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FULL PAPER

# Evaluation of hippocampus dose for patients undergoing intensity-modulated radiotherapy for nasopharyngeal carcinoma

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**Objective:** To evaluate the dose received by the hippocampus among patients undergoing intensity-modulated radiotherapy (IMRT) for nasopharyngeal cancer.

**Methods:** 10 patients with biopsy-proven, locally advanced nasopharyngeal cancer constituted the study population. The total prescribed dose to the planning target volume (PTV) was 70 Gy (*D*95%) delivered in 2.12-Gy daily fractions using IMRT. Using established anatomical guidelines, MRI co-registration and the assistance of a board-certified neuroradiologist, the right and left hippocampi were delineated on axial imaging from the CT scan obtained at simulation for each patient beginning at the most anterior portion of the lateral ventricle. IMRT treatment plans were generated without dose–volume constraints to the hippocampus. A range of dose–volume statistics was calculated.

**Results:** The mean hippocampus volume was 6.01 ± 2.61 $cm^3$. The mean *V*20 was 72.2%; *V*40 was 22.0%; *V*50 was 10.2%; and *V*60 was 5.5%. The average mean, minimum and maximum hippocampus doses were 30.27 Gy (range, 19.08–47.99 Gy); 17.54 Gy (range, 11.66–33.17 Gy); and 54.95 Gy (range, 35.59–75.57 Gy), respectively. The hippocampus received a maximum dose exceeding 70 Gy in 30% of cases.

**Conclusion:** Our dosimetric analysis suggests that, for patients undergoing IMRT for nasopharyngeal cancer, the hippocampus routinely receives significantly high doses.

**Advances in knowledge:** The hippocampus receives a fair amount of incidental radiation during treatment for nasopharyngeal cancer. Given the importance of this structure with respect to memory and neurocognitive function, consideration should be given to identifying the hippocampus as a critical organ at risk in the IMRT optimization process.

Although intensity-modulated radiotherapy (IMRT) has supplanted two-dimensional and three-dimensional radiotherapies as the standard treatment for patients with head and neck cancer, it has become increasingly clear that the generation of highly conformal plans with steep fall-off gradients may come at the expense of significant doses to non-delineated extra-target organs.[1] Owing to the anatomical proximity of many head and neck cancers to the central nervous system, studies investigating the effects of radiation exposure on specific structures in the brain responsible for neurocognitive functioning may be warranted.

Located within the temporal lobes, the hippocampus is a horseshoe-shaped paired structure that is a critical component of the limbic system. Its functions relate to the formation of new memories, spatial navigation and the connection of emotions and senses, such as smell and sound, to memories. Although the tolerance of this structure to radiation has yet to be fully established, it has been hypothesized that incidental exposure to this structure may contribute to both short-term toxicity, such as lack of inhibition and disequilibrium, as well as long-term memory loss.[2] Thus, the purpose of this study was to conduct a dosimetric analysis in patients with

nasopharyngeal cancer treated by IMRT to assess incidental exposure to the hippocampus.

## METHODS AND MATERIALS

### Patients

10 consecutive patients with biopsy-proven, locally advanced nasopharyngeal cancer treated by IMRT constituted the subject population. Table 1 lists patient and treatment characteristics. At simulation, the head, neck and shoulders were immobilized in a hyperextended position using a perforated, thermoplastic head mask with the neck supported on a Timo cushion (S-type; MedTec, South Plainfield, NJ) mounted on a carbon fibre board (S-type; MedTec, Orange City, IA) that allowed patient positioning to be indexed. The isocentre was placed within the primary tumour. Axial slices with 3-mm spacing were obtained on a CT-based simulator (Picker PQ 2000; Philips Healthcare, Andover, MA) and transferred into the Pinnacle treatment planning system (TPS).

