Scientific Article

The Hippocampus: A New Organ at Risk for Postoperative Radiation Therapy for Bucco-alveolar Cancer? A Dosimetric and Biological Analysis

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Abstract

Purpose: A significant proportion of patients with bucco-alveolar cancer are long-term survivors, warranting attention to survivorship issues. Decline in neurocognitive function after cranial irradiation for brain tumors correlates with a hippocampal maximum dose (Dmax) of more than 16 Gy, minimum dose (Dmin) of more than 9 Gy, and dose to 40% of the hippocampal volume (D40%) exceeding 7.3 Gy in 2-Gy equivalent dose (EQD2), respectively. We analyzed the utility of sparing the hippocampus in postoperative radiation therapy (PORT) for patients with bucco-alveolar cancer, given the proximity of target volumes to the hippocampus, by virtue of inclusion of the infratemporal fossa.

Methods and Materials: We instituted hippocampal sparing for patients with bucco-alveolar cancer receiving PORT in March 2018. Ten prior and 10 subsequent consecutive patients with pathologically staged I-IVA cancers of the buccal mucosa, alveolus, and retromolar trigone formed the control group (no hippocampal sparing) and the study group (hippocampal sparing), respectively. The brain and temporal lobes were prescribed dose constraints in both groups. Patients received doses of 60 to 66 Gy at 2 Gy per fraction using the image-guided intensity modulated radiation therapy / volumetric modulated arc therapy technique. Treatment plans were evaluated for (1) hippocampal dosimetric parameters, (2) planning target volume dosimetry and plan-quality indices, and (3) biological indices of equivalent uniform dose (EUD) and normal-tissue complication probability (NTCP) for impaired neurocognitive function.

Results: Hippocampal sparing significantly reduced the hippocampal DmaxEQD2, DmeanEQD2, and D40%EQD2 from 27 Gy to 10.9 Gy ($P = .002$), 14.3 Gy to 6.4 Gy ($P = .002$), and 15.5 Gy to 6.6 Gy ($P = .005$), respectively, with comparable plan-quality indices. The radiobiologically robust endpoints of ipsilateral hippocampal EUD ($P = .005$) and NTCP ($P = .01$) were statistically significantly improved.

Conclusions: Meaningful dosimetric benefit, corroborated with radiobiological indices, was observed with hippocampal sparing. The feasibility and benefit of hippocampal sparing supports our view that the hippocampus should be incorporated as an organ at risk and attention should be given to neurocognitive function in patients with bucco-alveolar cancer who are receiving PORT.

Introduction

Bucco-alveolar carcinomas are the most common oral cancers, which are widely prevalent in South Asian countries.[1] Second only to breast carcinoma overall, oral cancers account for 25% to 30% of all cancers in India.[2] Adjuvant (chemo)radiation therapy after surgery forms the current standard of care, owing to the statistically significant benefit in disease-free survival,[3,4] locoregional control,[3,4] and overall survival.[4] Contemporary series report that nearly 70% of patients with bucco-alveolar cancer are alive, disease free, at a median follow-up of 24 months.[5] The evolution of radiation therapy from the conventional to the intensity modulated radiation therapy (IMRT) era has led to an improved therapeutic ratio.[6] Notably, however, the significant reduction in xerostomia with parotid-sparing IMRT in the PARSPORT trial was also associated with an unexpected higher rate of acute fatigue in the IMRT arm.[7,8] The low dose bath associated with IMRT proved significant for causation of radiation-induced brain injury manifesting as fatigue (early) and impaired neurocognition (late).[9,10]

The hippocampus, located in the ventromedial portion of the temporal lobe, is the seat of neurogenesis, owing to the "stem cell niche," rendering it more radiosensitive than other brain substructures.[11] The positive correlation of impaired neurocognitive function (NCF) with temporal-lobe and hippocampal doses is not limited to cranial irradiation (primary and metastatic brain tumors); it has also been associated with head-neck radiation therapy (RT),[10,12-15] primarily thought to be a result of temporal-lobe injury as the mechanism of neurotoxicity.[9,16-19] The correlation between temporal-lobe injury and NCF decline could hypothetically be secondary to

hippocampal hypoxic injury owing to radiation. With the nasopharynx being the most studied primary head-neck subsite for neurotoxicity,[16-23] studies focusing on the hippocampus as an organ at risk (OAR) in bucco-alveolar primary are a rarity.

The proximity of the infratemporal fossa (ITF) to the hippocampus (Fig 1a) and the fact that the ITF is routinely included in the clinical target volume (CTV) in patients with bucco-alveolar carcinoma[24-26] formed the basis of this study.

This retrospective study analyzed the dosimetric benefit of hippocampal sparing in adjuvant (chemo)radiation therapy for bucco-alveolar carcinoma. The currently established dosimetric constraints of impaired neurocognition with hippocampal D40% (dose to 40% of the volume of the hippocampus) EQD2 (equivalent dose in 2-Gy fractions) of more than 7.3 Gy in prospective studies of RT in benign and low-grade brain tumors and with a hippocampal maximum dose (Dmax) and dose to 100% (D100) in whole-brain radiation therapy exceeding 16 Gy and 9 Gy, respectively, were used.[27,28]

To our knowledge, this is the first study to use biological indices of hippocampal equivalent uniform dose (EUD) and normal-tissue complication probability (NTCP) for impaired NCF for corroboration of the physical dosimetric results for this disease site.

