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FEASIBILITY OF HIPPOCAMPUS-SPARING VMAT IN LOCOREGIONALLY ADVANCED OROPHARYNGEAL CARCINOMA: A RETROSPECTIVE DOSIMETRIC EVALUATION

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ABSTRACT

Background: Radiotherapy generates incidental dose to non-target neural structures including the hippocampus, which is highly radiosensitive and linked to neurocognitive decline even at low doses. While hippocampal sparing is evolving in neuro-oncology, its feasibility in head-and-neck radiotherapy, particularly oropharyngeal carcinoma treated with volumetric-modulated arc therapy (VMAT), remains underexplored.

Methods: This retrospective dosimetric study included 20 patients with locoregionally advanced oropharyngeal carcinoma (LA-OPC) treated with radical VMAT between 2021–2022. Bilateral hippocampi were retrospectively contoured per RTOG atlas. Original clinical plans (non-hippocampus-sparing) were compared to re-optimized hippocampus-sparing VMAT plans using identical arc geometry. Dose–volume histogram parameters were analyzed for hippocampi (Dmean, Dmax), planning target volume (PTV) coverage (D90, D95, D98), plan quality indices, and 32 additional organs-at-risk (OARs). Constraints followed the Radiation Therapy Oncology Group (RTOG) 0933 protocol (Dmax <16 Gy, D100 <9 Gy). Statistical comparisons were performed using paired tests, with $p<0.05$ considered significant.

Results: Mean ipsilateral hippocampal dose reduced from 2.00 to 1.89 Gy ($p=0.001$) and maximum dose from 3.44 to 2.96 Gy ($p=0.001$). Bilateral hippocampal sparing met all constraint thresholds without compromising high-risk PTV coverage ($p>0.05$). Significant dose reductions were also observed in spinal cord ($p=0.001$), brainstem ($p=0.046$) and parotids ($p<0.01$), while conformity and homogeneity indices remained preserved. Intermediate and low-risk PTVs demonstrated improved dose uniformity ($p\leq0.041$). No clinically relevant increase was seen in any other OAR.

Conclusion: Hippocampus-sparing VMAT is dosimetrically feasible for LA-OPC, achieving significant neural dose reduction without detriment to target coverage or OAR safety. These findings support prospective evaluation of cognitive-preserving RT strategies in head-and-neck cancer survivors.

KEYWORDS: Hippocampal sparing, Oropharyngeal carcinoma, VMAT, Dosimetric analysis, Neurocognitive toxicity

INTRODUCTION

Head and neck cancers (HNCs) constitute a major global health burden, historically accounting for a substantial share of malignant disease worldwide [1]. In 2022, there were an estimated 947,211 new cases of HNC worldwide—4.7% of all cancer diagnoses—and 482,428 deaths, representing 4.9% of cancer-related mortality [1,2]. Oropharyngeal cancers account for a large share of this burden: across most regions they represent more than one-third of all HNCs, rising to 56% in South Central Asia, 53% in Australia/New Zealand and 76% in Melanesia. India bears a particularly heavy load; among the five countries with the highest HNC incidence, India reported 247,924 cases, the greatest number globally [2]. Oropharyngeal malignancies are consistently male-predominant: a recent Indian institutional study found that oral and oropharyngeal cancer occurred mainly in men aged in the fifth decade, with the base of tongue being the most common subsite [3]. A large cross-sectional analysis of over 103,000 U.S. oropharyngeal cancer cases diagnosed between 2006–2021 likewise reported that 80.3% were male, with the base of tongue and tonsil accounting for ~83% of primary sites, and most patients presenting with regional (stage III/IVA) disease [4]. These epidemiologic patterns underscore the need for

effective treatments that address both survival and long-term quality of life.