### Intensity-modulated radiotherapy treatment planning

Our institutional policy with respect to IMRT target volume delineation and planning has previously been described.[3] The gross tumour volume (GTV) was defined as the extent of tumour demonstrated by imaging studies and physical examination, including endoscopy. MRI registered with the CT data set was used to assist in defining the extent of tumour. Three clinical target volumes (CTVs) were defined: CTV1, which included the GTV with a 5- to 10-mm margin to account for microscopic spread (in cases with disease in close proximity to the brain stem and optic apparatus, the expansion could be as small as 1 mm); CTV2, which included nodal areas at high risk for recurrence; and CTV3 for low-risk nodal regions. An additional margin of 3 mm was added to the CTVs to compensate for the variabilities of treatment set-up and internal organ motion to create separate planning target volumes (PTVs) corresponding to PTV1, PTV2 and PTV3, respectively.

The IMRT goal was to deliver a prescribed dose of 70 Gy to at least 95% of the PTV1 and 59.4 and 54 Gy to at least 95% of the PTV2 and PTV3, respectively, over 33 treatments with once-daily fractionation. Plans were optimized using an inverse planning module that used a conjugate gradient optimization algorithm, which permitted real-time modification of the optimization parameters, encouraging user interactivity to minimize the overall optimization time. The dose prescription was based on a dose distribution corrected for heterogeneities. The plans were evaluated both quantitatively with dose–volume histogram (DVH) analysis and qualitatively by visually inspecting isodose curves on axial slices. The hippocampus was not specifically assigned as a critical structure delineated for avoidance.

Table 1. Patient characteristics

| Patient number | Age | Gender | Stage |
|---|---|---|---|
| 1 | 44 | F | T4N3b |
| 2 | 48 | F | T4N2 |
| 3 | 36 | M | T2N2b |
| 4 | 53 | M | T4N2 |
| 5 | 72 | M | T4N1 |
| 6 | 41 | M | T3N2 |
| 7 | 63 | M | T4N2 |
| 8 | 24 | M | T4N1 |
| 9 | 19 | F | T4N2 |
| 10 | 54 | M | T4N2 |

F, female; M, male.

### Hippocampus contouring

For each patient, the hippocampus was retrospectively delineated on axial images from CT obtained at the time of simulation. Using the established anatomical guidelines by Chera et al,[4] MRI coregistration and the assistance of a board-certified neuroradiologist, the right and left hippocampi were contoured beginning at the most anterior portion of the lateral ventricle, where the medial, lateral and anterior portions of the hippocampus were identified.[4] The superior boundaries of the hippocampus consisted of the most medial region of the temporal lobe. The inferior boundaries of the hippocampus were defined at the level of the pons and pituitary gland. A range of dose–volume statistics for each patient's hippocampus was then calculated. Figure 1 demonstrates sample contours of the hippocampus, with representative planning tumour volume and isodose lines. The one-way ANOVA test was used to assess for potential predictors of high hippocampus dose. Variables analysed included T-stage, intracranial extension, infratemporal fossa involvement and/or cranial nerve palsy. A $p$-value of 0.05 was considered statistically significant.

