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Comparison of conventional and hippocampus-sparing radiotherapy in nasopharyngeal carcinoma: In silico study and systematic review

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ABSTRACT

Background and purpose: Radiation-induced damage to the hippocampi can cause cognitive decline. International recommendations for nasopharyngeal cancer (NPC) radiotherapy (RT) lack specific guidelines for protecting the hippocampi. Our study evaluates if hippocampi-sparing (HS) RT in NPC ensures target coverage and meets recommended dose limits for other at-risk organs.

Materials and methods: In a systematic literature review, we compared hippocampal $D_{40\%}$ in conventional and HS RT plans. In an in silico dosimetric study, conventional and HS-VMAT plans were created for each patient, following international recommendations for OAR delineation, dose prioritization and acceptance criteria. We assessed the impact on neurocognitive function using a previously published normal tissue complication probability (NTCP) model.

Results: In four previous studies (n = 79), researchers reduced $D_{40\%}$ hippocampal radiation doses in HS plans compared to conventional RT on average from 24.9 Gy to 12.6 Gy.

Among 12 NPC patients included in this in silico study, statistically significant differences between HS and conventional VMAT plans were observed in hippocampal EQD_2 D_{max} (23.8 vs. 46.4 Gy), D_{min} (3.8 vs. 4.6 Gy), D_{mean} (8.1 vs. 15.1 Gy), and $D_{40\%}$ (8.3 vs. 15.8 Gy). PTV coverage and OAR doses were similar, with less homogeneous PTV coverage in HS plans ($p = 0.038$). This translated to a lower probability of memory decline in HS plans (interquartile range 15.8–29.6 %) compared to conventional plans (33.8–81.1 %) based on the NTCP model ($p = 0.002$).

Conclusion: Sparing the hippocampus in NPC RT is safe and feasible. Given the life expectancy of many NPC patients, their cognitive well-being must be paramount in radiotherapy planning.

Introduction

Definitive chemoradiotherapy (CRT) is widely recognized as the primary treatment modality for locally advanced NPC [1,2]. Although advanced radiotherapy (RT) techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), are commonly employed in NPC patients, the hippocampi are frequently exposed to significant radiation doses due to their close proximity to the target volumes [3–5].

To our knowledge, the longest follow-up analysis of post-IMRT quality of life in nasopharyngeal cancer patients revealed an initial decline, which subsequently improves after 6 years but worsens in cognitive and NPC-specific domains after 10 years [6]. Several preclinical and clinical studies have reported an association between radiation-induced damage to the hippocampi and subsequent neurocognitive decline following treatment [7–13]. Some smaller studies investigating hippocampus-sparing (HS) RT techniques in NPC patients have indicated that HS does not compromise target volume coverage or adherence to dose constraints for other organs at risk (OARs) [14–18]. However, the latest international recommendations for RT in NPC do not provide guidelines for delineating and restricting dose to the hippocampi [19].

In this context, our study aimed to assess whether HS-VMAT for locally advanced NPC achieves adequate target volume coverage while

Abbreviations: HS, hippocampal-sparing; NPC, nasopharyngeal cancer; VMAT, volumetric modulated arc therapy; NTCP, normal tissue complication probability.

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adhering to the recommended dose constraints for other OARs, as outlined in the international guidelines [19]. For this purpose, we also performed a systematic review of the literature for reports comparing hippocampal $D_{40\%}$ between conventional and HS radiotherapy plans and a dosimetric analysis in our group of patients with nasopharyngeal carcinoma. Moreover, we sought to determine the potential of HS-VMAT in mitigating cognitive decline in these patients, utilizing a previously proposed normal tissue complication probability (NTCP) model [10].

Materials and methods

Literature review

For the literature review an electronic search was performed and cross-checked by the authors (MP and GP) in August 2023 to identify previously published results comparing hippocampal $D_{40\%}$ between conventional and HS radiotherapy plans in three databases: PubMed, Embase, and Scopus. The following terms were used: ("nasopharynx" OR "nasopharyngeal" OR "epipharynx" OR "epipharyngeal") AND ("hippocampus" OR "hippocampal" OR "hippocampi").