Methods

Patients

We instituted hippocampal sparing (HS) in March 2018 for patients with T1-T4aN1-N2 (stage I-IVA)

Figure 1   (a) Axial section of planning computed tomography scan showing the proximity of the infratemporal fossa to the ipsilateral hippocampus. (b) Axial, sagittal, and coronal computed tomography sections (W80; L40) showing hippocampal contours.

cancers of the buccal mucosa, retromolar trigone, and alveolus requiring adjuvant (chemo)radiation therapy postoperatively. Ten consecutive patients treated before instituting HS formed the control group/no-hippocampal-sparing (NHS) group, and 10 subsequent patients with inverse plan optimization for HS constituted the study group (HS group). This was a retrospective proof-of-concept study assessing the benefit of HS in terms of (1) hippocampal dosimetric indices and (2) biological parameters of EUD and NTCP for impaired NCF in patients with bucco-alveolar carcinoma receiving adjuvant (chemo)radiation therapy.

Treatment planning

Treatment planning was initiated after obtaining written informed consent. Patients underwent individual immobilization with a 4-clamp head-neck thermoplastic cast and a planning contrast-enhanced computed tomography (CT) scan with slice thickness of 3 mm from vertex to carina for delineation of CTVs and OARs.

Target delineation

Preoperative CT, magnetic resonance imaging (MRI), positron emission tomography (PET)—CT images were registered with the planning CT. The high-risk CTV encompassed the preoperative gross disease, operative bed, flap with adequate margin including surgical clips and postoperative changes, masticator space, ITF, and involved nodal levels.[25,29]

The protocol for inclusion of neck-nodal levels has been previously reported.[30] The low-risk CTV included uninvolved at-risk nodal levels, ipsilateral nodal levels IA-V, and contralateral levels IB-IV for the node-positive neck and ipsilateral nodal levels IA-IV for the node-negative neck. The contralateral nodal levels IB-IV were also included for lesions involving the floor of the mouth or the lip and lesions reaching or crossing the midline. The sternocleidomastoid muscle was included along the length of the nodal level if abutted by a node or in the surgically violated neck.[30,31] Radiation Therapy Oncology Group (RTOG) guidelines for neck nodal delineation were referred to for contouring of neck nodal levels.[32]

The high-risk CTV and low-risk CTV were isotropically expanded by a 3-mm margin to generate the high-risk and low-risk planning target volume (PTV), respectively. Daily image guidance was performed.

Delineation of OARs

Critical normal structures delineated included the spinal cord, planning risk volume (PRV) spine (3-mm isotropic margin to the spinal cord), brain, temporal lobes, brain stem, optic apparatus, parotid glands, cochlea, normal oral cavity and mucosa, lens, lacrimal glands, larynx, and dysphagia- and aspiration-related structures.[32] The hippocampus was delineated prospectively for all patients in the study (HS) group and retrospectively for the control (NHS) group on the planning CT scan. A window width of 80 and level of 40, with manual adjustments as necessary, were used for delineation of hippocampi on the planning CT (Fig 1b), admittedly a deviation from the contouring recommendations advocating the use of T1-weighted MRI.[33] Hippocampus delineation followed anatomic principles as elucidated by Scoccianti et al.[34] The consistent approach was to identify the temporal horn of the lateral ventricle and the ambient and quadrigeminal cisterns as the lateral and medial landmarks, respectively, to contour the gray matter of the hippocampus.[34] The hippocampi were isotropically expanded by a margin of 5 mm to generate the PRV hippocampus.

Dose prescription and treatment planning

The high-risk PTV and low-risk PTV were prescribed a dose of 60 Gy and 52 Gy, respectively, in 30 once-daily fractions using simultaneous integrated boost, with IMRT/RapidArc and daily image guidance with cone beam CT scans. Patients with high-risk adverse features, microscopically positive or close margins, extracapsular extension, and/or perineural spread were prescribed doses of 66 Gy and 54 Gy in 33 once-daily fractions to the high-risk PTV and low-risk PTV, respectively. Concurrent chemotherapy was administered when necessitated as per guidelines.[3,4] Treatment planning was done using Eclipse (Varian Medical Systems, Palo Alto, California), and patients were treated using a Novalis Tx (Brainlab AG, Munich, Germany; Varian Medical Systems) linear accelerator. Inverse optimization was used to achieve dose constraints for OARs as per Quanititative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations.[35] In view of a lack of consensus regarding the dose constraint for the hippocampus in head-neck RT, unlike for other cranial OARs such as the left temporal lobe,[36,37] brain stem, and cerebellum,[8] we persisted with standard constraints of whole-brain irradiation of a hippocampal Dmax less than 16 Gy and D100 (dose to 100% of the volume of the hippocampus) less than 9 Gy, as per RTOG-0933.[28] The optimization objectives used for the PRV of the hippocampus and other OARs has been depicted in Figure E1.

