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Short Report

Feasibility of Hippocampal Avoidance Radiotherapy for Glioblastoma

K. Thippu Jayaprakash [*], K. Wildschut [†], R. Jena [*‡]

[*] Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[†] Department of Radiotherapy Physics, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[‡] Department of Oncology, University of Cambridge, Cambridge, UK

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Abstract

With improvements in survival for good performance status patients and in specific molecular subtypes of glioblastoma, some patients will survive to develop significant neurocognitive dysfunction. This retrospective planning study quantified hippocampal radiation doses in patients with glioblastoma receiving radical chemo-radiotherapy and compared this with the radiation doses that showed clinical correlation with neurocognitive dysfunction, and evaluated the potential for clinically meaningful hippocampal dose reduction using helical TomoTherapy®.

Key words: Glioblastoma; hippocampal avoidance radiotherapy; neurocognitive dysfunction

Introduction

Neurocognitive dysfunction (NCD) is an emerging survivorship issue in glioblastoma, as there has been an improvement in prognosis [1] and this is particularly relevant in patients with specific molecular subtypes who are expected to live longer [2,3]. Neurocognitive function relates to multiple pathways in the brain [4], but the principal effects of radiotherapy are on short-term memory and fine motor control. Loss of short-term memory is an early delayed radiation effect [5] and manifests as early as 4 months after radiotherapy [6] and with further improvements in survival is a realistic possibility for glioblastoma patients, the actuarial risk of a patient developing NCD is significant. There is conflicting evidence for a radiation dose volume effect for NCD in adults [7–9]. There are few established hippocampal dose volume histogram (DVH)-based constraints for hippocampal avoidance radiotherapy [8,9], which can be achieved in some glioblastoma patients with hippocampal avoidance planning [10]. The purpose of this study was to evaluate hippocampal radiation doses in a cohort of glioblastoma patients and compare them with radiation doses that showed a clinical correlation with NCD outcomes [8,11], perform hippocampal volumetric analysis and determine whether clinically relevant hippocampal avoidance radiotherapy would be feasible in glioblastoma.

Materials and Methods

Radiotherapy plan details of 25 consecutive glioblastoma patients treated with helical intensity-modulated radiotherapy (Tomotherapy HI-ART®, Accuray, USA) between October 2011 and December 2013 were obtained from institutional data archives. No specific selection criteria were used and local radiotherapy review board permission was obtained. Patients were immobilised with a thermoplastic beam direction shell. Radiotherapy planning computed tomography (slice thickness 3 mm) and magnetic resonance imaging scans were co-registered. T1 sequences with gadolinium were used to delineate the gross tumour volume (GTV). Margins (25 mm and 15 mm) were added to the GTV for 54 Gy and 60 Gy clinical target volumes (CTV)

Author for correspondence: K. Thippu Jayaprakash, Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Box 193, Hills Road, Cambridge CB2 0QQ, UK. Tel: +44-7891989554.
E-mail address: kthippujayaprakash@doctors.org.uk (K. Thippu Jayaprakash).

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and a 5 mm margin was added to CTVs for planning target volumes (PTV). The lens, optic pathway, pituitary gland, brainstem and cochlea were outlined as organs at risk. A simultaneous integrated boost technique was used to deliver 60 Gy in 30 fractions, five fractions per week using daily image guidance with positional correction and temozolomide chemotherapy was administered as per protocol [1].

Hippocampal image segmentation was carried out and a margin (5 mm) for the planning risk volume was added according to the RTOG 0933 trial protocol [12] and was verified by a neuroradiologist. Composite hippocampal planning risk volumes (HC-PRV) were created by combining the right and left hippocampal planning risk volumes (Figure 1A, B). The original clinical treatment dosimetry plans were overlaid to obtain hippocampal radiation dose statistics. Four patients, each one representing a cerebral lobe and one representing the posterior cranial fossa, were planned for hippocampal avoidance. The PTV coverage was not compromised and organs at risk dose constraints were not modified. The hippocampal avoidance plans were optimised using the following DVH-based parameters [8,9] to ascertain the feasibility of hippocampal avoidance planning; hippocampal maximum dose 3 Gy and HC-PRV V20 Gy $<$ 20%, V7.3 Gy and V14.9 Gy $<$ 40 % (Figure 1C, D). A data analysis was carried out using SPSS (IBM, USA) and graphs were generated with GraphPad Prism.

Results

In total there were 24 evaluable patients, as in one patient both hippocampi were within the PTV. The mean time taken for hippocampal image segmentation was 14.5 min. Fourteen tumours were located in temporal lobes and eight were in frontal lobes. One tumour arose from the parietal lobe and one from the posterior cranial fossa. The mean HC-PRV maximum dose was 54.7 Gy, which was higher than the threshold dose of 12.6 Gy above which a detrimental effect on neurocognitive function was observed [11]. The mean minimum and mean HC-PRV doses were 24.15 and 38.62 Gy, respectively.