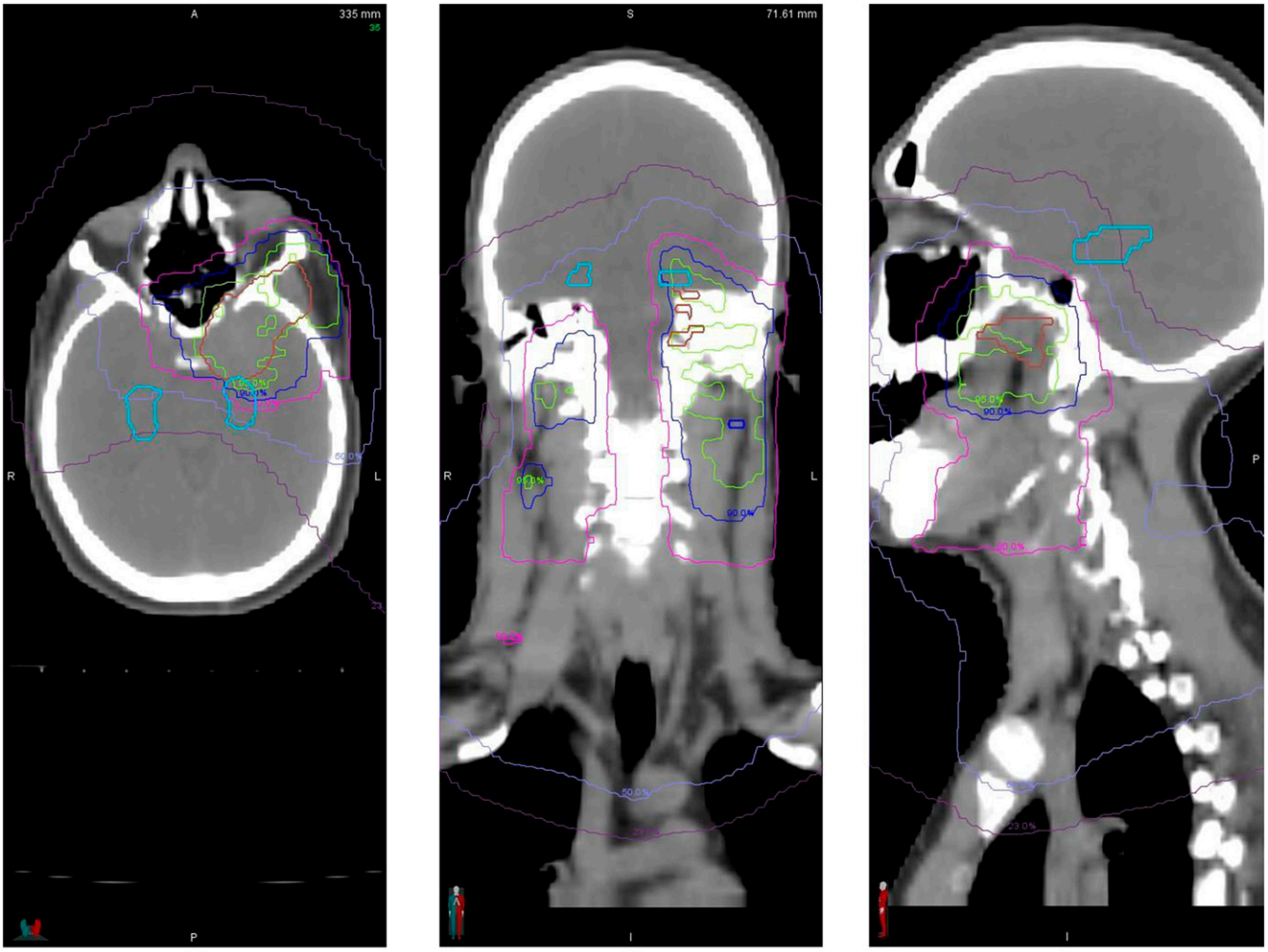
### Case study

The feasibility of hippocampus-sparing IMRT was then assessed prospectively in a single patient presenting with T4N0 nasopharyngeal cancer. The patient was first planned without designation of the hippocampus as an avoidance structure. Notably, the ipsilateral and contralateral temporal lobes were constrained (with a target of limiting the volume receiving 70 Gy to $<5\%$ of each structure). The patient was then replanned with intentional sparing of the hippocampus (using constraint limits of 40 Gy maximum and 20 Gy mean), and the dose–volume statistics were compared.

## RESULTS

The mean hippocampus volume was $6.01 \pm 2.61\ cm^3$. Table 2 summarizes the dosimetric characteristics for each respective patient. The mean irradiated hippocampus volumes receiving $\geq$20 Gy was $4.51 \pm 2.98\ cm^3$ ($V20$); $\geq$40 Gy was $1.45 \pm 1.87\ cm^3$($V40$); $\geq$50 Gy was $0.72 \pm 1.19\ cm^3$($V50$); and $\geq$60 Gy was $0.35 \pm 0.52\ cm^3$($V60$). The proportion of the hippocampus volume irradiated by $\geq$20 Gy was 72.2% (range, 32–100%); $\geq$40 Gy was 22% (range, 0–72%); $\geq$50 Gy was 10.2% (range, 0–35%); and $\geq$60 Gy was 5.5% (range, 0–21%). As summarized in Figure 2, the average minimum dose to the entire hippocampus was 17.54 Gy (range, 11.66–33.17 Gy); the average maximum point dose to the hippocampus was 54.95 Gy (range, 35.59–75.57 Gy); and the average mean dose to the entire hippocampus volume was 30.27 Gy (range, 19.08–47.99 Gy). None of the analysed variables, including T-stage, intracranial extension,