Locally advanced oropharyngeal carcinoma (LA-OPC) is traditionally treated with concurrent chemoradiation, delivered by intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT); both techniques achieve comparable target coverage, although VMAT offers shorter delivery times and improved dose conformity in locally advanced head and neck squamous cell carcinoma [5]. Established risk factors for oropharyngeal carcinoma include tobacco and alcohol use, areca-nut/betel-quid chewing, occupational and environmental exposures, and persistent infection with human papillomavirus (HPV), which together account for the majority of cases [6]. Radiotherapy is an effective primary and adjuvant modality; however, it is associated with acute toxicities (mucositis, dysphagia, xerostomia) and chronic sequelae that diminish quality of life [7,8]. Advances in conformal techniques—IMRT and more recently VMAT—have reduced parotid toxicity and improved dose homogeneity [9], yet concerns persist regarding neurocognitive effects from incidental irradiation of the hippocampus, a radiosensitive structure not conventionally regarded as an organ at risk (OAR) in head-and-neck radiotherapy.

Emerging evidence indicates that hippocampal radiation, even at comparatively low doses, contributes to impaired neurogenesis and memory decline. The phase II Radiation Therapy Oncology Group (RTOG) 0933 trial established that conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy (WBRT) preserves verbal memory function without compromising disease control, and defined the now widely adopted hippocampal dose constraints (Dmax <16 Gy, D100 <9 Gy) [10]. Building on this evidence, a recent meta-analysis of hippocampal-sparing whole-brain radiotherapy (HS-WBRT) demonstrated significantly better verbal learning and delayed recall compared with conventional WBRT [11]. Despite this, most head-and-neck radiotherapy protocols do not consider the hippocampus as an OAR, and dosimetric data on incidental hippocampal exposure during VMAT for oropharyngeal carcinoma remain limited.

Given rising survival rates and the relatively younger age of many LA-OPC patients, understanding and mitigating radiation-induced cognitive risk is increasingly important. This study addresses this gap by retrospectively evaluating the incidental hippocampal doses delivered in 20 patients with locoregionally advanced oropharyngeal carcinoma treated with VMAT between 2021–2022. We quantify baseline hippocampal exposure, re-optimize plans to achieve hippocampal-sparing constraints, and assess whether such sparing can be achieved without compromising target coverage or other organ-at-risk dosimetry. To the best of our knowledge, this is among the first dosimetric studies to specifically evaluate the feasibility of hippocampal sparing during VMAT for oropharyngeal carcinoma, thereby extending a strategy previously validated mainly in whole-brain and nasopharyngeal radiotherapy to a new anatomical and clinical setting.

MATERIALS AND METHODS

Study Design and Objectives

This was a retrospective, non-interventional dosimetric analysis conducted at the Department of Radiation Oncology, Government Medical College and Rajindra Hospital, Patiala, Punjab, to evaluate the hippocampus as an organ at risk (OAR) in patients with locoregionally advanced oropharyngeal carcinoma (LA-OPC) treated with volumetric-modulated arc therapy (VMAT). The study aimed to quantify the incidental radiation doses received by the hippocampus in previously delivered non-hippocampus-sparing VMAT plans and to assess the dosimetric feasibility of generating hippocampus-sparing re-optimized VMAT plans without compromising target volume coverage or violating other OAR dose constraints. The analysis included all eligible patients treated between January 2021 and December 2022.

Patient Selection and Inclusion Criteria

Medical records and treatment plans of adult patients (≥18 years) with histologically confirmed squamous cell carcinoma of the oropharynx who underwent radical VMAT with or without concurrent chemotherapy were retrospectively reviewed. Patients were included if their disease stage corresponded to T1–T4a, N1–N2, and M0, consistent with stage I–IVA according to the American Joint Committee on Cancer (AJCC), 8th edition. All patients had completed radical chemoradiation with total prescribed doses between 66 Gy and 70 Gy delivered in daily 2 Gy fractions. Patients with recurrent disease, previous head and neck irradiation, or incomplete planning data were excluded. The study population comprised 20 patients fulfilling the inclusion criteria, and all data were anonymized before analysis.

