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Short Communication

Hippocampus sparing volumetric modulated arc therapy in patients with loco-regionally advanced oropharyngeal cancer

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ABSTRACT

This study aimed to assess the incidental radiation exposure of the hippocampus (HC) in locoregionally-advanced oropharyngeal cancer patients undergoing volumetric modulated arc therapy and the feasibility of HC-sparing plan optimization. The initial plans were generated without dose-volume constraints to the HC and were compared with the HC-sparing plans. The incidental D_{mean} median doses to the bilateral, ipsilateral and contralateral HC were 2.9, 3.1, and 2.5 Gy in the initial plans and 1.4, 1.6, and 1.3 Gy with HC-sparing. It was feasible to reduce the HC dose with HC-sparing plan optimization without compromising target coverage and/or dose constraints to other OARs.

1. Introduction

Several studies have evaluated neurocognitive function in locoregionally-advanced head and neck cancer (HNC) patients and suggested association between chemoradiation and post-treatment cognitive decline [1–4]. It remains understudied whether the low dose radiation to the brain causes long-term neurotoxicity, but there is increasing evidence suggesting different radiation susceptibility based on anatomical brain lesions [5,6]. The hippocampus (HC) is a highly radiosensitive brain region involved in learning and memory, and irradiation can lead to changes in the dentate gyrus of the HC by depleting neural stem cells and progenitor cells [7,8]. Damage to the dentate gyrus caused by radiation treatment was found to be a major contributing factor to neurocognitive dysfunction [9]. Gondi *et al.* suggested significant neurocognitive damage would occur when radiation to 40 % of bilateral HC is greater than 7.3 Gy [10]. While knowledge of the effects of low-dose irradiation (LDIR) to the HC is sparse, animal studies on LDIR-induced bioeffects have suggested radiation dose of as low as 1 Gy can affect mitochondrial and synaptic signaling pathways in murine HC and cortex [11,12]. Recently, researchers investigated radiation dose to HC in locally-advanced nasopharyngeal cancer intensity modulated radiotherapy (IMRT) and reported a significant amount of radiation exposure to HC [13,14]. Data evaluating radiation exposure of HC and feasibility of HC-sparing plan optimization in oropharyngeal cancer (OPC) is scarce. Although the oropharynx is not considered as an adjacent organ to the HC, its location is close enough for incidental exposure to radiation during head and neck directed IMRT.

In this study, we retrospectively evaluated the HC dose volume parameters of volumetric modulated arc therapy (VMAT) plan for locoregionally-advanced OPC (LA-OPC) to determine the radiation exposure of the HC in the initial plans. Subsequently, we generated new plans to compare with the initial plan and test the feasibility of plan optimization to minimize the dose to HC. We hypothesized that modulation of a VMAT plan to reduce the dose to HC could be achieved without compromising the target coverage and the dose constraints to other critical organs.

2. Materials and methods

2.1. Patient selection

Medical records of a consecutive series of patients who underwent VMAT for oropharyngeal cancer between 2014 and 2018 were retrospectively reviewed. Patients were identified from a departmental database and included if they were treated for LA-OPC. Among 75 patients, 10 patients were identified to also have undergone magnetic resonance imaging (MRI) of the brain, with a T1-weighted scan of the brain in 3 mm slice thickness or finer resolution; this was coregistered

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for volume delineation of the HC. This retrospective study was approved by the institutional review board.

The total prescribed doses to the planning target volumes (PTV) were 69.7–70.0 Gy (D95%) in 2.0–2.1 Gy daily fractions in 9 out of 10 patients, and 66.0 Gy in 2.0 Gy daily fractions in 1 patient who was treated postoperatively. Eight patients received radiation therapy to the bilateral neck whereas two patients received treatment to the unilateral neck. Patient and tumor characteristics are summarized in Table S1 in supplementary material.

2.2. HC delineation and treatment planning

Initial VMAT plans had been generated without dose-volume constraints to the HC. PTVs were generated from clinical target volumes (CTV) corresponding to areas of high, intermediate and low risk disease. For each patient, 32 organs at risk (OAR) and dose-volume histograms (DVH) were generated for their routine clinical care. All patients were immobilized using standard head and neck aquaplast masks and planning computed tomography (CT) scans were performed with 3 mm slice thickness. CT and T1-weighted MRI scans were fused using rigid co-registration for all 10 patients in Phillips Pinnacle 3 treatment planning software (Fitchburg, WI). Two central nervous system specialized radiation oncologists delineated the HC on the fused images using the RTOG HC atlas [15], and HC dose volume parameters on the clinically-delivered plan was recorded. HC-sparing VMAT plans were then generated with a maximum dose optimization objective of 1–2 Gy to the HC without compromising the dose distributions on the targets and surrounding OARs. All HC-sparing plans were generated utilizing Pinnacle inverse planning version 9.10. A range of dose-volume statistics was calculated. The HC-sparing plans were reviewed by a head and neck specialized radiation oncologist and deemed acceptable only if they did not compromise tumor coverage and increase the dose to the rest of the OARs.

