Table 1. Mean values and standard deviation of dose distribution statistics in the group of 59 VMAT HA-WBRT plans.

	Left hippocampus physical dose	Right hippocampus physical dose	p-value	Left hippocampus EQD_2	Right hippocampus EQD_2	p-value
D_{mean}	12.0 Gy (0.8 Gy)	11.9 Gy (0.7 Gy)	0.65	9.6 Gy (0.4 Gy)	9.5 Gy (0.4 Gy)	0.64
D_{100}	8.5 Gy (0.7 Gy)	8.5 Gy (0.6 Gy)	0.88	6.1 Gy (0.3 Gy)	6.0 Gy (0.3 Gy)	0.87
D_{80}	10.7 Gy (0.9 Gy)	10.6 Gy (0.8 Gy)	0.64	8.2Gy (0.6 Gy)	8.1 Gy (0.4 Gy)	0.63
D_{50}	12.2 Gy (1.0 Gy)	12.2 Gy (0.9Gy)	0.77	9.8 Gy (0.6 Gy)	9.8 Gy (0.5 Gy)	0.75
D_{40}	12.6 Gy (1.0 Gy)	12.5 Gy (0.9 Gy)	0.76	10.3 Gy (0.6 Gy)	10.2 Gy (0.5 Gy)	0.75
D_{20}	13.3 Gy (0.9 Gy)	13.2 Gy (0.9 Gy)	0.66	11.0 Gy (0.5 Gy)	11.0 Gy (0.5 Gy)	0.65
D_{10}	13.7 Gy (0.9 Gy)	13.6 Gy (0.9 Gy)	0.59	11.5 Gy (0.5 Gy)	11.4 Gy (0.4 Gy)	0.58
D_2	14.2 Gy (0.8 Gy)	14.2 Gy (0.8 Gy)	0.84	12.1 Gy (0.4 Gy)	12.1 Gy (0.4 Gy)	0.84
D_1	14.4 Gy (0.8 Gy)	14.4 Gy (0.8 Gy)	0.92	12.3 Gy (0.4 Gy)	12.3 Gy (0.4 Gy)	0.92
D_{max}	15.2 Gy (0.9 Gy)	15.3 Gy (0.9 Gy)	0.79	13.4 Gy (0.5 Gy)	13.5 Gy (0.5 Gy)	0.79

Abbreviation: D_{mean} - mean dose, D_X - dose to X% of the hippocampus volume, D_{max} - maximum point dose, EQD_2- 2 Gy per fraction equivalent dose, α/β ratio =2 Gy.

Table 2. Mean values and standard deviation of the probability of NCF impairment in the VMAT HA-WBRT and VMAT WBRT plans.

	VMAT HA-WBRT	VMAT WBRT 25 Gy	VMAT WBRT 30 Gy	p-value
probability of left hippocampus NCF impairment	38.7% (5.1%)	89.9% (1.0%)	97.1% (1.0%)	<0.05
probability of right hippocampus NCF impairment	38.4% (4.8%)	90.0% (1.0%)	97.1% (1.0%)	<0.05

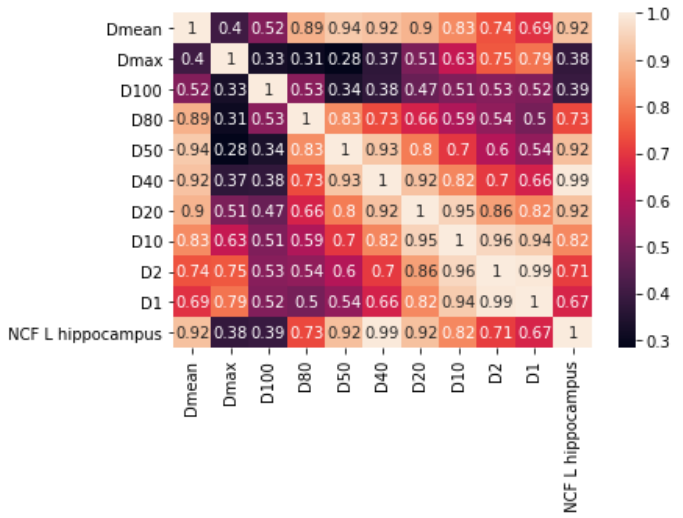

Figure 2a. Heat matrix, a correlation between NCF impairment and physical dose distribution parameters for the left hippocampus.