DVH analysis showed that HC-PRV-based parameters D10, D40, D50, D80 and D100 doses were above the threshold doses that showed a significant clinical correlation with NCD [8,11] for all patients (Figure 2).

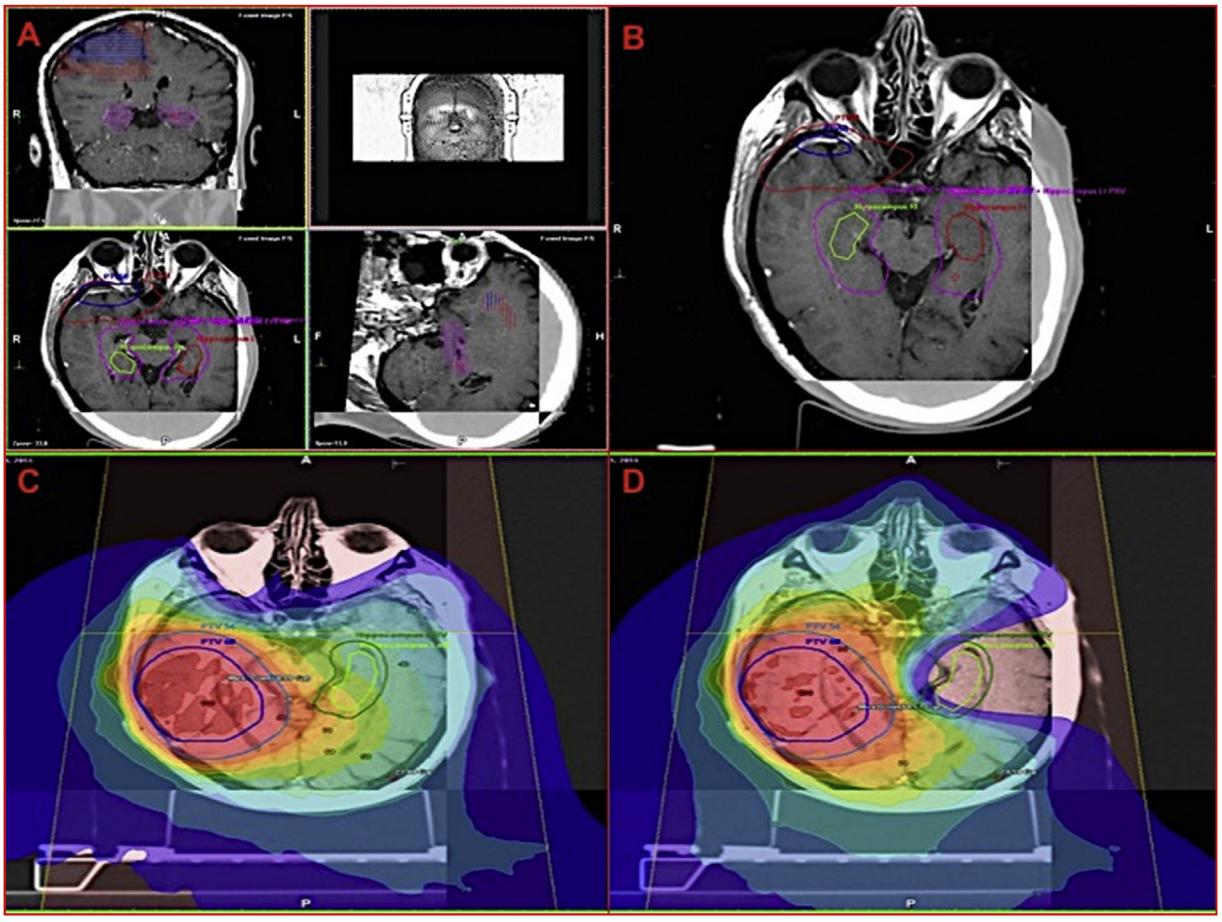

Fig 1. (A, B) Hippocampal contouring. Contour lines; pink, composite hippocampal planning risk volume (HC-PRV); red, left hippocampus; green, right hippocampus; blue and red, planning target volumes (PTV) 60 and 54. (C, D) Radiation doses shown in colour wash for original treatment plan (C) and hippocampal avoidance (D) for a right temporal tumour. Contour lines; light green, left hippocampus; dark green, HC-PRV; dark and light blue, PTV 60 and 54.