Patient selection and RT simulation

Patients were identified from the National Cancer Registry of Slovenia database. Only patients with nasopharyngeal carcinoma (NPC) who received VMAT treatment at the Institute of Oncology Ljubljana, Slovenia, between June 2017 and December 2021, and had cT3-4 stage NPC, were included in this study. Additionally, patients needed to have undergone simulation CT scans (with a slice thickness of 2–3 mm) with intravenous contrast, as well as MRI scans with T1 and T2 sequences (with a slice thickness of 1.7–2.9 mm), performed within a span of less than 1 month. This study was approved by the Institute of Oncology Ljubljana Research Ethics Committee (number ERIDNPVO-0037/2022).

Target and OAR definition

All patients underwent standard treatment preparation procedures using 5-point thermoplastic head masks for immobilization. CT-MR scan fusions were used for contouring. Original target volumes delineations were not changed for the purpose of this study. OARs delineations were reviewed by two RT oncologists and re-contoured according to the latest international recommendations where necessary [20]. Hippocampi were contoured as a single organ according to the hippocampal contouring atlas from the RTOG 0933 study [11].

Treatment planning

One conventional (without HS) VMAT and one HS-VMAT plan with simultaneously integrated boost were created for each patient. In HS plans, the focus was on trying to reach the desired dosimetric constraints for the hippocampi without exceeding the dose constraints and recommendations for all other parameters with higher priority as in conventional plans. Dosimetric restrictions used for the hippocampi were EQD_2 equivalents ($\alpha/\beta = 2$ Gy) from the NRG CC001 study protocol: $D_{100\%} \leq 11.2$ Gy (D_{min}) and $D_{0.03cc} \leq 21.9$ Gy (D_{max}) [7] and with an aim to achieve $D_{40\%} \leq 7.3$ Gy (Gondi et al. 2013). Dose prioritization and acceptance criteria were applied according to the latest international recommendations [19]. Hippocampi were given fourth priority level on OAR prioritization list [19]. The dose prescribed to the high-dose PTV was 70 Gy in 35 fractions. Induction chemotherapy (CT) before RT was allowed.

Sample size and plan comparison

According to previous studies, HS-VMAT can reduce hippocampal $D_{40\%}$ by approximately 12 Gy compared to conventional VMAT (Table 1) [14–16,18]. A sample size of 12 patients was calculated using a paired samples *t*-test with a 0.01 alpha and a 0.05 beta to detect a mean difference of 12 Gy between VMAT and HS-VMAT hippocampal $D_{40\%}$ (MedCalc® Statistical Software, 2023). Wilcoxon signed-rank test in the SPSS statistical package was used for the statistical comparison of the DVH parameters between conventional and HS plans as well as for NTCP comparison. A p-value below 0.05 was considered significant.

NTCP model

The NTCP model of neurocognitive function impairment, derived from adult patients who received fractionated stereotactic RT for benign or low-grade primary brain tumors, was employed to examine the relationship between the probability of decline in short-term memory function as measured by Wechsler Memory Scale-III Word List (WMS-WL) delayed recall at 18 months and the EQD_2 ($\alpha/\beta = 2$ Gy) for $D_{40\%}$ of the bilateral hippocampi [10].

Results

We identified 16 papers reporting on hippocampal doses in RT of NPC, of which 4 reported on hippocampal $D_{40\%}$ in both conventional and HS plans, involving 79 patients (Fig. 1 and Table 1). On average across these studies, the authors were able to reduce the hippocampal $D_{40\%}$ from 24.9 Gy in conventional RT plans to 12.6 Gy in HS plans.

The study group included the first 12 nasopharyngeal cancer patients

Table 1
Results of a systematic literature review. Peviously published studies comparing doses received by 40 % of hippocampal volume ($D_{40\%}$) between conventional and hippocampus-sparing (HS) radiotherapy (RT) plans.

Study	Number of patients	Tumor stages	RT	HC contouring	Dose received by 40 % of HC ($D_{40\%}$ in Gy, cohort mean)	Dose to HC with HS plans ($D_{40\%}$ in Gy, cohort mean)	$D_{40\%}$ difference to HC between conventional and HS plans (in Gy, cohort mean)	Statistically significant reduction in dose to HC with HS
Gu, 2017 [15]	11	T3-4	VMAT	RTOG [10] and Chera et al [21]	13.8	6.4	7.2	Yes ($p = 0.001$)
Dunlop, 2015 [14]	8	T1-4	IMRT, VMAT	RTOG [10]	23.5 (range 14.5–35.0)*	8.6 (range 4.2–24.7)*	14.9	Yes ($p = 0.001$)
Han, 2014 [16]	8	T3-4	IMRT	RTOG [10]	27.1 (SD 5.4)	13.8 (SD 1.7)	13.3	Yes ($p < 0.01$)
Shen, 2020 [18]	52	NA	IMRT	NA	27.2 (SD 5.0)	14.3 (SD 3.0)	12.9	Yes ($p < 0.001$)

RT – radiotherapy technique; HC – hippocampi; HS – hippocampus-sparing; NA – not available; VMAT - volumetric modulated arc therapy; IMRT – intensity modulated radiotherapy; SD – standard deviation* – equivalent dose in 2 Gy fractions.