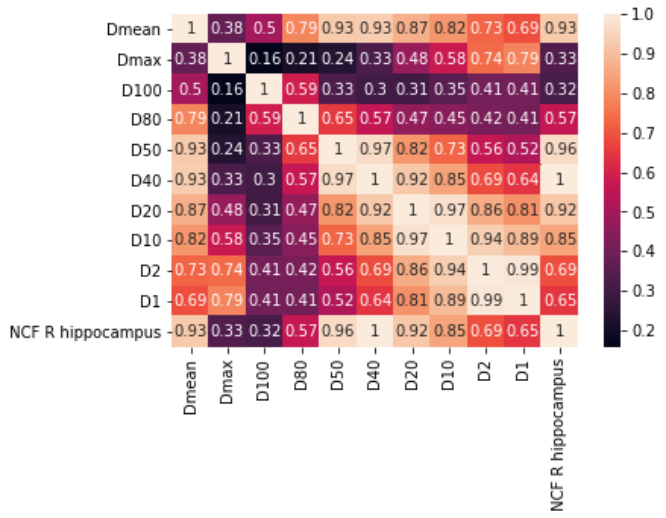

Figure 2b. Heat matrix, a correlation between NCF impairment and physical dose distribution parameters for the right hippocampus.

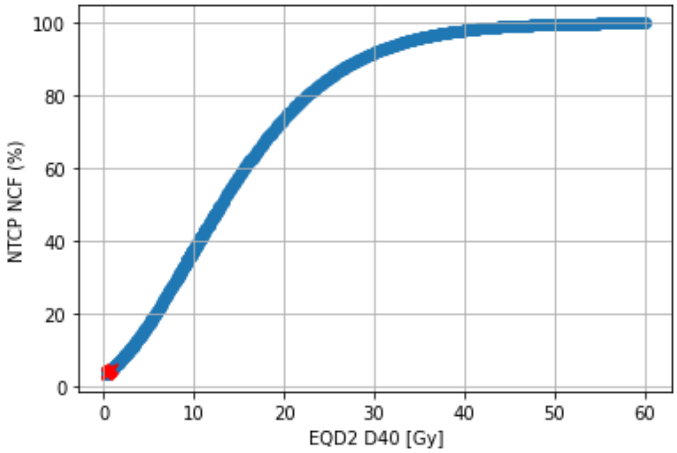

Figure 3a. The relationship between EQD_2 D_{40} and hippocampus NCF impairment.

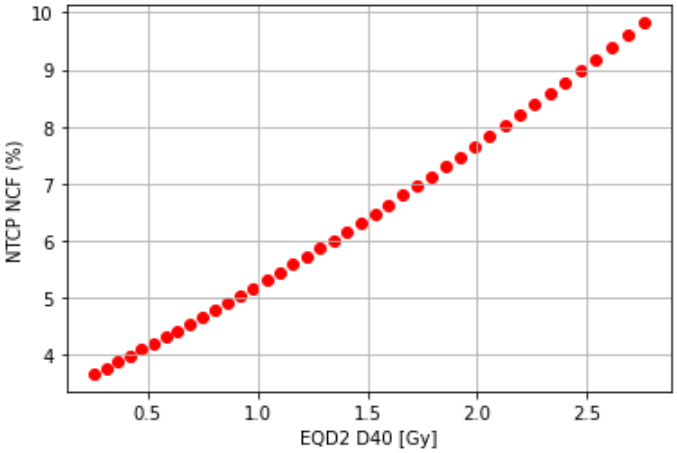

Figure 3b. The relationship between EQD_2 D_{40} and hippocampus NCF impairment. Highlighted red area, NCF impairment 4% - 10% range.