2.3. Plan evaluation

Wilcoxon signed-rank test was utilized to evaluate the statistical significance of differences in the volume parameters, doses to the target volume and doses to the OARs, between the initial plans vs HC-sparing optimized plans. All tests were two-sided with an alpha level of 0.05. Analyses were conducted in SAS v9.4.

3. Results

Compared to the initial VMAT plans, HC-sparing VMAT plans had no significant effect on the dose parameters for target coverage. The dose volume parameters of two plans are presented in Table S2 in supplementary material. No statistically significant difference was observed in the coverage between initial plans and HC-sparing plans except for D98% and D95% of PTV intermediate (61.6 vs 61.9 Gy and 62.7 vs 62.9 Gy, $p < 0.05$). The HC-sparing VMAT plan showed significantly lower doses on the HC as shown in Table 1. In the initial plan, D_{mean}_median and D_{max}_median to the bilateral HC were 2.9 Gy (range, 1.7–3.8 Gy) and 4.0 Gy (2.6–8.0 Gy), respectively. In the HC-sparing plan, the doses were significantly lowered to 1.4 Gy (range, 0.9–3.6 Gy) and 2.4 Gy (1.9–4.4 Gy), respectively. D_{mean}_median and D_{max}_median to the HC ipsilateral to the primary lesion were 3.1 Gy (range, 2.0–5.1 Gy), 3.9 Gy (2.6–8.0 Gy) in the initial plan, and 1.6 Gy (1.1–3.6 Gy), 2.4 Gy (1.9–4.4 Gy) in the HC-sparing plan ($p < 0.05$). D_{mean}_median and D_{max}_median to the HC contralateral to the primary lesion were 2.5 Gy (range, 1.5–3.6 Gy), 3.4 Gy (2.1–4.6 Gy) in the initial plan, and 1.3 Gy (range, 0.7–3.5 Gy), 1.8 Gy (1.2–4.4 Gy) in the HC-sparing plan ($p < 0.05$). HC point maximum dose was 8.0 Gy in the initial plan and 4.4 Gy in the HC-sparing plan.

The dose-volume parameters of 32 OARs were compared between initial plans vs HC-sparing plans as shown in Table S3 in supplementary material. The doses to the brain stem, optic apparatus, pituitary, bilateral cochleae and right parotid were lower in HC-sparing plan without any significant increase in doses to the other OARs. An example of dose distributions in the contoured hippocampi and isodose lines in the initial plan and the HC-sparing plan are shown in Fig. 1.

4. Discussion

We evaluated the incidental radiation exposure of the HC in LA-OPC patients undergoing VMAT and the feasibility of HC-sparing plan optimization. We found that the incidental dose to the HC with VMAT in LA-OPC is in the range that is reported to induce persistent compromise to the HC microenvironment in animal models, and it is feasible to reduce the HC dose significantly with VMAT plan optimization without compromising target coverage and/or increasing the dose to other OARs. The HC-sparing plans also tended to lower the doses to the OARs that were adjacent to HC or above the level of HC.

In this study, the mean doses to the bilateral, ipsilateral and contralateral HC in the HC-sparing plans were 1.4 Gy, 1.6 Gy, and 1.3 Gy, respectively. McDonald *et al.* [16] recently evaluated brain dose volume parameters of 15 LA-OPC patients and reported similar mean dose of 3.1 Gy (range, 2.1–5.9 Gy) to the medial temporal lobe. It is also noteworthy that one of the initial treatment plans evaluated in this study was with a HC point maximum dose of 8.0 Gy. This brings up the concern that in selected cases, HC may get the dose greater than what is clinically reported to affect cognitive function.

Pre-clinical evidence in rodents has repeatedly shown the LDIR effect on HC suggestive of neurocognitive decline (Table 4 in supplementary material). Achanta *et al.* [17] showed significant dose-dependent decrease in HC granule cell neurogenesis and HC-dependent trace fear conditioning while no differences were observed for HC-independent tasks between irradiation and control groups, in rats that received 0/0.3/3.0, or 10.0 Gy whole brain radiation. Mizumatzu *et al.* also demonstrated decreasing hippocampal neurogenesis with increasing radiation using 0/2/5, or 10 Gy [18,19]. Rola *et al.* [20] showed decrease in proliferating subgranular zone cells and their progeny immature neurons in dose-dependent fashion in mice model when irradiated with whole brain irradiation (2.0–10.0 Gy). Schmal *et al.* [21]

Table 1
Comparison of initial plan vs HC-sparing plan maximum, mean, D40% doses to hippocampus and brainstem.