Plan evaluation—hippocampus

Dosimetric objectives

Plans were assessed for the EQD2 of the Dmax, the mean dose (Dmean), the minimum dose (Dmin/D100), and the dose to 40% of the volume (D40%) of the bilateral, ipsilateral, and contralateral hippocampi using a

hippocampal α/β value of 2.[27] The biological indices EUD and NTCP were calculated.

Biological indices

The EUD, the single-metric representation of a nonuniform dose distribution, was calculated as elaborated by Niemierko et al.[38] The calculation of NTCP was based on the EUD model, a simpler alternative to the Lyman model and known to replicate the Lyman calculation to within approximately 0.3%[39] (Fig E1).[38−45]

Plan evaluation—PTV

Dose-volume histogram evaluation of high-risk PTV and low-risk PTV for comparison of coverage between the HS and the NHS groups was performed. In addition, comparative plan-quality indices, homogeneity index,[40] a modification of coverage index,[40,44] and Paddick conformity index[41] were used to assess the effect on PTV coverage, although this is not a part of our routine clinical practice in head-neck RT (Fig E1).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 22.0 (IBM Corp, Armonk, New York) or R-environment, version 3.2.0 (R core team, Austria). Continuous parameters such as DmaxEQD2, DminEQD2, DmeanEQD2, and D40%EQD2 were compared using Student t tests. Statistical significance was set at $P < .05$.

Results

Patient characteristics

Patients in both groups, HS and NHS, had comparable characteristics (Table 1), with a notable exception of the radiation technique. Seven patients in the HS group received VMAT and 3 received IMRT, whereas only 1 patient in the NHS group was treated with the VMAT technique and none with IMRT. The retrospective discovery of the unintentional noncomparable technique distribution in the 2 patient cohorts was presumed to be a potential confounder and prompted us to perform a second analysis using replanning with VMAT for both patient cohorts (pan-VMAT analysis). However, replanning of both cohorts with VMAT was done, keeping the status quo of hippocampal sparing (for patients in the HS group) or not sparing (for patients in the NHS group) intact.

Table 1   Patient characteristics

Characteristic	Hippocampal sparing group, no. (n = 10)	No hippocampal sparing group, no. (n = 10)
Age, y	57	55
Wide local excision	1	3
Composite resection	9	7
Neck dissection		
Modified	4	4
Radical	3	4
Supraomohyoid	3	2
Tumor characteristics		
Mandible involvement	4	4
Perineural invasion	4	5
RMT involvement	5	5
Extra-capsular extension	1	1
Tumor stage		
I	1	2
II	1	1
III	3	1
IVA	5	6
Radiation technique		
IMRT	3	9
VMAT	7	1
Radiation technique for analysis 2		
IMRT	0	0
VMAT	10	10

Abbreviations: IMRT = intensity modulated radiation therapy; RMT = retromolar trigone; VMAT = volumetric modulated arc therapy.

Treatment parameters—PTV

The high-risk PTV and low-risk PTV volumes in the HS and NHS groups were comparable, and evaluation of all the plans revealed comparable PTV coverage in both the cohorts, as shown in Table 2. Comparison of the plan-quality indices showed no statistically significant difference between the HS and NHS groups (Table 2), thus establishing a treatment isoeffect, which was found to be sustained after second analyses using VMAT for all patients.

Treatment parameters—hippocampus

Dosimetric parameters

Bilateral hippocampal DmaxEQD2, DmeanEQD2, DminEQD2, and D40%EQD2 showed statistically significant reduction from the mean value of 27 Gy to 10.9 Gy, of 14.3 Gy to 6.4 Gy, of 6.1 Gy to 3.7 Gy, and of 15.5 Gy to 6.6 Gy in the NHS and HS groups, respectively

Table 2 Plan evaluation parameters

PTV Parameters	No hippocampal sparing group (n = 10)	Hippocampal sparing group (n = 10)	P value
High-risk PTV volume, cm³*	673.46 ± 145.7	690.0 ± 367.4	.89
Low-risk PTV volume, cm³*	212.0 ± 158.6	242.4 ± 111.7	.62
High-risk PTV 100% coverage, %	86.4	88.9	.48
High-risk PTV 95% coverage, %	98.9	98.2	.12
Low-risk PTV 100% coverage, %	89.7	86.4	.63
Low-risk TV 95% coverage, %	98.7	98.0	.51
Plan quality indices*			
Homogeneity index	11.9 ± 2.2	10.59 ± 4.5	.40
Coverage index	0.96 ± 0.01	0.97 ± 0.02	.25
Paddick conformity index	0.85 ± 0.08	0.78 ± 0.09	.11
Organs at risk			
Brain stem maximum dose, Gy,*	42.5 ± 8.1	43.8 ± 6.8	.71
Brain stem mean dose, Gy,*	27.0 ± 9.1	21.3 ± 3.9	.09
Whole-brain mean dose, analysis 1, Gy*	13.6 ± 3.3	10.9 ± 3.7	.11
Whole-brain mean dose, analysis 2, Gy*	10.7 ± 3.7	10.1 ± 4.3	.74
Left temporal lobe, analysis 1, Gy,*			
Mean dose	22.06 ± 5.7	16.92 ± 5.1	.04
V13, %	32.41 ± 8.5	26.56 ± 8.9	.15
V23, %	28.25 ± 7.4	21.97 ± 6.6	.06
Left temporal lobe, analysis 2, Gy*			
Mean dose	17.1 ± 6.2	15.6 ± 4.6	.54
V13 %	26.0 ± 10.6	24.8 ± 7.5	.78
V23 %	23.1 ± 7.8	20.3 ± 5.6	.37
Spinal cord maximum dose, Gy*	40.8 ± 2.8	39.9 ± 1.4	.38
PRV spinal cord maximum dose, Gy*	45.1 ± 1.5	45.8 ± 2.2	.43