The Spearman correlation coefficient heat matrices are presented in **Figure 2**. Correlation between the probability of NCF impairment and physical dose distribution parameters for the left (r_{sL}) and right hippocampus (r_{sR}) were: D_{mean} (r_{sL} = 0.92, r_{sR} = 0.93), D_{100} (r_{sL} = 0.39, r_{sR} = 0.32), D_{80} (r_{sL} = 0.73, r_{sR} = 0.57), D_{50} (r_{sL} = 0.92, r_{sR} = 0.96), D_{40} (r_{sL} = 0.99, r_{sR} = 1.0), D_{20} (r_{sL} = 0.92, r_{sR} = 0.92), D_{10} (r_{sL} = 0.82, r_{sR} = 0.85), D_1 (r_{sL} = 0.67, r_{sR} = 0.65), D_{max} (r_{sL} = 0.38, r_{sR} = 0.33).

Figure 3 presents the NCF impairment NTCP sigmoid curve as a function of the D_{40} EQD_2. The blue sigmoid curve simulates the NCF impairment relationship from 0.3 Gy to 60 Gy. NCF impairment curve was generated using TD_{50} = 14.88 Gy, m = 0.54 parameters.[12] The red colour in the right-hand graph of **Figure 3** represents the 4% - 10% NTCP range, representing the more accurate values in **Figure 3a**. The range of low NTCP values corresponds to low EQD_2 D_{40} values.

Discussion

The hippocampus is a paired structure located in the temporal lobe, constituting part of the limbic system. The function of the hippocampus is to cooperate in consolidating and retrieving information, learning, and formation of new memories.[14] The nature of NCF dysfunction is complex and has many types of clinical manifestations. Retrospective clinical studies indicate NCF decline resulting from hippocampi radiation injury, unilateral or bilateral responsible for neurocognitive function impairment such as memory and learning.[15] In the group of pediatric patients irradiated due to a brain tumor, 5 years after radiotherapy, longitudinal IQ decline was found if the mean dose in the temporal lobe was 45 Gy or more.[16] A similar correlation between temporal lobe means dose and decline in short-term memory was reported by Hsiao.[17] Results of the RTOG0933 study with hippocampal sparing in brain metastases patients suggest a reduction of cognitive dysfunction to 7% compared to

30% in the WBRT control group, evaluated in the Hopkins Verbal Learning Test.[7] There are a negligible number of articles available that provide parameters to calculate NTCP using the LKB model. In the Gondi paper[12] the probability of NCF impairment was defined as impairment in Wechsler Memory Scale-III Word Lists (WMS-WL) Delayed Recall at 18 months was correlated with EQD_2 D_{40} of the hippocampus, TD_{50} = 14.88 Gy, m = 0.54. In the E. Kendall paper hippocampus damage is associated with maximum dose, TD_{50} = 48 Gy, m = 0.15, and n = 0.25.[6]

In this paper, the LKB model was used to compare probability NCF impairment between hippocampal-sparing VMAT HA-WBRT vs. non-hippocampal-sparing WBRT VMAT plans. Based on the Gondi parameters[12], the calculated probability of NCF impairment was significantly decreased in VMAT HA-WBRT and was approximately 38.% compared to 90.% in 25 Gy WBRT VMAT and 97.1% in 30 Gy WBRT VMAT ($p < 0.05$). No statistical differences were shown between the NCF impairment of the right and left hippocampus in the VMAT HA-WBRT ($p = 0.5$). The cognitive dysfunction value obtained in our study differs from the results obtained in the RTOG0933 study assessed using the Hopkins Verbal Learning Test, 7% vs. 30% in the WBRT group. The difference may result from the use of different tests to assess cognitive function in the RTOG0933 study and Gondi's paper.[12] Unfortunately, the literature lacks parameters for estimating NTCP using the LKB model for data from the RTOG0933 study.