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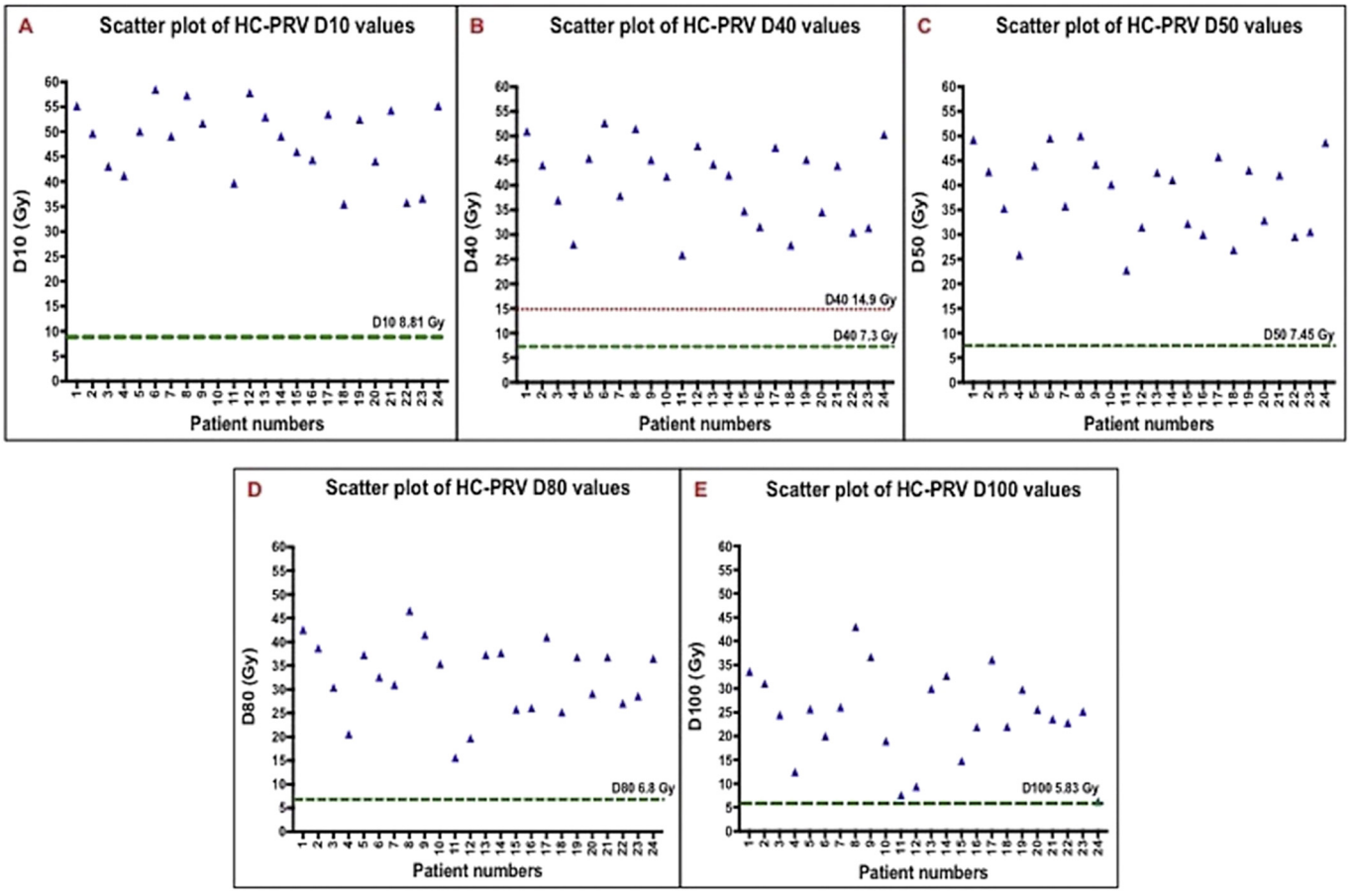

Fig 2. Comparison of dose volume histogram-based composite hippocampal planning risk volume (HC-PRV) parameters of the study population with the hippocampal dose volume histogram-based parameters that showed a clinical correlation with neurocognitive dysfunction. D10, D40, D50, D80 and D100, radiation doses received by 10%, 40%, 50%, 80% and 100% of HC-PRVs.

Volumetric analysis (Table 1) showed that the overlapping volumes between HC-PRV and PTV54 were minimal.

The results of hippocampal avoidance plans of four patients were compared with the original treatment plans for clinically correlated DVH parameters (Table 2). There was no clinically meaningful dose reduction in the maximum HC-PRV and D10 doses in all four patients and for any DVH parameter for the posterior fossa tumour. However, for all other three tumours, D80 and D100 doses were reduced to below threshold doses, and there were mixed results for D40 and D50 parameters.