Abbreviations: PRV = planning risk volume; PTV = planning target volume; V13 % = dose received by 13% volume of left hippocampus in Gy; V23 % = dose received by 23% volume of left hippocampus in Gy.

  * Mean ± standard deviation.

(Table 3). Ipsilateral hippocampal dosimetric parameters also showed statistically significant reduction with HS, as detailed in Table 3 and depicted as a representative dose-volume histogram comparison in Figure 2. The benefit was sustained after the second analysis for correction of technique and remained statistically significant, except for DminEQD2. With application of hippocampal dose constraints as per RTOG-0933,[28] the criteria suggested for gliomas, that the hippocampal D40%EQD2 should not exceed 7.3 Gy, could be met in only 1 patient in the NHS group and 6 patients in the HS group.

Biological indices

Hippocampal EUD. Hippocampal sparing significantly reduced both the bilateral and ipsilateral hippocampal EUD from 58.6 Gy to 21 Gy (P = .003) and from 62.1 Gy to 22.7Gy (P = .005), respectively. Statistically significant reduction of EUD was also noted after pan-VMAT analysis in the HS group (Table 3).

NTCP for NCF impairment. The NTCP for impaired NCF was reduced from 0.4 to 0.00004 (P = .01) for the

bilateral hippocampus and from 0.4 to 0.0001 (P = .01) for the ipsilateral hippocampus (Table 3).

Contralateral hippocampi

Evaluation of the contralateral hippocampus in both the first and second analyses revealed a statistically significant reduction in dosimetric parameters (Table 3). Figure 3 depicts a rare instance of the Dmax of the contralateral hippocampus exceeding that of the ipsilateral hippocampus, signifying the importance of achieving dose constraints for bilateral hippocampi.

Nonhippocampal cranial OARs

Hippocampal sparing did not lead to a consequential increase in doses of other cranial subregions (Table 2). The whole-brain Dmean in the HS group and the NHS group were 10.1 Gy and 10.7 Gy, respectively (P = .74). The left temporal doses were reduced in the HS group; however, only the reduction in Dmean from

Table 3　Hippocampal parameters

Parameter	Analysis 1[*]			Analysis 2[†]		
	No hippocampal sparing group, mean (range) (n = 10)	Hippocampal sparing group, mean (range) (n = 10)	P value	No hippocampal sparing group, mean (range) (n = 10)	Hippocampal sparing group, mean (range) (n = 10)	P value
Bilateral hippocampus						
DmaxEQD2, Gy[‡]	27 (11.2-50)	10.9 (5.63-15)	.002	22.7 (11.2-49.2)	10.2 (5.6-15.0)	.008
DmeanEQD, Gy[‡]	14.3 (5.8-28.7)	6.4 (3.78-10.5)	.002	9.6 (4.7-16)	5.8 (2.5-10.5)	.024
D40%EQD, Gy[‡]	15.5 (7.5-33.1)	6.6 (4.0-10.7)	.005	9.9 (4.6-16.6)	5.6 (2.4-10.7)	.02
EUD, Gy[‡]	58.6 (23.1-113.5)	21 (10.9-31.4)	.003	44.1 (18.8-90.9)	19.4 (9.8-31.4)	.007
NTCP for impaired NCF	0.4	0.00004	.01	0.22	0.00004	.05
Ipsilateral hippocampus						
DmaxEQD2, Gy[‡]	26.5 (10.9-51.2)	10.9 (5.37-15)	.04	22.5 (10.9-49.2)	10.2 (5.3-15.1)	.009
DmeanEQD, Gy[‡]	16.8 (6.95-29.8)	7.2 (4.09-10.8)	.004	11.9 (5.3-18.4)	6.5 (3.2-10.8)	.008
D40%EQD, Gy[‡]	19.1 (7.5-36.7)	7.5 (4.2-10.1)	.006	12.9 (5.1-20.2)	6.8 (3.6-10.9)	.008
Equivalent uniform dose, Gy[‡]	62.1 (24.8-120.6)	22.7(11.2-32.3)	.005	48.3 (20.6-102.2)	20.7 (11.0-32.3)	.007
NTCP for impaired NCF	0.4	0.0001	.01	0.3	0.0001	.03
Contralateral hippocampus						
DmaxEQD2, Gy[‡]	20.2 (9.5-40.4)	8.6 (5.6-13.6)	.002	13.3 (7.1-27.8)	8.1 (4.2-13.6)	.037
DmeanEQD, Gy[‡]	12.2 (5.1-28.7)	5.5 (3.5-10)	.01	7.3 (3.9-14.6)	5.5 (2.5-10)	.137
D40%EQD, Gy[‡]	13.5 (6.4-32.5)	5 (1.3-10.3)	.007	7.7 (3.8-15.7)	4.4 (1.3-10.3)	.051