Imaging and Simulation

All patients underwent contrast-enhanced computed tomography (CECT) simulation on a dedicated radiotherapy planning CT scanner with 2.5 mm slice thickness. Immobilization was achieved using a four-clamp thermoplastic head-neck-shoulder mask and customized headrest to ensure reproducible positioning. The scans extended from the vertex to the carina to allow adequate visualization of both the target and adjacent critical structures. The images were transferred to the Eclipse Treatment Planning System (TPS; Varian Medical Systems, version 13.7) for contouring and plan generation.

Target and Organ Delineation

Clinical target volumes (CTV) and planning target volumes (PTV) were delineated according to institutional protocols consistent with international contouring guidelines for head and neck cancer. The high-risk PTV included the gross tumor volume and involved nodal regions receiving 66–70 Gy, while intermediate- and low-risk PTVs encompassed subclinical regions receiving 60 Gy and 54 Gy, respectively. All relevant organs at

risk—including brainstem, spinal cord, optic apparatus, cochleae, parotids, mandible, oral cavity, and constrictor muscles—were delineated on the planning CT. The hippocampus was contoured bilaterally by two independent radiation oncologists using the RTOG hippocampal contouring atlas as reference [12]. In the original clinical plans, the hippocampus was not considered an OAR; for this study, it was retrospectively delineated and used for dose evaluation and optimization in re-planning.

Treatment Planning and Optimization

All VMAT plans were created using two full coplanar arcs with 6-MV photon beams on the Eclipse TPS, employing the Analytical Anisotropic Algorithm (AAA) for dose calculation. The initial plans represented the clinically delivered non-hippocampus-sparing VMAT treatments. Subsequently, hippocampus-sparing re-optimized plans were generated for each patient using the same beam geometry and optimization parameters, with additional dose-volume objectives applied to the hippocampal contours. The optimization aimed to achieve hippocampal dose constraints consistent with RTOG 0933 recommendations—maximum dose (Dmax) < 16 Gy and minimum dose to the entire volume (D100) < 9 Gy—while maintaining clinically acceptable PTV coverage and sparing of other OARs.

Dosimetric Evaluation

Dose-volume histograms (DVHs) were generated for all structures in both initial and hippocampus-sparing plans. For the hippocampus, the parameters recorded included maximum dose (Dmax), mean dose (Dmean), minimum dose to the entire volume (D100), and dose to 40% of the volume (D40%), expressed as equivalent dose in 2-Gy fractions (EQD2) assuming an α/β ratio of 2.27 Gy. For PTVs, dosimetric indices such as D98%, D95%, and D90% (the dose received by 98%, 95%, and 90% of the target volume, respectively) were compared between the two plan sets to assess target coverage. Plan quality was further evaluated using the homogeneity index (HI) and conformity index (CI). The HI was calculated as $HI = (D2 - D98)/D50$, where D2, D98, and D50 represent the doses received by 2%, 98%, and 50% of the PTV volume, respectively, in accordance with ICRU-83 recommendations; values closer to zero indicate greater dose homogeneity. The CI was calculated as the ratio of the treated volume receiving the prescription isodose to the PTV volume ($CI = V100\%/V_P^{Tv}$), with values closer to unity indicating optimal conformity. Additionally, mean and maximum doses were recorded for 32 other OARs to verify that hippocampal sparing did not compromise surrounding tissue protection.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 22.0; IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation and median (range). Paired Student's t-test and Wilcoxon signed-ranks test were applied to compare dosimetric parameters between the initial and hippocampus-sparing plans, depending on data normality. A two-sided p-value < 0.05 was considered statistically significant. Results were tabulated for PTVs, hippocampal doses (bilateral, ipsilateral, and contralateral), and all OARs.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee, Government Medical College, Patiala (Approval No. Trg 9(310)2023/14803, dated 16 May 2023), and was conducted in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments. As this was a retrospective dosimetric study using de-identified treatment data, no informed consent was required. Patient confidentiality was strictly maintained throughout the analysis.