Effective dose D_{40} used in the LKB equation is extracted from hippocampus DVH, which reduces a 3D dose distribution into a 2D graph, losing organ spatial information.[18] To convert the fraction dose to EQD2, different values of α/β ratio are used with no clear α/β ratio consensus. For normal brain tissue, the α/β ratio of 2.9 Gy is used.[19] For the hippocampus, if the neural stem cells are considered, an α/β ratio of 10 Gy is used[20] and if the hippocampus is considered, the α/β ratio value is in the range of 2 Gy - 3 Gy.[1] In this paper, we have assumed α/β ratio of 2 Gy.

During the optimization of the VMAT HA-WBRT plan, the left and right hippocamp, the $D_{100} < 9$ Gy, and the point dose $D_{max} < 16$ Gy were minimalized based on RTOG 0933 criteria.[7] A weak correlation between physical dose distribution parameters and NTCP was the fund with D_{100} ($r_{sL} = 0.39$, $r_{sR} = 0.32$) and D_{max} ($r_{sL} = 0.38$, $r_{sR} = 0.33$). A very strong correlation was shown for, D_{50} ($r_{sL} = 0.92$, $r_{sR} = 0.96$), and D_{20} ($r_{sL} = 0.92$, $r_{sR} = 0.92$). NCF NTCP is very strongly correlated with hippocampal D_{40} ($r_{sL} = 0.99$, $r_{sR} = 1.0$) and very strongly correlated with the hippocampal mean dose ($r_{sL} = 0.92$, $r_{sR} = 0.93$). Dose distribution parameters D_{40} is very strongly correlated with D_{50} ($r_{sL} = 0.93$, $r_{sR} = 0.97$), and the mean dose ($r_{sL} = 0.92$, $r_{sR} = 0.93$), so limiting the mean hippocampal physical dose may be an easily optimized parameter.

Neurocognitive function impairment in Gondi paper[12] is associated with a low value of TD_{50} = 14.88 Gy in contrast to other brain structure endpoints such as brainstem necrosis TD_{50} = 65 Gy[22] or optic nerve neuropathy TD_{50} = 52 Gy[22]. Preclinical evidence suggests that low doses of level 2 Gy result in neuronal stem cell apoptosis, reducing survival fraction by over 50%, and reducing the fraction of cells undergoing neuronal differentiation.[23] Neurocognitive dysfunction manifests at a level of dose below 10 Gy.[23] New hippocampal granule cells are differentiated from self-renewal mitotically active neural stem cells (NSCs) located in the subgranular zone of the dentate gyrus from where they migrate into the granular cell layer of the hippocampus.[24] The subgranular zone of the hippocampus is the center responsible for learning and memory.[25] Apoptosis during irradiation of the precursor cells results in a significant reduction in hippocampal neurogenesis during the generating of new differentiated cells.[14] In our paper, based on the Gondi parameters,[12] the NCF impairment NTCP curve was reconstructed from a dose range from 0.3 Gy arbitrary to a dose of 60 Gy, which is the standard total dose in glioblastoma radiotherapy.[26] To obtain an NCF impairment at a level of 5%, the value of the D_{40} should be below 1 Gy. Reducing the D_{40} to 1 Gy, representing 4% of the 25 Gy prescribed dose and 3.3% of the 30 Gy dose, may adversely affect the dose distribution in the PTV volume.

The use of radiobiological models is always burdened with errors due to estimated parameters in the model and a limited number of clinical data. However, radiobiological model can complement the physical dose distribution, representing dose-volume dependent endpoints enabling comparison of treatment plans.

Conclusions

The probability of NCF impairment was 51-59 percentage points lower in VMAT HA-WBRT compared to VMAT WBRT plans. To achieve a 5% probability of NCF impairment, the EQD_2 D_{40} value should be lowered to about 1 Gy. However, due to the complicated nature and types of NFC impairment further analysis and strategies of dose distribution optimization are required.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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