Abbreviations: DmaxEQD2 = maximum dose in 2 Gy per fraction equivalent dose in Gy; DmeanEQD2 = minimum dose in 2 Gy per fraction equivalent dose in Gy; D40%EQD2 = dose received by 40% volume of hippocampus in 2 Gy per fraction equivalent dose in Gy; NTCP = normal tissue complication probability; NCF = neurocognitive function.

　* Noncorrected for varied technique distribution of intensity modulated radiation therapy and volumetric modulated arc therapy in study and control groups, respectively.

　† Corrected for technique distribution, volumetric modulated arc therapy for both study and control groups.

　‡ Mean (Range).

22 Gy (NHS group) to 16.9 Gy (HS group) was statistically significant.

Discussion

The functioning of the memory formation system has been a widely researched subject and is understood to be a well-orchestrated relay of information between substructures of the medial temporal lobe of the brain. The neocortex forms the entry point for the new information, which then is relayed through the perirhinal cortex to reach the dentate gyrus and the CA3 and CA1 subregions of the hippocampus. The hippocampus is the seat where new information is integrated and processed into a memory, and whereas all medial temporal lobe substructures are important for acquiring, storing, and retrieval of facts and events, hippocampal integrity is critical for the conscious recollection of new information, also termed as declarative memory.[46] Impaired microcirculation secondary to radiation results in hypoxic injury, most severely affecting the CA1 subregion of the hippocampus, which is crucial for memory formation and recall; thus, neurocognitive decline results.[9]

Neurocognitive decline in head-neck cancer remains a sparingly discussed and documented problem, even more so in bucco-alveolar carcinoma. Among the studies focusing on treatment-induced NCF decline in non−central nervous system cancers, the majority have investigated cancers of the nasopharynx and paranasal sinuses, given the rather high incidental low-dose bath to the brain tissue in these subsites.[16-23] However, patients with bucco-alveolar carcinoma receiving adjuvant (chemo)radiation therapy also inadvertently receive a subnecrotic but potentially significant low-dose bath to
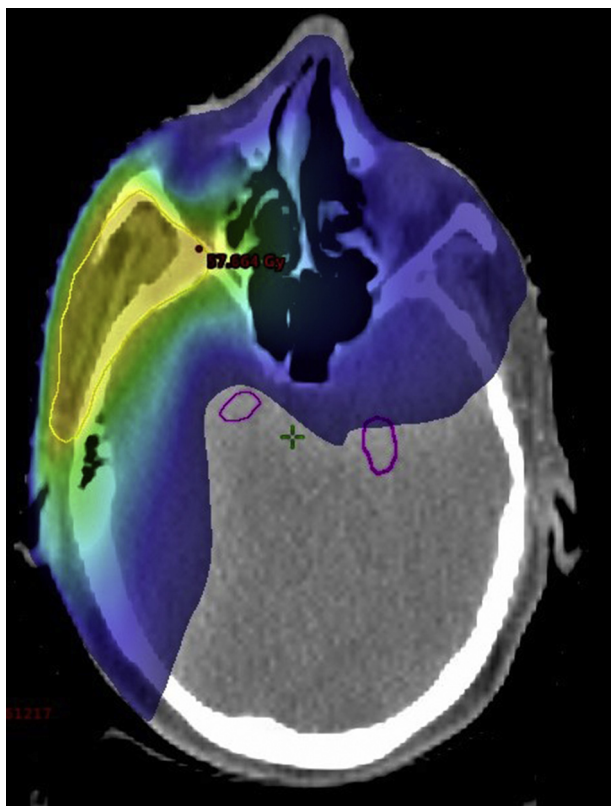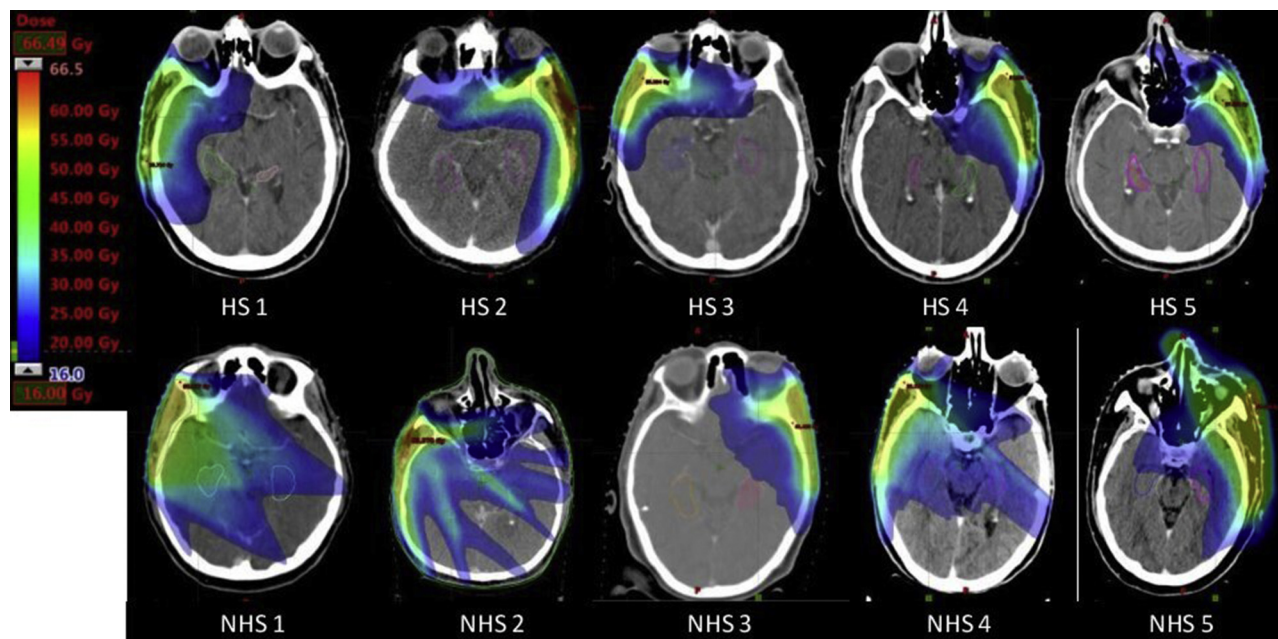
Figure 2 Axial section of planning CT depicting a HS plan with the dose spill reaching upto contralateral hippocampus.