RESULTS

Dosimetric outcomes were compared between non-hippocampus-sparing and hippocampus-sparing VMAT plans and are presented below by structure group, with statistical significance defined as $p<0.05$ for each parameter.

1. Patient and Tumor Characteristics

The study cohort comprised 20 male patients with a mean age of 56.7 ± 12.0 years (range 24–70). The most common primary site was the base of tongue (55%), followed by tonsil (35%) and soft palate (10%). All patients had histologically confirmed squamous cell carcinoma and received radical chemoradiation. The majority presented with Stage IVA disease (60%), and none had distant metastases. The overall clinical and treatment characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the study cohort (n = 20), including age distribution, gender, primary tumor subsite, histological type, and disease stage (American Joint Committee on Cancer, 8th edition). SD: standard deviation; RT: radiotherapy.

Parameter	Category	Frequency (n)	Percentage (%)
Age group (years)	21–30	1	5
	31–40	1	5
	41–50	3	15
	51–60	7	35
	61–70	8	40
Mean ± SD (years)		56.7 ± 12.0	—
Gender	Male	20	100

Primary site	Base of tongue	11	55
	Tonsil	7	35
	Soft palate	2	10
Histology	Squamous cell carcinoma	20	100
Stage	III	5	25
	IVA	12	60
	IVB	3	15
RT intent	Radical	20	100

2. Target Volume Coverage

PTV dose coverage remained clinically acceptable for both non–hippocampus-sparing and hippocampus-sparing VMAT plans. No significant differences were observed in the high-risk PTV ($p > 0.05$ for D98%, D95%, D90%), confirming that hippocampal optimization did not compromise tumor coverage. However, the intermediate PTV D98% ($p = 0.041$) and low-risk PTV D95% ($p = 0.008$) and D90% ($p = 0.004$) showed modest but statistically significant improvements in the hippocampus-sparing re-plans, reflecting enhanced dose homogeneity in these regions (Table 2).

Overall, these results confirm no clinically or statistically significant compromise in high-risk PTV coverage ($p>0.05$), while low- and intermediate-risk PTV parameters showed small but statistically significant gains in dose homogeneity ($p<0.05$).

Table 2. Comparison of planning target volume (PTV) dose–coverage parameters between non-hippocampus-sparing (Non–HC-Sparing) and hippocampus-sparing (HC-Sparing) VMAT plans across high-risk, intermediate-risk, and low-risk PTV levels. D98, D95, and D90 denote the dose (Gy) received by 98%, 95%, and 90% of the target volume, respectively; SD: standard deviation. A two-sided $p<0.05$ was considered statistically significant.

PTV Level	Parameter	Non–HC-Sparing (Mean ± SD)	HC-Sparing (Mean ± SD)	p-value
High-risk PTV	D98	62.97 ± 0.80	62.58 ± 0.99	0.064
	D95	63.86 ± 0.57	63.64 ± 0.72	0.062
	D90	64.47 ± 0.42	64.37 ± 0.57	0.235
Intermediate PTV	D98	57.33 ± 0.89	56.95 ± 0.97	0.041
	D95	58.16 ± 0.67	57.90 ± 0.62	0.064
	D90	58.76 ± 0.53	58.54 ± 0.43	0.359
Low-risk PTV	D98	51.96 ± 0.69	51.69 ± 0.73	0.159
	D95	52.61 ± 0.38	52.36 ± 0.44	0.008
	D90	53.02 ± 0.27	52.78 ± 0.38	0.004