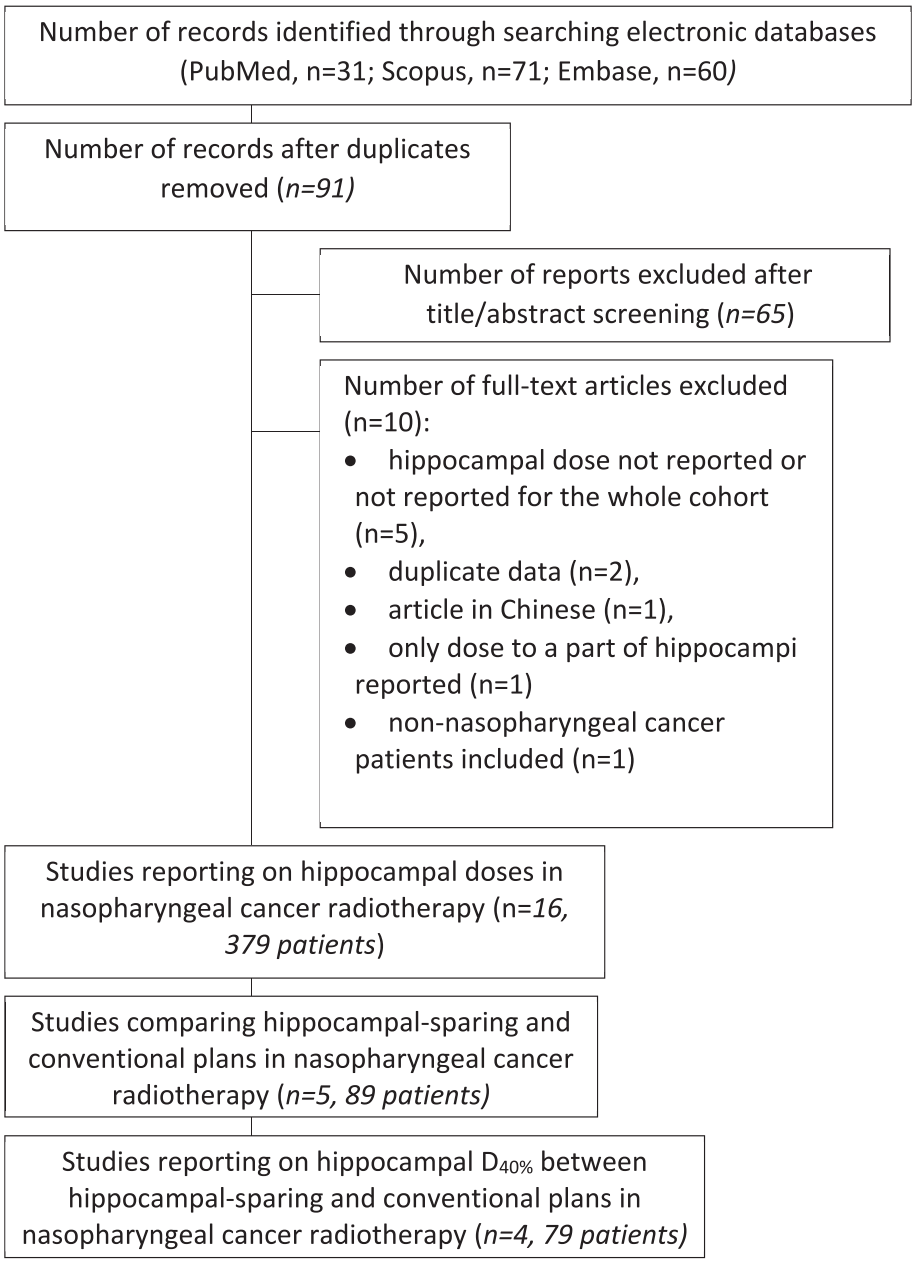

Fig. 1. Flowchart of a systematic review. Flowchart of the systematic literature review to identify previously published results comparing hippocampal $D_{40\%}$ between conventional and hippocampal-sparing radiotherapy plans.