	VMAT plan	Dmax (Gy)Median (range)	P value	Dmean (Gy)Median (range)	P value	D40% (Gy)Median (range)	P value
HC_Total	Initial Plan	4.0 (2.6–8.0)	<0.01	2.9 (1.7–3.8)	<0.01	3.0 (1.7–4.1)	<0.01
	HC Sparing Plan	2.4 (1.9–4.4)		1.4 (0.9–3.6)		1.5 (0.9–3.7)	
HC_ Ipsi	Initial Plan	3.9 (2.6–8.0)	<0.01	3.1 (2.0–5.1)	<0.01	3.3 (2.1–5.6)	<0.01
	HC Sparing Plan	2.4 (1.9–4.4)		1.6 (1.1–3.6)		1.7 (1.2–3.7)	
HC_Contr	Initial Plan	3.4 (2.1–4.6)	<0.01	2.5 (1.5–3.6)	<0.01	2.6 (1.5–3.7)	<0.01
	HC Sparing Plan	1.8 (1.2–4.4)		1.3 (0.7–3.5)		1.4 (0.7–3.6)	
Brainstem	Initial Plan	35.9 (24.6–48.9)	greater than0.01	11.5 (7.5–19.4)	<0.1	11.0 (6.1–22.7)	<0.01
	HC Sparing Plan	34.3 (10.9–52.5)		7.5 (3.1–16.3)		5.4 (3.1–19.6)	

VMAT, Volumetric Modulated Arc Therapy; HC, hippocampus; Rt, right; Lt left; Ipsi, ipsilateral; Contr, contralateral.

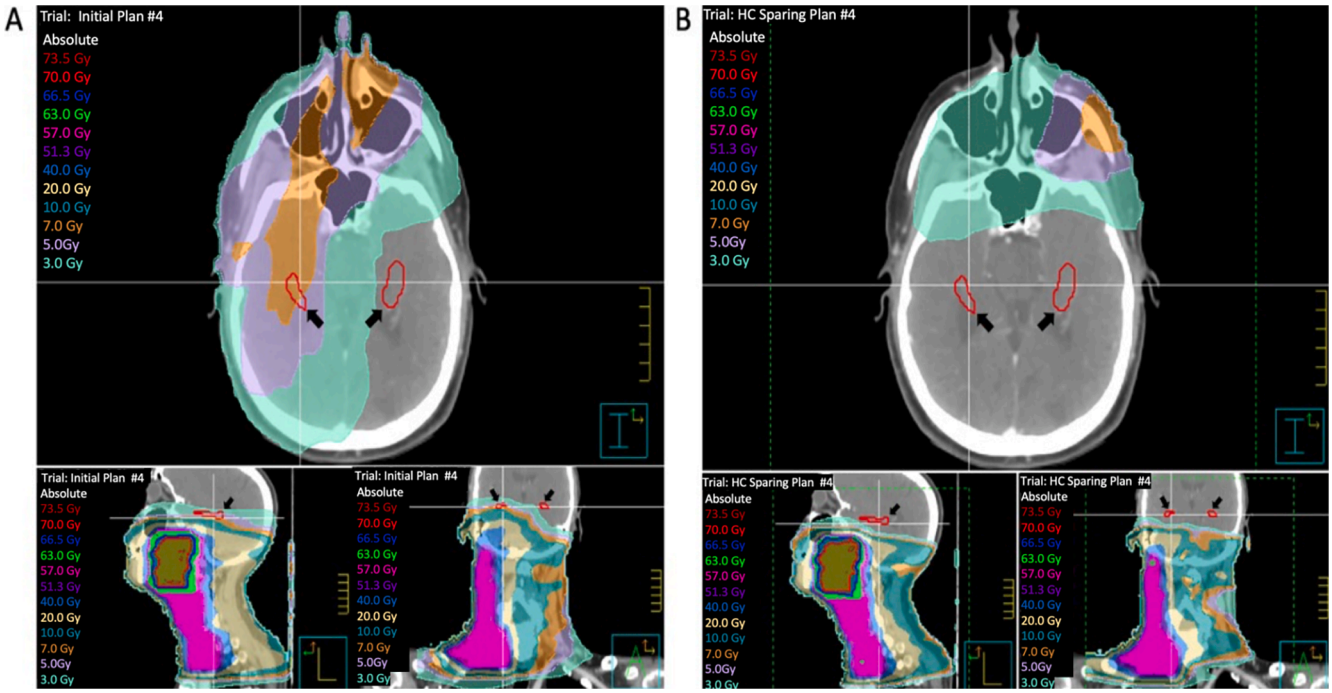

Fig. 1. Example of dose distributions in the contoured hippocampus and isodose line in (A) initial plan and (B) HC-sparing plan in axial, coronal and sagittal views on CT image. Black arrow indicates the hippocampus.