3. Hippocampal Dose Metrics

Hippocampal dosimetry demonstrated statistically significant dose reduction in the re-optimized VMAT plans. Mean dose to the ipsilateral hippocampus decreased from 2.00 ± 0.71 Gy to 1.89 ± 0.58 Gy ($p = 0.001$), while maximum dose reduced from 3.44 ± 2.62 Gy to 2.96 ± 1.15 Gy ($p = 0.001$). Similarly, contralateral hippocampal Dmean decreased from 1.93 ± 0.64 Gy to 1.85 ± 0.53 Gy ($p = 0.002$), and Dmax from 3.16 ± 1.74 Gy to 2.89 ± 1.08 Gy ($p = 0.004$). All re-optimized plans achieved the RTOG 0933 constraint of Dmax < 16 Gy and D100 < 9 Gy. Detailed comparisons are presented in Table 3.

All hippocampal dose comparisons reached statistical significance ($p\leq0.004$), confirming a consistent and reproducible sparing effect across both hemispheres.

Table 3. Comparison of mean (Dmean) and maximum (Dmax) hippocampal doses (Gy) between non-hippocampus-sparing (Non–HC-Sparing) and hippocampus-sparing (HC-Sparing) VMAT plans for the ipsilateral, contralateral, and total (bilateral) hippocampus (HC). SD: standard deviation.

Region	Parameter	Non–HC-Sparing (Mean ± SD)	HC-Sparing (Mean ± SD)	p-value
Ipsilateral HC	Dmean	2.00 ± 0.71	1.89 ± 0.58	0.001
	Dmax	3.44 ± 2.62	2.96 ± 1.15	0.001
Contralateral HC	Dmean	1.93 ± 0.64	1.85 ± 0.53	0.002
	Dmax	3.16 ± 1.74	2.89 ± 1.08	0.004
Total HC (bilateral)	Dmean	1.99 ± 0.69	1.89 ± 0.53	0.003
	Dmax	3.49 ± 2.61	2.96 ± 1.18	0.001