Figure 1. Visual illustration of the contoured hippocampus in (a) axial, (b) coronal and (c) sagittal views on CT image. The hippocampus contour is represented bilaterally. Starting from the centre, planning tumour volume and isodose lines (95%, 90%, 80%, 50% and 23%) are represented by the progressive contours shown. Maximal point dose for this patient was 75.57 Gy. Of interest, a significant portion of both ipsilateral and contralateral hippocampus contours received incidental radiation from intensity-modulated radiotherapy. HPC, hippocampus; PTV 54, low-dose planning target volume; PTV 70, high-dose planning target volume.




(a) (b) (c)

infratemporal fossa involvement or cranial nerve palsy, predicted for maximum dose to the hippocampus ($p > 0.05$, for all).

For the case subject who was planned prospectively, the maximum and mean doses were 65.7 and 47.3 Gy, respectively, without designation of the hippocampus as an avoidance structure. However, with hippocampus-sparing IMRT planning, the maximum and mean doses decreased to 47.9 and 15.7 Gy, respectively, which represented 37% and 67% reduction in these values. Notably, coverage of the PTV1, PTV2 and PTV3 was not compromised, with the dose to 95% of the target volume ($D95$) remaining essentially stable. Dose to other critical structures remained unchanged. The graphical DVH depicting the hippocampus as well as PTVs and other selected critical avoidance structures are shown in Figure 3. The ability of IMRT to conform around the hippocampus is also shown on coronal and axial sections for the patient who underwent the hippocampus-sparing protocol (Figure 4).

## DISCUSSION

The results of the present study demonstrate that patients with nasopharyngeal cancer undergoing IMRT receive significant doses of incidental radiation to the hippocampus. Indeed, 100%, 50% and 30% of the patients in our dosimetric analysis received a maximum dose of >30, 50 and 70 Gy, respectively, to the hippocampus. No patient received a mean dose of <19 Gy, and the lowest point dose to any region of the hippocampus for all patients was 11 Gy. Furthermore, the maximum dose to the hippocampus exceeded 70 Gy in 30% of the subjects.

Although the clinical consequences of these observations are uncertain, they do raise concerns whether studies assessing neurocognitive functioning for these patients may be warranted to better define a dose–response relationship and to identify possible dose constraints, which may be useful for future IMRT planning. Notably, the vast majority of published literature assessing neurocognitive changes after radiation therapy for

Table 2. Hippocampus dose characteristics

| Patient number | Min. dose (Gy) | Max. dose (Gy) | Mean dose (Gy) | *V*20 Gy (%) | *V*40 Gy (%) | *V*50 Gy (%) | *V*60 Gy (%) |
|---|---|---|---|---|---|---|---|
| 1 | 33.17 | 72.14 | 47.99 | 100 | 72 | 33 | 21 |
| 2 | 14.89 | 35.59 | 20.74 | 48 | 0 | 0 | 0 |
| 3 | 13.22 | 43.24 | 21.72 | 50 | 15 | 0 | 0 |
| 4 | 12.50 | 37.45 | 20.18 | 45 | 0 | 0 | 0 |
| 5 | 15.93 | 74.12 | 30.71 | 79 | 18 | 10 | 7 |
| 6 | 20.54 | 69.43 | 43.80 | 100 | 56 | 35 | 12 |
| 7 | 23.06 | 49.25 | 31.50 | 100 | 6 | 0 | 0 |
| 8 | 11.66 | 75.57 | 33.94 | 74 | 30 | 21 | 15 |
| 9 | 16.72 | 56.61 | 33.06 | 94 | 23 | 3 | 0 |
| 10 | 13.66 | 36.14 | 19.08 | 32 | 0 | 0 | 0 |

Max., maximum; Min., minimum; *V*20, hippocampus volume receiving ≥20 Gy; *V*40, hippocampus volume receiving ≥40 Gy; *V*50, hippocampus volume receiving ≥50 Gy; *V*60, hippocampus volume receiving ≥60 Gy.

nasopharyngeal cancer has primarily analysed the temporal lobe as a single entity. No studies, to our knowledge, have specifically contoured the hippocampus and conducted dosimetric analysis.