reported that when genetically defined mouse strains with varying DNA repair capacities were exposed to fractionated LDIR (5x/10x/15x/20x0.1 Gy) and analyzed 72 h after last exposure as well as at 1,3, and 6 months, the radiation induced DNA damage accumulation led to progressive decline of HC neurogenesis, showing that HC is highly sensitive to repetitive LDIR.

Increasing evidence shows that radiation related injury to the HC is associated with neurocognitive dysfunction. Gondi *et al.* reported the biologically equivalent dose of 2.0 Gy fractions (EQD2) greater that 7.3 Gy to the bilateral HC in cranial irradiation was significantly associated with neurocognitive impairment [10]. Tsai *et al.* reported that EQD2 values of < 12.6 Gy, <8.8 Gy, <7.5 Gy and < 5.8 Gy to the 0, 10, 50, 80 % of HC were associated with neurocognitive preservation as indicated by the immediate recall of Word List Test of Wechsler Memory Scale-III [22]. A retrospective study by Gan *et al.* [23] evaluated an association between HNC radiotherapy and cognitive function, and showed an association of radiation dose to the temporal lobe and cerebellum with memory impairment and impaired dexterity. Sharma *et al.*[24] evaluated neurocognitive late effects and quality of life (QOL) following radiotherapy for sinonasal cancer and showed dose–response correlation of the doses to the whole brain, right temporal lobe, both frontal lobes, and HC and the outcomes of the Digit Span of Wechsler's Adult Intelligence Scale IV.

Previous studies evaluating neurocognitive toxicity of RT in HNC have mainly focused on nasopharyngeal cancer [25–31]. Ongoing efforts to lower the radiation doses to HC and related toxicities utilizing hippocampal-sparing plans also mainly focus on the patients with CNS malignancies and nasopharyngeal cancer [32–35]. Since OPC patients are also at risk of receiving radiation doses to the HC, incidental exposures to HC in OPC patients need to be further investigated. This is especially important given the rise in the rates of HPV-positive OPC [36–38]. The patients diagnosed with HPV-positive OPC tend to be younger, non-smokers, non-drinkers, and generally otherwise healthy with excellent overall survival [39–42]. Since increasing evidence showed the toxicity of LDIR on HC in animal models and clinical data, we raised a concern that the LDIR to the HC may adversely affect the neurocognitive function and QOL of LA-OPC patients many of whom are in their working-age and have a long life expectancy. As we were able to decrease the HC dose significantly without compromising coverage and constrains utilizing HC-sparing IMRT, this seems to be a feasible way to potentially help LA-OPC patients preserve neuro-cognitive capacity and QOL after their treatments.

This study has several limitations. First, the sample size was small as only 10 % of LA-OPC patients treated with VMAT had undergone brain MRI that was required to contour the HC. Therefore, the results from this study will require validation in a larger number of patient population, and the cost-effectiveness of obtaining MRI for HC delineation in LA-OPC patients needs to be investigated. Second, dose-volume parameters and the effect of HC dose optimization on other structures outside of the 32 organs were not evaluated in this study. Third, other factors that may have contributed to the lower doses to the OARs in the HC-sparing plans such as versions of the treatment planning system or planner factors were not evaluated. Lastly, the inference on the effect of LDIR on neurocognitive functions is derived mostly from animal studies. Therefore, the clinical advantage of HC-sparing IMRT needs to be validated by conducting prospective studies with larger sample size and utilizing neuro-psychological assessment.

In conclusion, it is feasible and safe to reduce radiation dose to the HC by utilizing HC-sparing IMRT in LA-OPC patients. As more LA-OPC patients are presenting in their working-age with good overall prognosis, HC-sparing needs to be considered in this population. However, whether the LDIR to HC reported in the current study translates into a meaningful impact on neurocognitive function is unknown and should be explored further ahead.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Tim Kruser reports personal fees from AstraZeneca, personal fees from Onc Live, outside the submitted work. Michelle Gentile reports personal fees from Gem Pharmaceuticals, personal fees from STATinMED, outside the submitted work. Rest of authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2022.09.008.

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