who satisfied the inclusion criteria. Statistically significant differences between conventional and HS plans were observed in several parameters, in all cases the dose was lower in the HS plans (Table 2): hippocampal D_{max} (EQD_2 values 23.82 ± 20.13 Gy in HS plans, compared to 46.42 ± 23.87 Gy in conventional plans), hippocampal D_{min} (EQD_2 values 3.75 ± 1.90 Gy in HS plans, 4.61 ± 2.93 Gy in conventional plans), D_{mean} (EQD_2 values 8.05 ± 3.97 Gy in HS plans, 15.06 ± 7.36 Gy in conventional plans), and $D_{40\%}$ (EQD_2 values 8.31 ± 3.96 Gy in HS plans, 15.78 ± 7.74 Gy in conventional plans). There were no significant differences in PTV $V_{100\%}$, PTV $V_{95\%}$, the Paddick Conformity Index for PTV, and doses to OARs. However, this was at the expense of less homogeneous PTV coverage in HS plans ($p = 0.038$) (Table 2). The average dose redistribution in HS VMAT plans, as compared to conventional VMAT plans, is illustrated in Fig. 2, showing selected sections of the brain where the dose differences were most pronounced.

In the conventional VMAT plans, the interquartile range (IQR) of the $D_{40\%}$ of the hippocampi was 11.5 Gy–22.0 Gy. According to the NTCP model this corresponds to an IQR of 33.8 %–81.1 % probability of decline in short-term memory function as measured by WMS-WL. In the HS VMAT plans, the IQR of the $D_{40\%}$ of the hippocampi ranged from 6.8 Gy to 10.6 Gy, which translates to an IQR probability of decline in short-term memory function as measured by WMS-WL of 15.8 %–29.6 % (p-value = 0.002) (Fig. 3).

Discussion

In the present in silico study, we managed to achieve a statistically significant reduction in hippocampal $D_{40\%}$, D_{mean}, D_{max} and D_{min} doses compared to conventional VMAT plans, all while maintaining target coverage and doses to organs at risk according to the latest international guidelines [19]. Furthermore, applying the previously proposed NTCP model to assess neurocognitive function impairment at 18 months post-radiotherapy for benign or low-grade primary brain tumors highlighted the clinical significance of attaining a lower hippocampal D40%.

Table 2
Comparison of dose parameters between conventional volumetric modulated arc therapy (VMAT) and hippocampus-sparing VMAT in twelve cT3-4 nasopharyngeal cancer (NPC) patients.