the hippocampal avoidance region, consequent to the proximity of the ITF and the PTV to the ipsilateral hippocampus.

The ITF is at risk for recurrence in patients with bucco-alveolar primaries secondary to retrograde spread of the tumor through the inferior alveolar and mental nerve and possibly soft-tissue spread through the retromolar trigone and the pterygoid muscles to the ITF and skull base.[24] Yao et al, in their retrospective study, noted that of 49 patients who received postoperative IMRT for oral cavity squamous cell carcinoma, 9 patients failed locoregionally. Two of those failed in the ITF, and both had retrograde tumor extension through the inferior alveolar nerve and extensive perineural invasion.[24] Unlike nodal recurrences, which are often managed by salvage surgery, ITF recurrences can be difficult to salvage. Based on their experience, Yao et al advocated inclusion of the ITF in all cases with ITF or retromolar trigone involvement where the tumor is adjacent to the mental/inferior alveolar nerve, when there is extensive perineural invasion, or when the tumor invades pterygoid muscle. Lai et al, in their study of 150 patients, reported ITF failure in 5 patients, all of whom had perineural invasion; 4 of the 5 failures were marginal, implying suboptimal coverage of the ITF.[26] As an institutional policy, we include the ITF in high-risk CTV up to 60 Gy and the suprazygomatic region in low-risk CTV.

The prospective studies of hippocampal sparing in cranial irradiation by Gondi et al proved the association of impaired NCF with hippocampal D40%EQD$_2$ of more than 7.3 Gy in primary brain tumors warranting partial brain treatment and with the hippocampal Dmax exceeding 16 Gy and the D100 exceeding 9 Gy in the metastatic setting requiring whole-brain radiation


Figure 3 Representative axial sections of planning computed tomography scans of 5 patients in the hippocampal sparing group (top row) and 5 in the no hippocampal sparing group (bottom row), depicting the 16-Gy isodose washes with hippocampal contours. The substantial overlap between hippocampi and dose spill can be appreciated in the no-hippocampal-sparing plans. The 16-Gy isodose corresponds to an equivalent dose, in 2-Gy fractions, of 10 Gy.

therapy.[27,28] In view of this, as a proof of concept for further prospective clinical studies, we analyzed the dosimetric benefit (or the lack thereof) of hippocampal sparing in patients with bucco-alveolar carcinoma receiving adjuvant (chemo)radiation therapy without negatively affected plan quality. In addition, biological indices of hippocampal EUD and NTCP were compared for corroboration of the effect of dosimetry on NCF impairment.

In this study, patients whose radiation prescription did not include dose constraints for the hippocampus (the NHS group) were noted to have an incidental bilateral hippocampal D40%EQD2 of 15.5 Gy (range, 7.5-33.12 Gy), a twofold increase from the recommended dose limit ascertained by Gondi et al; this is depicted in Figure 4, which shows considerable overlap between the 16-Gy

dose wash and the hippocampi in NHS plans. In comparison, patients treated with plans using hippocampal dose constraints (the HS group) had a corresponding D40%EQD2 of 6.6 Gy (range, 4.0-10.7 Gy), thus achieving a statistically significant ($P = .005$) and substantial 57.4% reduction with hippocampal sparing. This validates our premise of the feasibility and utility of hippocampal sparing in patients with bucco-alveolar carcinoma. Similarly, the DmaxEQD2, DmeanEQD2, and DminEQD2 of the bilateral hippocampus also showed statistically significant percentage reductions of 59.6%, 55.2%, and 38.1%, respectively.