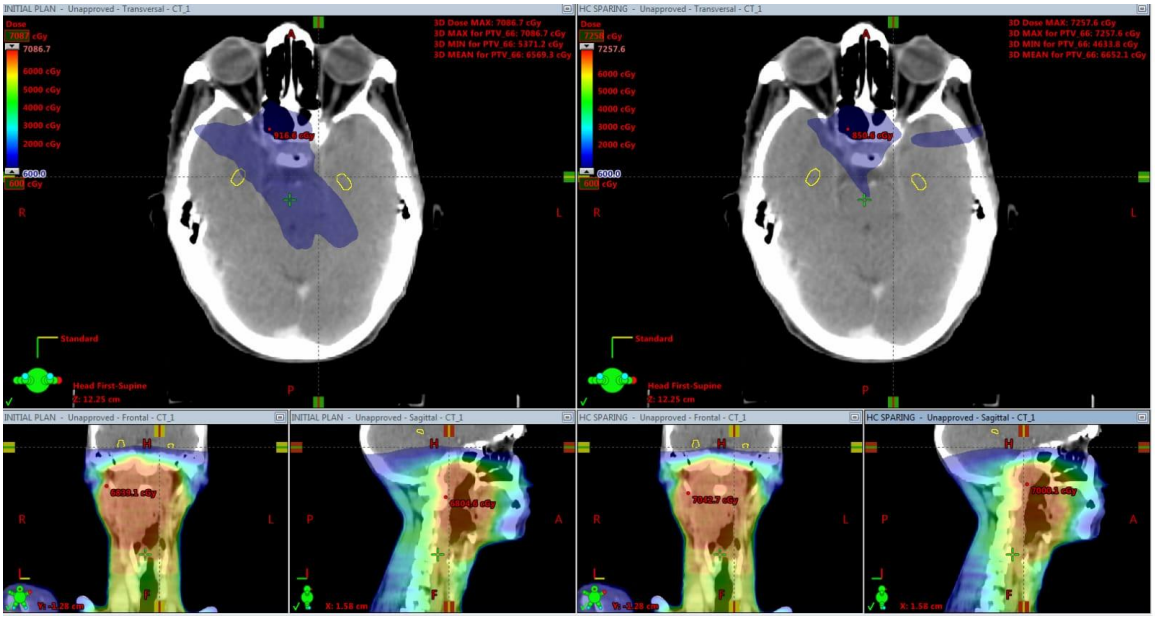

Figure 1. Representative treatment-planning system screenshots comparing the Initial Plan (non-hippocampus-sparing, left) and the HC Sparing (hippocampus-sparing, right) VMAT plans for a representative patient. Top row: transversal CT slices with color-wash dose distribution showing the high-risk PTV (PTV_66, blue-purple wash) relative to the bilaterally contoured hippocampi (yellow contours); reported 3D maximum, minimum, and mean doses to PTV_66 were comparable between the Initial Plan (7086.7/5371.2/6569.3 cGy) and HC Sparing plan (7257.6/4633.8/6652.1 cGy). Bottom row: frontal and sagittal reconstructions confirming maintained target coverage across both plans.

4. Organ-at-Risk (OAR) Doses

Among the evaluated OARs, significant dose reductions were achieved for the brainstem (Dmean 9.96 → 9.48 Gy, $p = 0.046$), spinal cord (Dmean 43.76 → 28.48 Gy, $p = 0.001$), and cochleae ($p<0.01$), whereas parotid gland Dmean increased marginally but significantly (~35 Gy → ~36 Gy, $p < 0.01$). All other critical structures—including optic nerves, mandible, and oral cavity—remained within acceptable tolerance limits ($p > 0.05$). These findings confirm that hippocampal dose reduction did not compromise other OAR constraints (Table 4).

Significant changes ($p<0.05$) were thus limited to the brainstem, spinal cord, cochleae, and parotids, while all other OAR parameters were statistically unchanged ($p>0.05$).

Table 4. Comparison of mean (Dmean) and maximum (Dmax) doses (Gy) to major organs at risk (OARs) between non-hippocampus-sparing (Non–HC-Sparing) and hippocampus-sparing (HC-Sparing) VMAT plans. R: right; L: left; SD: standard deviation.

Organ	Parameter	Non–HC-Sparing (Mean ± SD)	HC-Sparing (Mean ± SD)	p-value
Brainstem	Dmean	9.96 ± 5.47	9.48 ± 4.95	0.046
Spinal cord	Dmean	43.76 ± 1.84	28.48 ± 4.81	0.001
	Dmax	44.04 ± 2.22	27.07 ± 7.05	0.001
Optic nerves (R/L)	Dmean	2.33 ± 0.80 / 2.33 ± 0.83	2.32 ± 0.79 / 2.33 ± 0.81	>0.05
Cochlea (R/L)	Dmean	17.2 ± 6.1 / 11.8 ± 4.5	7.7 ± 5.4 / 3.9 ± 3.0	<0.01
Parotids (R/L)	Dmean	35.5 ± 7.2 / 35.9 ± 4.9	36.4 ± 7.1 / 36.8 ± 5.5	0.002 / 0.008
Mandible	Dmax	68.7 ± 1.4	69.1 ± 1.7	>0.05
Oral cavity	Dmean	41.9 ± 10.2	40.9 ± 10.8	>0.05

5. Plan Quality Parameters

Plan quality indices, including homogeneity and conformity, were comparable between both plan sets, demonstrating that hippocampal dose optimization had negligible impact on overall plan integrity. The conformity index and homogeneity index remained within clinically acceptable limits, ensuring robust PTV coverage. Key parameters are summarized in Table 5.

Table 5. Comparison of plan quality indices — conformity index (CI) and homogeneity index (HI) — and the coverage index between non-hippocampus-sparing (Non–HC-Sparing) and hippocampus-sparing (HC-Sparing) VMAT plans. SD: standard deviation.