Structure	Parameter	Constraints (desirable dose)	Constraints (acceptable dose)	Priority level	Conventional plan mean ± SD	HS plan mean ± SD	p-value
Hippocampi	D_{max} [Gy]	≤21.9	≤23.9	4	50.30 ± 22.10	29.90 ± 19.48	0.002
	D_{max} EQD_2 [Gy]	≤14.4	≤15.7		46.42 ± 23.87	23.82 ± 20.13	0.002
	D_{min} [Gy]	≤11.2	≤14.9	4	8.01 ± 4.68	6.72 ± 3.19	0.034
	D_{min} EQD_2 [Gy]	≤6.5	≤7.5		4.61 ± 2.93	3.75 ± 1.90	0.034
	D_{mean} [Gy]			4	21.96 ± 9.81	13.17 ± 5.81	0.002
	D_{mean} EQD_2 [Gy]				15.06 ± 7.36	8.05 ± 3.97	0.002
	$D_{40\%}$ [Gy]			4	22.79 ± 10.18	13.55 ± 5.81	0.002
	$D_{40\%}$ EQD_2 [Gy]	≤7.3			15.78 ± 7.74	8.31 ± 3.96	0.002
Homogeneity Index for PTV T	$(D_{2\%}-D_{98\%})/D_{median}$				0.16 ± 0.06	0.17 ± 0.06	0.038
PTV T	$V_{100\%}$ [%]	≥ 95		2	67.42 ± 22.06	69.43 ± 16.53	0.583
	$V_{95\%}$ [%]		≥ 95	2	96.00 ± 2.05	95.67 ± 2.54	0.209
GTV T	D_{min} [Gy] (100 % dose)	≥ 68.6 (98 % dose)	≥ 66.5 (95 % dose)	2	64.78 ± 3.85	64.53 ± 3.87	0.05
Pituitary	$D_{0.03cc}$ [Gy]	≤60	≤65	4	59.93 ± 23.10	58.98 ± 22.60	0.477
Brain stem	$D_{0.03cc}$ [Gy]	≤54	≤60	1	51.84 ± 2.95	51.99 ± 3.77	0.638
Spinal cord	$D_{0.03cc}$ [Gy]	≤45	≤50	1	45.20 ± 1.13	44.85 ± 1.24	0.071
Optic chiasma	$D_{0.03cc}$ [Gy]	≤54	≤60	1	33.80 ± 19.26	33.20 ± 19.77	0.308
Temporal lobes	$D_{0.03cc}$ [Gy]	≤70	≤72	2	66.32 ± 7.70	65.93 ± 9.08	0.583
Optic nerves	$D_{0.03cc}$ [Gy]	≤54	≤60	3	35.68 ± 19.55	34.90 ± 19.86	0.272
Lenses	$D_{0.03cc}$ [Gy]	≤6	≤15	3	7.22 ± 2.93	7.01 ± 2.92	0.477
Eyeballs	$D_{0.03cc}$ [Gy]		≤50	3	26.81 ± 18.68	27.27 ± 17.90	0.388
Right parotic gland	D_{mean} [Gy]	<26	<30 (at least one gland)	4	29.41 ± 10.23	29.41 ± 10.68	1
Left parotic gland	D_{mean} [Gy]	<26	<30 (at least one gland)	4	31.52 ± 5.71	31.73 ± 5,98	0.182
Right eyeball	D_{mean} [Gy]	≤35		3	8.16 ± 3.63	8.09 ± 3.49	0.789
Left eyeball	D_{mean} [Gy]	≤35		3	7.85 ± 3.87	7.61 ± 3.80	0.126
Right cochlea	D_{mean} [Gy]	≤45	≤55	4	45.46 ± 14.82	45.02 ± 15.40	0.239
Left cochlea	D_{mean} [Gy]	≤45	≤55	4	48.95 ± 14.72	48.83 ± 15.33	0.724
Mandible	D2% [Gy]	≤70	≤75	4	62.36 ± 7.74	62.02 ± 7.86	0.084
Temporomandibular joints	D2% [Gy]	≤70	≤75	4	56.12 ± 12.45	57.56 ± 11.60	0.209
The Paddick Conformity Index					0.77 ± 0.13	0.77 ± 0.14	0.281

SD – standard deviation; EQD_2 – equivalent dose in 2 Gy fractions; Dxx = the dose to the xx part of the structure volume; HS – hippocampal sparing; PTV T – planning target volume of the primary tumor; GTV T - gross tumor volume of the primary tumor.