Two separate analyses were performed, addressing the skew toward VMAT in the study group. A comparison of IMRT versus VMAT for whole-brain hippocampal sparing treatment plans by Kendall et al has shown that
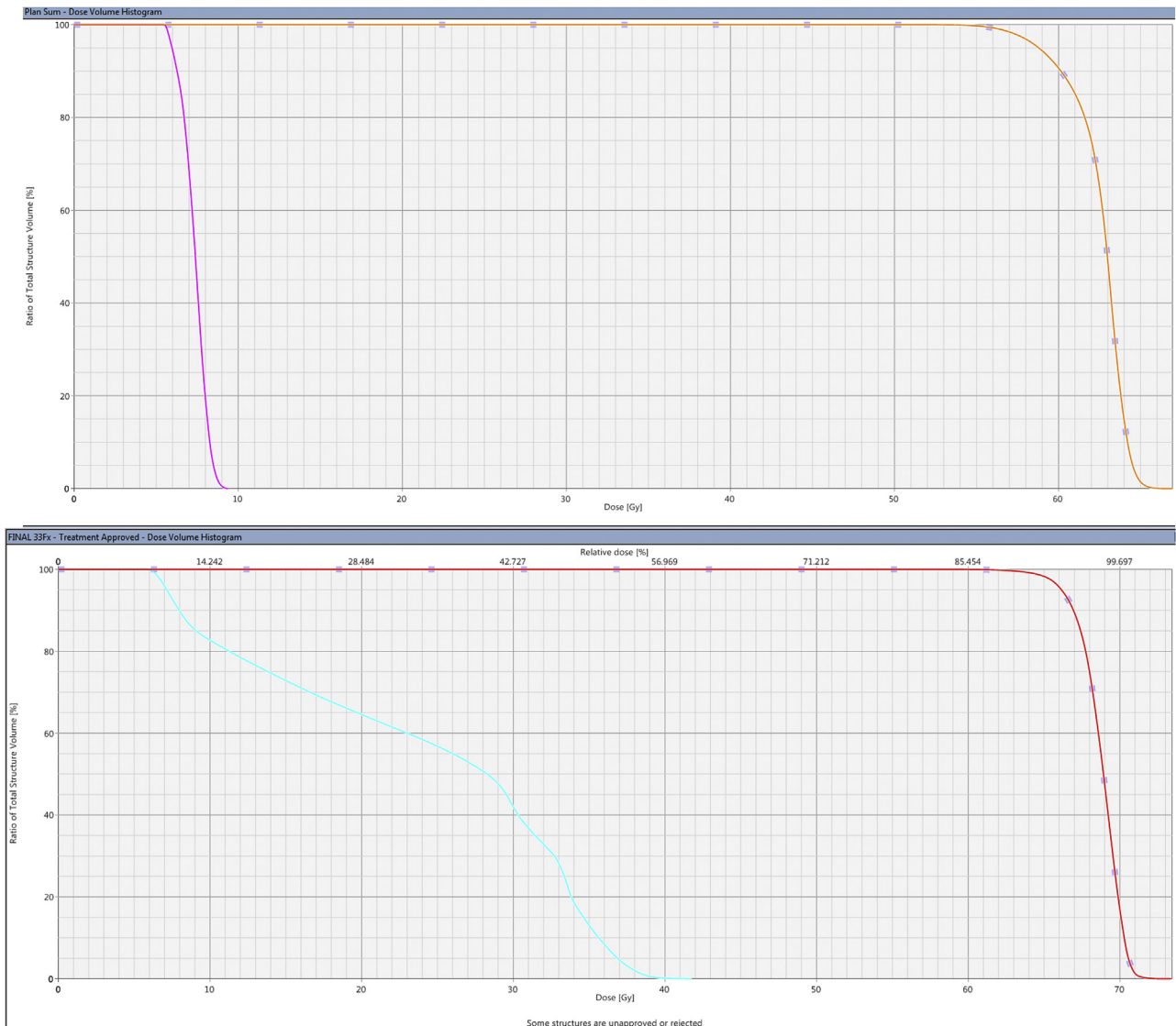
Figure 4 Dose-volume histograms (DVHs) of representative patients in hippocampal sparing (above) and no hippocampal sparing group (below) depicting doses to PTV and the ipsilateral hippocampi.

IMRT plans had a higher NTCP value.[42] Thus, the second replanning (with VMAT plans) and analysis was aimed at eliminating this potential confounder; the findings confirmed the dosimetric benefit of hippocampal sparing in all parameters but DminEQD2, with statistically significant percentage reductions of 55.0%, 39.5%, and 43.4% of the DmaxEQD2, DmeanED2, and D40%EQD2, respectively. The 20.1 % reduction in the DminEQD2 with the HS technique, however, was not statistically significant. We considered it pertinent to compare and report the findings of both the analyses to highlight the close congruency of the dosimetric and biological benefit derived from hippocampal sparing between what was delivered for the patients in our routine clinical practice compared with what was planned in retrospect using VMAT for the entire cohort.