Parameter	Non–HC-Sparing (Mean ± SD)	HC-Sparing (Mean ± SD)
Conformity Index (CI)	1.05 ± 0.08	1.07 ± 0.09
Homogeneity Index (HI)	0.12 ± 0.02	0.13 ± 0.03
Coverage Index	0.95 ± 0.01	0.96 ± 0.02

Note: p-values for CI, HI, and coverage index were 0.321, 0.278, and 0.164, respectively (all $p>0.05$).

6. Summary of Significant Dosimetric Differences

Overall, hippocampus-sparing VMAT plans achieved statistically significant hippocampal dose reductions ($p \leq 0.004$), improved dose homogeneity in low/intermediate PTVs ($p \leq 0.041$), and maintained comparable plan quality indices. The spinal cord, brainstem, and parotids also showed meaningful sparing benefits. A summary of key statistically significant parameters is shown in Table 6.

Table 6. Summary of dosimetric parameters that differed significantly ($p<0.05$) between non-hippocampus-sparing and hippocampus-sparing VMAT plans, showing the direction of change and corresponding p-value for each structure. PTV: planning target volume; HC: hippocampus.

Parameter	Structure	Direction of Change	p-value
D98	PTV intermediate	↑ Improved	0.041
D95, D90	PTV low	↑ Improved	0.008, 0.004
Dmean, Dmax	Ipsilateral hippocampus	↓ Decreased	0.001
Dmean, Dmax	Contralateral hippocampus	↓ Decreased	0.002–0.004
Dmean	Brainstem	↓ Decreased	0.046
Dmean, Dmax	Spinal cord	↓ Decreased	0.001
Dmean	Parotids	↑ Increased (marginal)	0.002–0.008

DISCUSSION

This retrospective dosimetric study demonstrates that hippocampal sparing is feasible during VMAT for locoregionally advanced oropharyngeal carcinoma (LA-OPC), achieving clinically meaningful reductions in incidental hippocampal dose without compromising planning target volume (PTV) coverage or other organ-at-risk (OAR) constraints. Our study was designed to address a specific gap: whether hippocampal dose reduction is feasible in LA-OPC patients treated with VMAT. Although hippocampal avoidance is well established in whole-brain radiotherapy, its adoption for head-and-neck cancers has been slow despite preclinical evidence that even low doses can impair neurogenesis and memory. A recent systematic review of hippocampal-sparing whole-brain radiotherapy (HS-WBRT) reported significantly reduced cognitive decline compared with conventional WBRT; HS-WBRT improved verbal learning and delayed recall with standardised mean differences of 0.42 and 0.25 ($p\approx0.02$) and reduced Montreal Cognitive Assessment deficits ($p<0.00001$) [11]. This meta-analysis underscores the clinical relevance of hippocampal dose reduction and provided the impetus for evaluating similar strategies in extracranial sites.

The demographic profile of our cohort (mean age 56.7 years, all male) mirrors contemporary epidemiological patterns. A 2023 institutional review of oral and oropharyngeal malignancies from India reported that oropharyngeal cancer was predominantly diagnosed in men, with the fifth decade being the most common age group; the base of tongue was the most frequent subsite [3]. Similarly, a 2025 cross-sectional analysis of over 103,000 U.S. OPC cases (2006–2021) found that 80.3% were male and that base of tongue and tonsil were the leading subsites, with the majority of cases presenting with regional disease [4]. Our cohort's predominance of base-of-tongue primaries (55%) and Stage IVA disease (60%) therefore aligns with both regional and national trends, strengthening the generalizability of our dosimetric findings. These demographic congruencies suggest that the patient population most likely to benefit from hippocampal avoidance includes middle-aged men with advanced base-of-tongue or tonsillar tumors—precisely the group represented in our analysis.