Table 1
Volumetric analysis of composite hippocampal planning risk volume (HC-PRV). Group 1, only contralateral HC-PRVs were outside the planning target volumes (PTVs); group 2, both HC-PRVs were outside the PTVs

	Group 1	Group 2
Number of patients	17	7
Mean HC-PRV	23.85 cm^3	44.94 cm^3
Mean PTV54	410.13 cm^3	432.81 cm^3
HC-PRV and PTV54 overlapping volume	1.55 cm^3	9.34 cm^3

Discussion

Preservation of neurocognitive function, which was observed with hippocampal avoidance in brain metastasis [9,13], could be achieved in glioblastoma patients with hippocampal avoidance. However, large target volumes and its proximity to hippocampi, and high tumour prescription doses in glioblastoma are challenging.

A clinical correlation between hippocampal radiation doses and NCD was reported when the hippocampal maximum dose was more than 12.6 Gy, a hippocampal volume of 40% (D40) received 7.3 Gy or more and 14.9 Gy [8] and also when hippocampal maximum, D10, D50, D80 and D100 radiation doses were >12.6 Gy, >8.81 Gy, >7.45 Gy, >6.8 Gy and >5.83 Gy, respectively [11]. In another study, the required HC-PRV V20 and the hippocampal V3 constraints were less than 20% [9]. In our study, these DVH parameters could not be achieved with all clinical treatment plans and the central location of the hippocampal avoidance complex and the large CTV volumes make it difficult to reduce the hippocampal doses. Reduced CTV and PTV margins could help to achieve the reduction of hippocampal doses [14] and this might be the only way to achieve the above DVH parameters.

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Table 2
Comparison of composite hippocampal planning risk volume (HC-PRV) dose volume histogram parameters between clinical treatment and hippocampal avoidance plans

	Right frontal			Right temporal			Left parietal			Posterior fossa		
	Treatment	Hippocampal avoidance	Reduced below threshold dose?	Treatment	Hippocampal avoidance	Reduced below threshold dose?	Treatment	Hippocampal avoidance	Reduced below threshold dose?	Treatment	Hippocampal avoidance	Reduced below threshold dose?
HC-PRV maximum dose	53.17	51.88	No	51.28	45.33	No	56.88	55.91	No	52.63	61.02	No
D10	41.2	24.1	No	49.7	33.5	No	46	23.8	No	50.1	57.1	No
D40	28	9.7	Yes for 7.3 Gy	44.1	14.3	Yes for 7.3 Gy	34.8	5.3	Yes for 7.3 and 14.9 Gy	45.5	45.6	No
D50	25.9	8.2	No	42.8	10.7	No	32.2	5.1	Yes	44	40	No
D80	20.6	5.4	Yes	38.7	5.9	Yes	25.8	3.8	Yes	37.3	20.5	No
D100	12.5	2.8	Yes	31.1	4.2	Yes	14.8	2.7	Yes	25.7	6.3	No

However, these radiation doses with a clinical correlation with NCD were based only on a small number of patients, and therefore it is essential to generate data from a large number of patients and for a range of radiation doses, which will help to guide hippocampal avoidance planning in glioblastoma, and also in low grade glial tumours. Several such studies are now being conducted or in the planning stage in the treatment of brain metastasis, meningioma, pituitary adenoma and small cell lung cancer [15]. Alternatively, an imaging correlate for subclinical hippocampal injury would have great utility in determining dose and volume response [16].

Several planning studies have suggested the feasibility of hippocampal avoidance in a variety of clinical settings. In our study, despite higher tumour prescription doses, with hippocampal avoidance, the mean hippocampal doses were below the 12.5 Gy and 14.3 Gy that were achieved for prophylactic cranial irradiation and whole brain radiotherapy [17] for two patients. Hippocampal avoidance reduced radiation doses to the cryptic neural structures by 11% [18] and also a reduction in the radiation dose to the contralateral hippocampus in high grade gliomas [19] and in glioblastoma [20]; with partial brain radiotherapy there was a reduction of up to 56.8% in the limbic system radiation doses [21]. Our study showed that it was possible to reduce radiation doses below some clinically relevant hippocampal doses in specific anatomical locations, which could potentially preserve neurocognitive function in some glioblastoma patients. The risk of glioblastoma relapse is higher near the hippocampal region [22], which poses another challenge for hippocampal avoidance and, therefore, caution is needed when selecting patients.

Conclusions

Our study showed that we could not routinely achieve adequate hippocampal sparing according to the current published evidence in glioblastoma with current CTV/PTV margins. Prospective clinical data correlating hippocampal radiation doses to NCD are needed to establish suitable hippocampus threshold doses for hippocampal avoidance planning purposes, and to realise the benefits of this technique.

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