The reductions in the dosimetric parameters observed for the bilateral hippocampi with hippocampal sparing were mirrored for ipsilateral and contralateral hippocampi. This dosimetric benefit, importantly, did not come at the expense of an increase in the doses to other OARs or deterioration in plan-quality metrics.

The left hippocampus, whether ipsilateral or contralateral, warrants close attention because it asserts a stronger effect on verbal episodic memory compared with the right hippocampus.[47] Notwithstanding the fact that dose constraints for the left temporal lobe were given for both cohorts, left temporal lobe sparing was noted to be significantly better in the HS group than the NHS group, as reflected by Dmeans of 16 Gy and 22 Gy, respectively. This difference, however, was not sustained in the second analysis using VMAT for all patients. Thus, the contribution of hippocampal sparing to reduced left temporal doses is still uncertain and warrants further study.

The study of the biological consequences of radiation has evolved from estimating the absorbed dose in tumors and normal tissues with experience and statistically driven concepts of dose, time, and fractionation to radiobiologically more robust EUD and TCP/NTCP-modeled biologically based treatment planning.[48] These postulate that a single parameter, unlike multiple dose volume constraints, can capture a dosimetric snapshot of the biological response correlating with the risk of radiation injury.[43] Our analysis indicated a statistically significant reduction in hippocampal EUD and NTCP for impaired NCF, in addition to the dosimetric parameters, implying a biological corroboration of the dosimetric benefit of hippocampal sparing.

The calculated NTCP for impaired NCF in the NHS group of this study is in close agreement with the results of Dunlop et al,[49] who compared standard IMRT plans and hippocampal- and brain-sparing RT plans for 10 patients with head-and-neck cancer. The patients in the current study's control group (NHS group) had a mean NTCP for impaired NCF of 0.4, whereas the 2 non-nasopharyngeal patients in the study by Dunlop et al, both of whom had squamous cell carcinoma of unknown primary, had corresponding probabilities of 0.05 and 0.11.[49] The marginally higher NTCP in this study's analysis is possibly a result of the relative proximity of the CTV and the hippocampus, leading to an increase in the number of shared axial planes between them, secondary to ITF inclusion in the high-risk/low-risk CTV (Figs 1 and 4). Thus, the NTCP of impairment in NCF for patients with bucco-alveolar carcinoma, although lower compared with that of nasopharyngeal patients, is higher than that reported for squamous cell carcinoma of unknown primary, and in our experience, it can be significantly reduced further by a simple planning maneuver. To our knowledge, the present study is the first to focus on the dosimetric and radiobiological utility of hippocampal sparing in this disease site.

The hippocampal NTCP model suggested by Gondi et al[27] was evaluated in a retrospective study by Jaspers et al in a cohort of patients with low-grade glioma.[50] The authors inferred an overestimation of cognitive decline when assessed by the model of D40% of the bilateral hippocampus and advocated for caution in extrapolation of this model outside of the specified dose-volume parameters. An important caveat, however, was the relatively shorter endpoint of 18 months chosen for neurocognitive assessment after radiation therapy. This was reinforced by studies that found significant cognitive decline only after a longer follow-up of about 5 years after treatment[51,52] and also studies with a shorter follow-up that showed only transient and insignificant neurocognitive decline.[53]

The strengths of this study, in addition to the premise that underscores the relevance of neurocognition preservation in bucco-alveolar cancers, are (1) both dosimetric and biologic endpoints were used to quantify the benefit of hippocampal sparing, (2) the 2 analyses that were done primarily to account for a confounder also serve to offer a glimpse of the real clinic scenario. The relatively small sample size and the imaging modality used for hippocampal delineation are 2 important limitations in this study. The hippocampus was delineated using multiple modulations of the window-level widths on CT images; however, the same cannot substitute a T1-weighted MRI sequence. Notwithstanding the uncertainties associated with hippocampal delineation on CT, 2 facets should encourage further studies using T1-weighted MRI for hippocampal sparing in this group of patients. First, the use of a 5-mm uniform margin for the hippocampal avoidance region resulted in an avoidance volume significantly larger than the hippocampus, thus offering reasonable confidence that the hippocampus was encompassed. Second, our work in this study was proof of principle and used retrospective analyses of 2 planning

approaches in a tumor subsite that routinely does not necessitate postoperative MRI scans. In our opinion, this proof of principle of the benefit of hippocampal sparing in patients with bucco-alveolar carcinoma requiring adjuvant radiation therapy should be further validated in a prospective study in a larger cohort using postoperative planning MRI for hippocampal delineation.

Conclusion

Hippocampal sparing in adjuvant radiation therapy for bucco-alveolar carcinoma results in a significant reduction of all dosimetric parameters, hippocampal EUD, and NTCP for impaired NCF. Prospective studies with a larger sample size and with clinical neuropsychological assessments are required to further the understanding of neurocognitive decline in this subset of patients. However, dosimetric benefit, corroborated with biological parameters, substantiates our hypothesis and warrants attention to the hippocampus as an organ at risk in bucco-alveolar carcinoma patients receiving adjuvant radiation therapy.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2021.100681.

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