Our dosimetric endpoints demonstrate that hippocampus-sparing optimization achieved statistically significant hippocampal dose reductions while preserving tumor coverage, consistent with hippocampal-sparing dosimetric studies in other treatment sites and techniques. A 2024 in silico study comparing conventional and hippocampus-sparing VMAT in nasopharyngeal carcinoma reported comparable reductions in EQD2-converted hippocampal Dmax, Dmean and D40%, with target coverage and other OAR doses maintained despite a modest reduction in PTV homogeneity [13]. Similarly, dosimetric studies evaluating hybrid IMRT/VMAT and fixed-field VMAT techniques for whole-brain radiotherapy have shown that hippocampal dose constraints can be reliably achieved without sacrificing plan quality, reinforcing the generalizability of hippocampal-sparing optimization across arc-based delivery techniques [14,15]. Our data similarly show no significant difference in high-risk PTV coverage, while intermediate- and low-risk PTVs exhibited modest improvements in dose homogeneity, and we additionally observed significant collateral dose reductions to the brainstem and spinal cord. These results extend prior hippocampal-sparing dosimetric findings to oropharyngeal cancer and highlight the potential for incidental hippocampal dose reduction even when baseline exposure is already relatively low.

Comparative literature from other head-and-neck sites reinforces our conclusions. A 2025 retrospective cohort study on postoperative buccal mucosa cancer with infratemporal fossa involvement replanned IMRT cases with hippocampal constraints and achieved substantial reductions in ipsilateral hippocampal Dmax and D40%, without compromising other dosimetric parameters or clinically significant neurocognitive decline [16]. Our study's smaller absolute dose reductions reflect the more distant anatomical relationship between the hippocampus and oropharyngeal PTVs; nevertheless, the consistent direction of benefit across studies supports the rationale for hippocampal sparing in extracranial radiotherapy. When placed alongside prospective evidence that hippocampal avoidance reduces cognitive decline in whole-brain radiotherapy, our data strengthen the argument that even lower incidental doses may contribute to neurocognitive preservation [17].

Clinically, these findings suggest that hippocampal sparing should be considered in VMAT planning for LA-OPC, particularly for patients expected to have long-term survival, as reducing hippocampal dose does not appear to compromise PTV coverage or other OAR constraints. **Limitations:** The retrospective design and small sample size (n = 20) limit statistical power and preclude subgroup analyses; all participants were male, reducing generalizability to female patients. Neurocognitive assessments were not performed, so the clinical impact of the observed dose reductions remains inferred from external literature rather than directly measured. Additionally, the findings derive from a single institution using a specific treatment planning system, which may limit reproducibility across centers. Despite these constraints, this study adds to a growing body of post-2021 evidence indicating that hippocampal dose reduction is both feasible and potentially beneficial in head-and-neck radiotherapy. Prospective trials incorporating neurocognitive endpoints and quality-of-life measures are needed to confirm whether these dosimetric gains translate into clinically meaningful benefits.

CONCLUSION

Hippocampus-sparing VMAT in locoregionally advanced oropharyngeal carcinoma significantly reduces incidental hippocampal, spinal cord, and parotid doses while preserving target coverage and plan integrity. These data support integrating neural avoidance strategies into head-and-neck radiotherapy to minimize potential neurocognitive sequelae without compromising oncologic outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Consideration

This study was approved by the Institutional Ethics Committee of Government Medical College and Rajindra Hospital, Patiala, Punjab (Approval No. Trg 9(310)2023/14803, dated 16 May 2023), and was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments.

Authors' Contribution

SP and NB conceived and designed the study. SP, GS, and VKD contoured the hippocampi, generated the hippocampus-sparing re-optimized plans, and collected the dosimetric data. GS and VKD performed the dosimetric and statistical analysis. SP drafted the manuscript. NB, AB, AKS, S, VKD, and RPSB critically reviewed and revised the manuscript for important intellectual content. RPSB supervised the study and provided overall guidance. All authors read and approved the final manuscript.

[Drafted contribution statement – please confirm or edit individual author roles before submission.]

Declaration of AI Usage

No AI tool was used during the development of this manuscript.

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