Dosimetric comparison of hippocampal sparing technologies in patients with low grade glioma.

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Authors’ contributions

AW, PH & SN planned and coordinated the study. NF & SYF contoured the hippocampi. PH & JP performed the VMAT planning. PMcL undertook the statistical analysis. AW drafted the manuscript. PH, SN, AJ, AC critically revised the manuscript. All authors read and approved the final manuscript.

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Abstract

Radiotherapy (RT) plays an integral role in the management of low-grade gliomas (LGG). Late toxicity from RT can cause progressive neurocognitive dysfunction. Radiation-induced damage to the hippocampus (HCP) plays a considerable role in memory decline. Advancements in photon planning software have resulted in the development of multi-criteria optimization (MCO) and HyperArc technologies which may improve HCP sparing while maintaining PTV target coverage.

Methods

Three planning methods for hippocampal sparing (HS) were compared, VMAT without HS (VMAT_noHS), VMAT with HS (VMAT_HS), MCO with HS (VMAT_MCO), and HyperArc with HS (HyperArc_HS).

Results

25 patients were identified. The contralateral HCP was spared in 16 patients and bilateral HCP in 9 patients with superiorly located tumours. All three HS planning techniques showed significant reductions in dose to the spared HCP in contralateral cases but only VMAT_HS and HyperArc_HS achieved this in bilateral cases (p < 0.008). Only VMAT_MCO was superior to VMAT_HS in lowering the dose to both contralateral HCP and bilateral HCP in all measured metrics (p<0.008). PTV and OAR (organ at risk) dose constraints were achieved for all plans.
Conclusion

This retrospective dosimetric study demonstrated the feasibility of hippocampal sparing for low-grade glioma. All three HS planning techniques achieved significant dose reductions to the spared contralateral hippocampus, but only MCO_HS and VMAT_HS achieved this in bilateral cases. MCO was superior to other planning techniques for sparing of both bilateral and contralateral hippocampi.

Keywords:

Low grade glioma, hippocampal sparing, photon planning, hyperarc, multi-criteria optimiser
Key points:

Innovations in photon planning software, with the development of volumetric modulated arc therapy (VMAT), multi-criteria optimisation (MCO) and HyperArc technologies, improve HCP sparing for low grade glioma patients while maintaining PTV target coverage.

Importance of this study

Sparing of the hippocampus (HCP) for low grade glioma patients undergoing fractionated radiotherapy, presents technical challenges with respect to hippocampal contouring and radiotherapy treatment planning. Innovations in photon planning software, with the development of volumetric modulated arc therapy (VMAT), multi-criteria optimisation (MCO) and HyperArc technologies, may improve HCP sparing while maintaining PTV target coverage. Our retrospective dosimetric study demonstrates the feasibility of HCP sparing for low-grade glioma using different photon planning techniques without compromising PTV or other OAR’s. The three planning solutions included in our study are available within the majority of radiotherapy facilities. We believe that this paper will be of interest to radiotherapy physicists and radiation oncologists who wish to developed HCP sparing within their departments. This paper highlights the use of this technology, the planning methods involved and identifies the optimal photon planning method for HCP sparing.
Introduction

Radiation therapy (RT) is integral in the management of primary brain tumours. Low-grade gliomas (LGG) are rare primary brain tumours with relatively slow but infiltrative growth. The optimum management for LGG patients comprises of surgery followed by sequential radiotherapy and chemotherapy which often result in life expectancies of a decade or more. With such a prolonged prognosis the adverse late effects of RT on quality of life and neurocognitive functioning are of crucial importance.

The hippocampi are cerebral structures that are now understood to play a crucial role in cognition. Traditionally, the hippocampus has not been considered an organ at risk (OAR) in radiotherapy planning, unlike other structures such as the optic chiasm or brainstem. However, there is increasing evidence to suggest that irradiation of the hippocampus can result in neurocognitive decline. Studies have identified a relationship between RT dose to the hippocampus, hippocampus volume and neuro-cognitive deficit. Preclinical and clinical research suggest that hippocampal sparing may provide a useful intervention for reducing the adverse cognitive effects of cranial irradiation. Doses in excess of 7.3 equivalent dose in 2Gy per fraction (EQD2 Gy) to 40% of the bilateral hippocampus have been found to significantly correlate with a decrease in verbal memory performance.