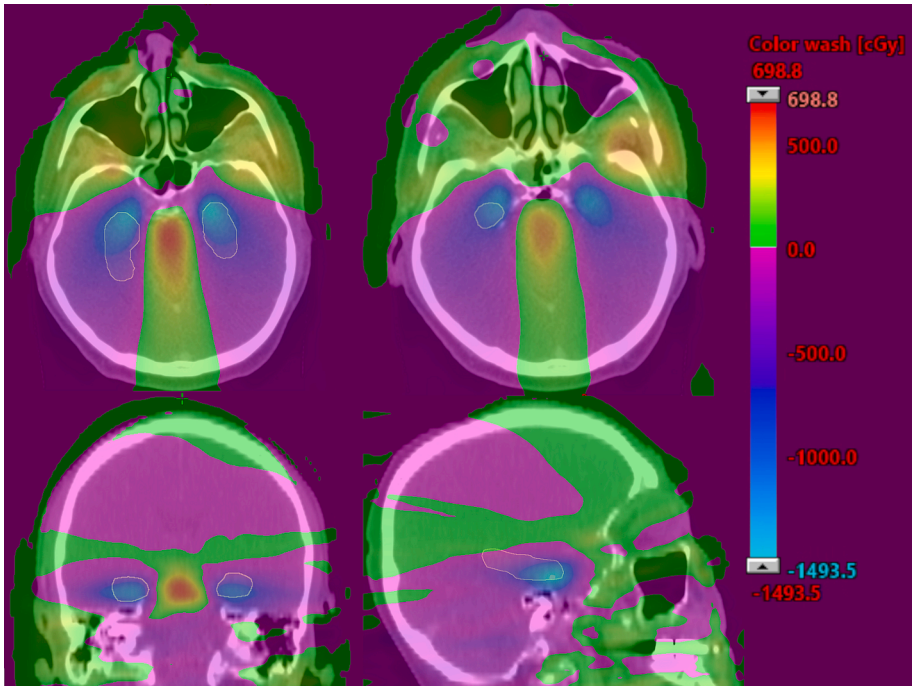

Fig. 2. The average dose difference between hippocampus-sparing (HS) and conventional plans. The average dose difference between hippocampus-sparing (HS) and conventional plans derived from all twelve patients and displayed on the anatomy of a single randomly selected patient (blue color in the color scale shows where on average the dose is lower in HS plans versus conventional plans, whereas green, yellow, orange and red colors show where on average the dose is higher in HS plans than in conventional plans). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

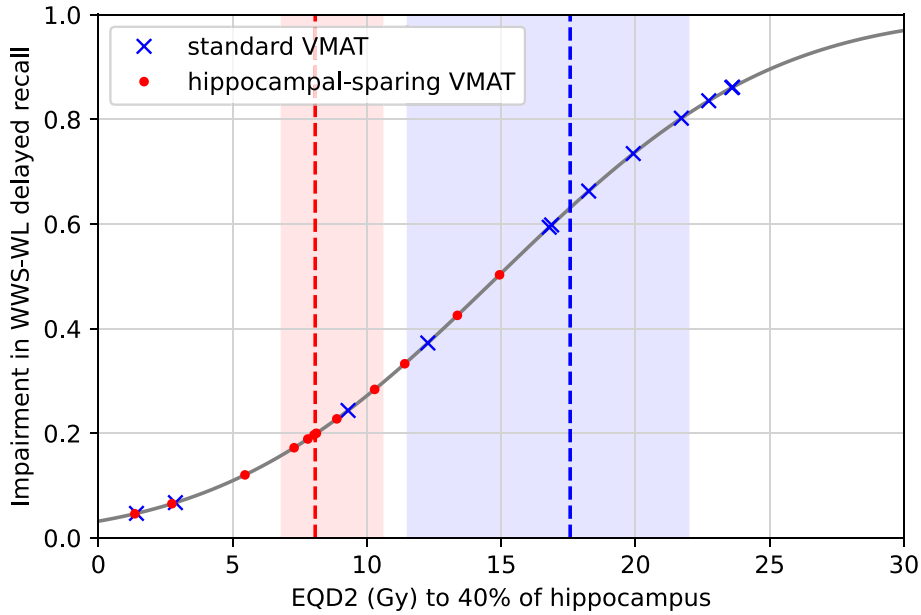

Fig. 3. Bilateral hippocampal EQD_2 $D_{40\%}$ data for conventional VMAT plans (blue) and hippocampi-sparing plans (red) on the previously published NTCP model of neurocognitive function after brain RT [10]. Neurocognitive function is defined as short-term memory function measured by Wechsler Memory Scale-III Word List (WMS-WL) delayed recall at 18 months. The dashed lines show the median values; the shaded areas show the interquartile range. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

However, we were unable to achieve the desired dose of $\leq$ 7.3 Gy using HS VMAT [10].

While previous publications on hippocampal sparing in nasopharyngeal cancer have also demonstrated significant reductions in relevant hippocampal dose-volume parameters when employing hippocampus-sparing techniques compared to conventional RT plans, these studies have exhibited variability in patient populations, radiotherapy methods, and treatment planning objectives [14–16,18]. The strengths of our study are a homogeneous patient cohort, and hippocampal sparing using exclusively VMAT with planning objectives aligned with the latest guidelines [19]. Furthermore, the sample size of 12 patients was calculated to be sufficient to provide reliable conslusions about significant differences observed between HS and conventional VMAT. As for the limitations of our study, Fig. 2 in the manuscript reveals significant, also unwanted changes in dose distribution after employing the HS VMAT plans, affecting different brain regions. The clinical implications of these changes remain unclear, and its potential harm cannot be determined definitively. To assess these dose redistribution effects accurately, a prospective observational study incorporating regular radiological and cognitive function assessments would be necessary, which was not available for these patients. Another limitation of the study is the utilization of Gondi's NTCP model, which was derived from the cognitive functioning results of only 18 evaluable patients after whole-brain radiotherapy [10]. Subsequently, the model was prospectively tested in low-grade glioma patients, where it consistently overestimated the observed cognitive decline based on hippocampal $D_{40\%}$ in the majority of patients [22].