Previous studies have suggested that hippocampus-dependent deficits of learning and memory occur in patients with nasopharyngeal cancer after high-dose radiation therapy. Lee et al[5] evaluated 16 patients with nasopharyngeal cancer at a mean follow-up of nearly 6 years after completing radiation therapy. Dosimetric analysis revealed that the inferior temporal lobe, which includes only a portion of the hippocampus, received an average dose of 53 Gy. In comparison with control subjects who have yet to be treated, these patients had lower overall intelligence quotient, deficits in non-verbal memory recall and a significantly greater number of memory-related complaints. Hsiao et al[6] performed a prospective study comparing the neurocognitive function of patients with nasopharyngeal cancer before and after IMRT. They observed that patients who received a mean dose >36 Gy to the temporal lobe scored significantly lower on the neurocognitive examination at a mean of 18 months after treatment. The investigators also found that patients who received >60 Gy to at least 10% of their temporal lobe scored significantly lower on the

Figure 2. Hippocampus dose characteristics of 10 nasopharyngeal carcinoma patients contoured for the present study. The individual minimum point dose (diamond), mean dose (triangle) and maximum point dose (square) of the bilateral hippocampus are depicted for each of the 10 patients. The median doses as well as quartile lines have been demarcated. The median minimum point dose was 17.54 Gy. The median mean dose was 31.11 Gy. The median maximum point dose was 52.93 Gy. Note that each data set has been arranged by ascending values, and data points in each column do not necessarily coincide with the same patient.

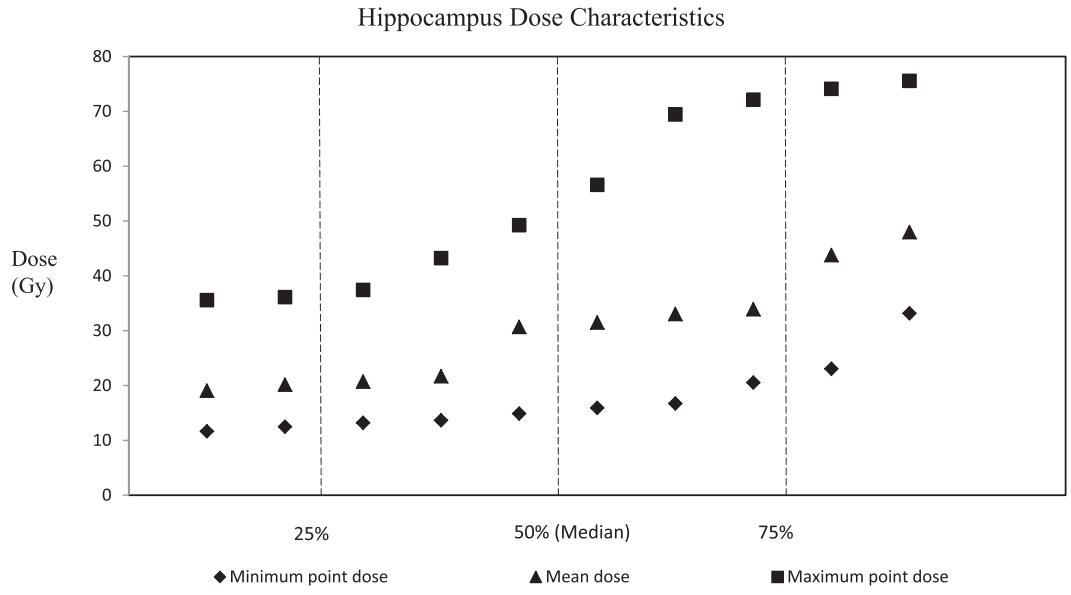
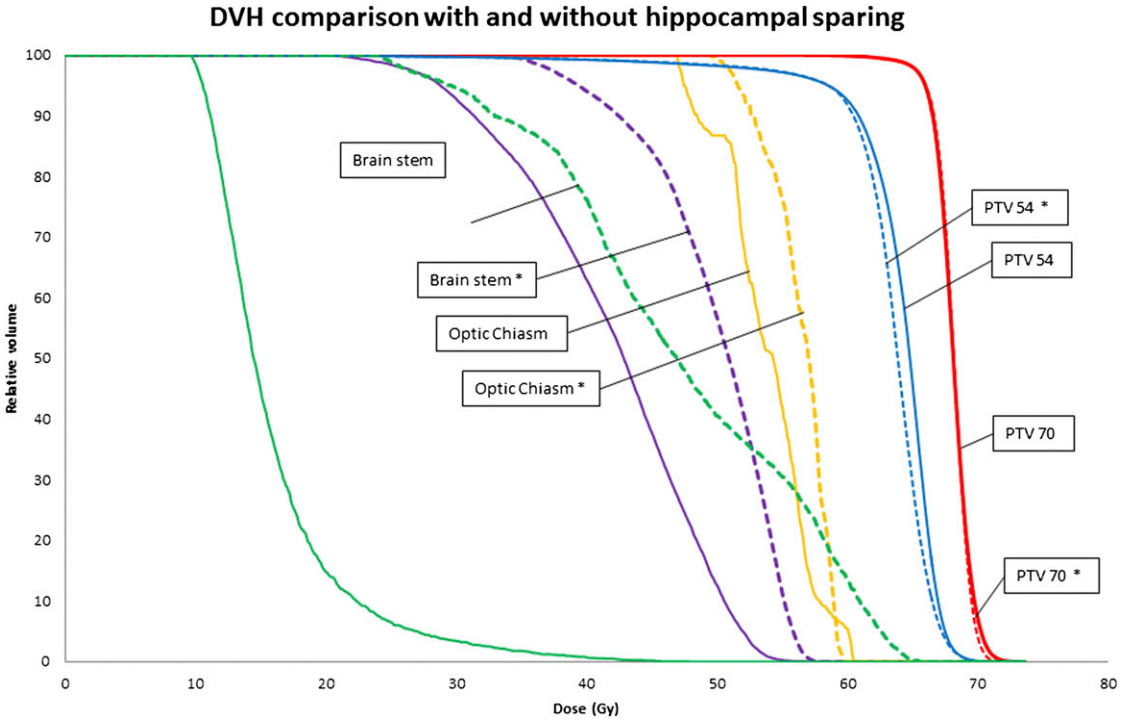


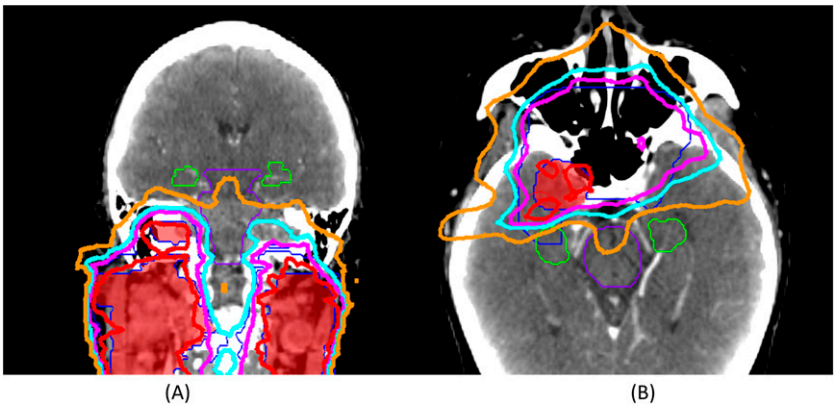
Figure 3. A graphical dose–volume histogram (DVH) depicting the hippocampus as well as planning target volumes (PTVs) and other selected critical avoidance structures for the case patient who underwent intensity-modulated radiotherapy (IMRT) with and without hippocampus sparing. The solid and dashed lines represent the IMRT plans with and without designation, respectively, of the hippocampus (*) as an avoidance structure to be used in inverse planning and optimization. The PTV 70, PTV 54, optic chiasm and brainstem are shown and labelled.




neurocognitive examination. If one were to make an analogous assumption that such a threshold exists for the hippocampus, 3 of the 10 patients received greater than the referenced 10% threshold.