Until now, mounting preclinical evidence underscored the toxicity of hippocampal irradiation [12,23–28], while growing clinical data emphasizes the significance of HS in preserving long-term cognitive function post-radiotherapy for NPC, brain tumors, and other head and neck tumors [7–11,13,14,29,30]. An important longitudinal study investigated early RT-related neurotoxicity using MRI in NPC patients within six months post-RT. Significant atrophy was found in the hippocampus and its subfields, correlated with radiation dose. Greater volume losses in specific regions were associated with faster cognitive decline, indicating a potential link between hippocampal atrophy and cognitive impairment in NPC patients [31]. However, not only irradiation of the hippocampi, but other factors also play a role in post-radiation cognitive decline. Different studies show the importance of microenvironmental changes due to endothelial damage, loss of oligodendrocytes, demyelination, white substance necrosis, inflammatory response [32], changes in synapses and neurogenesis impairment [33–35], changes in the blood–brain barrier [36,37], and thus increased brain exposure to neurotoxic cytostatic agents given concomittantly with RT, such as cisplatin [38,39]. Growing evidence shows that damage to other specific brain areas such as the septum pellucidum of the basal forebrain also plays a part in memory impairment [40]. In addition to radiation-related brain damage, injuries to the carotid arteries and thyroid gland caused by radiation may also contribute to cognitive impairment, highlighting the need for further investigation into their cumulative effects [6]. Therefore, different factors are very likely to intertwine in their contribution to cognitive decline. The likely multifactorial origin limits the utility of NTCP models of cognitive decline based on a single factor, as shown in the study mentioned above [22].

Furthermore, nowadays the most commonly used hippocampal constraints $D_{min} \leq 9$ Gy and $D_{max} \leq 16$ Gy in whole-brain RT (WBRT) with 10 fractions [11], the EQD_2 equivalents of which were used also in our study, are one of the first constraints that were published and turned out to be achievable in the following WBRT studies. They were, however, never prospectively compared to other hippocampal constraints.

This raises the question of whether other constraints might be more appropriate. For example, a prospective study of hippocampal dosimetry in patients receiving WBRT reported that other dose constraints were associated with neurocognitive preservation after WBRT in 24 patients, as observed in immediate recall in Wechsler Memory Scale-III Word List (WMS-WL) (for verbal memory testing). These constraints included hippocampal EQD2 values of Dmax $<$ 12.6 Gy, D10% $<$ 8.81 Gy, D50% $<$ 7.45 Gy, D80% $<$6.80 Gy, and Dmin $<$ 5.83 Gy. As expected, similar correlations also existed between hippocampal dosimetry specific to the left hippocampus, but not to that of the right hippocampus [41].

The importance of left versus right hippocampus for cognitive functioning was also observed in a study of young patients with brain tumors, where only the dose to the left hippocampus was associated with cognitive decline [9]. The authors propose a new recommendation of left hippocampal $D_{mean} \leq 30$ Gy ($EQD_2 \leq 22.5$ Gy) to avoid cognitive

decline. In addition, further studies are needed on the concurrent use of substances such as memantine, donepezil, and celecoxib, all of which have demonstrated neuroprotective effects until now [7,8,42].

Conclusion

Incorporating hippocampal sparing into radiotherapy for locally advanced NPC, while maintaining target volume coverage and adhering to dose constraints for other established OARs, is feasible. However, further clinical studies are imperative to more precisely determine the dose-volume-effect relationship concerning hippocampal irradiation and the dose redistribution effects of the hippocampal-sparing approach. Given that many NPC patients are of working age and possess a considerable life expectancy, their cognitive well-being must be paramount in radiotherapy planning. Currently, sparing the hippocampi stands as the approach with the most robust supporting evidence.

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CRediT authorship contribution statement

Monika Peternel: Investigation, Formal analysis, Writing – original draft. **Aljaša Jenko:** Investigation, Writing – review & editing. **Primož Peterlin:** Formal analysis, Methodology, Writing – review & editing, Visualization. **Larisa Petrovič:** Investigation, Writing – review & editing. **Primož Strojan:** Writing – review & editing, Funding acquisition. **Gaber Plavc:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Supervision.

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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