It is likely that hippocampus-dependent complications relate to temporal lobe necrosis. This represents a radiation-induced reactive white matter inflammation, which leads to hypodense or cystic findings on CT and MRI. The incidence of temporal lobe necrosis has been cited to range from 5% in 10 years with conventional fractionation to as high as 35% in 5 years with accelerated fractionation.[7–9] A dosimetric analysis of 259 patients with nasopharyngeal cancer treated by IMRT was recently reported;[9] compared with the 219 patients who did not develop temporal lobe necrosis after treatment, 40 patients did have significantly higher radiation exposures. Based on their analysis, a threshold *V*40 of 10% and *V*40 of 5 ml would allow for a 5-year incidence of temporal lobe necrosis of $<5\%$. Cheung et al[10] observed significantly greater neurocognitive deficits after radiation therapy in patients with nasopharyngeal cancer who developed temporal lobe necrosis than in those who did not. These deficits included declines in verbal and visual memory, language, motor ability, planning and abstract thinking. Interestingly, Lam et al[11] observed

Figure 4. Isodose distributions in the (a) coronal and (b) axial planes for a patient who underwent hippocampus-sparing intensity-modulated radiotherapy. Starting from the centre, the bolded contours progressively represent the 66-, 60-, 54- and 40-Gy isodose lines. The hippocampus and brainstem are depicted using the thin contours.



that post-irradiation neurocognitive changes are not isolated to patients who develop temporal lobe necrosis. Compared with healthy educationally matched controls, a cohort of irradiated patients developed deficits in short-term memory regardless of the development of temporal lobe necrosis. Although a dosimetric evaluation of the hippocampus was not specifically conducted in these studies, the total prescription dose ranged from 59 to 71 Gy. Evidence suggesting a dose–response relationship for temporal lobe necrosis is emerging, but other causes of radiation-induced neurocognitive changes must still be investigated.

It must be recognized that the hippocampus is one of the two regions of the brain where multipotent stem cells reside, the other being the subventricular zone of the lateral ventricle. These neuronal stem cells within the dentate gyrus' subgranular zone of the hippocampus undergo active cell division, differentiation and migration through adulthood.[12] It has been found that these neuronal stem cells are considerably sensitive to radiation. *In vivo* animal studies targeting the subgrandular zone have reported that 10 Gy of radiation exposure will lead to both declines in neurogenesis and deficits in cognitive function, with the threshold for injury being as little as 5 Gy of the exposure.[13–17] It has been found that many of these progenitor stem cells may undergo apoptosis, while many of the surviving cells adopt a glial rather than neuronal fate. It is hypothesized that the lack of neurogenesis depletes a population of cells essential for the functions of hippocampus-dependent learning and memory.

Finally, the delineation of the hippocampus is considered quite complicated, and interobserver variability may hamper efforts to develop constraint guidelines. In an editorial letter debating hippocampus contouring, it was suggested that significant resources would be needed to fuse images, contour structures, develop a plan, deliver therapy with IMRT and provide quality assurance by a skilled team.[18] Nonetheless, increasing attention has recently been focused on avoiding the hippocampus, particularly in patients with brain metastasis who have to undergo whole-brain radiation therapy. Gondi et al[19] demonstrated the feasibility of delivering whole brain radiation using IMRT to a total dose of 30 Gy, while constraining the hippocampus volume receiving $\geq$10 Gy to $<$50% and the maximum hippocampus point dose to $<$16 Gy. In pursuit of recognizing the hippocampus as a critical structure, the Radiation Therapy Oncology Group established protocol 0933 to assess for neurocognitive changes with hippocampus avoidance during whole-brain radiation therapy.

In conclusion, our data may further generate awareness regarding the need to assign the hippocampus as an organ at risk for patients undergoing IMRT treatment for nasopharyngeal cancer. Although limited by the small sample size, this hypothesis-generating exercise shows that patients undergoing radiation therapy for nasopharyngeal cancer receive doses to the hippocampus that may be significant. We acknowledge that the clinical implications, which may become increasingly relevant as patients survive longer with improvements in treatment, were not specifically studied. Prospective studies assessing the relationship between hippocampus dose and neurocognitive functioning are under way and may better define constraints for this organ in the future.

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