Modern radiotherapy techniques, such as volumetric modulated arc therapy (VMAT), allow improved conformality of the RT dose to the target volume with reduction of dose to OARs. Recent advancements in photon planning software include multi-criteria optimisation (MCO) (Varian Medical Systems, Palo Alto, CA), an inverse planning technology; and HyperArc...
(Varian Medical Systems, Palo Alto, CA), eclipse treatment planning software feature. Studies have shown that MCO and Hyperarc improve dosimetric quality and efficiency for photon beam planning and delivery for brain metastases, head and neck, prostate and lung cancers. MCO planning aims to achieve the optimal plan by allowing a planner to trade-off different dose objectives in real time to reach the best compromise. HyperArc, primarily designed to treat brain metastases, incorporates several specialised functions for radiotherapy planning including automated settings for locating the isocenter, non-coplanar beam arrangements and optimisation of steep dose gradients outside the PTV. HyperArc plans offer the possibility of delivering a more conformal dose to the target while reducing doses to surrounding tissues and have been explored in the context of hippocampal sparing for whole brain irradiation.

This dosimetric study was conducted to identify the optimal photon planning method for hippocampal sparing by comparing VMAT, MCO and Hyperarc plans in patients with LGG.

**Methods**

**Study design**

This is a retrospective planning study comparing three different hippocampal sparing (HS) planning techniques in patients with low grade glioma. Patients were planned using the following techniques: to provide a contemporary comparator, original plans (VMAT_noHS) were recalculated using an updated dose calculation algorithm subsequently adopted by the department (Acuros 15.5.07). Three planning methods for hippocampal sparing (HS) were compared, VMAT without HS (VMAT_noHS); VMAT with HS (VMAT_HS), MCO with HS (VMAT_MCO); and HyperArc with HS (HyperArc_HS). Each HS technique was then compared
to the recalculated original plan. For patients in whom the planning target volume (PTV) overlapped the hippocampus we sought to spare only the hippocampus on the contralateral side. In other patients with PTV’s not including one or both hippocampus, bilateral hippocampal sparing was the objective.

**Patient Selection and methods**

For this study, all adult patients with histopathologically confirmed WHO grade 2 oligodendroglioma or grade 2 astrocytoma who were treated with radiotherapy in our local centre between 2015 and 2019 were included in this study. All patients were identified retrospectively and all patients who fitted this criteria were included.

The patient characteristics are shown in Table 1.

**Patient Simulation and Outlining**

All patients were immobilised in a supine position using a three point thermoplastic fixation device (Civco Medical Solutions, Kalona, Iowa, USA). Patients underwent a 15 mm slice non-contrast computed tomography (CT) scan. All patients also underwent imaging on a 1.5 tesla MR scanner (Philips Medical Systems, Best, The Netherlands), with 1.5mm axial T2-weighted and gadolinium contrast enhanced T1-weighted sequences acquired. CT simulation and MR images were co-registered on Varian Aria V15.1 using a rigid registration algorithm. The gross tumour volume (GTV) was defined as the area of increased signal intensity on T2 MRI imaging plus the surgical resection cavity. A margin of 15 mm was added to define the clinical target volume (CTV). The CTV margin was applied in all directions of likely tumour spread along the white
matter tracts but was modified to respect anatomical barriers. The planning target volume (PTV) was generated by adding a geometric isotropic margin of 3 mm. All contours were delineated by an experienced neuro-oncology clinical oncologist and each delineation was peer-reviewed by the local neuro-oncology team.

The hippocampus was retrospectively delineated by a neuro-radiologist on gadolinium contrast-enhanced T1 weighted MRI. Delineation was performed on the axial slices as per the RTOG 0933 atlas. The contours were then reviewed and verified in sagittal, coronal and axial planes by another neuro-radiologist. A hippocampal avoidance zone (HAZ) was generated by adding a 3 mm isotropic margin.

**Treatment Planning**

**Original Clinical VMAT plans without Hippocampus optimization**

The clinically delivered VMAT plans (VMAT_noHS) were created by experienced planners between 2015 - 2019 using Eclipse Treatment Planning System (TPS) (version 13.6 – 15.5 Varian Medical Systems Palo Alto). Plans consisted of two full coplanar arcs with a $30^\circ$ complimentary collimator tilt; the hippocampus was not considered in plan optimization. To reduce inter-operator and TPS version variability, for this study the original plans were replanned by two experienced planners (greater than 10 years’ experience) using our department’s RapidPlan Model (RP) (version 15.5.11) and calculated with Acuros 15.5.07. The same two planners performed all subsequent planning and analysis. The field geometry of the plans was unchanged.
VMAT Plans with Hippocampus optimization

The VMAT_noHS plans described above were then created in Eclipse 15.5, using the RP model to generate PTV and OAR objectives. Hippocampal sparing was then introduced by manually adding hippocampus optimisation objectives. Planners aimed to achieve hippocampus D40% <12Gy without compromising PTV coverage or other OAR constraints. The D40% value of <12Gy was selected as this was the lowest mean dose to the hippocampus achieved in published peer reviewed papers pertaining specifically to hippocampal sparing for low and high grade gliomas. After careful consideration and discussion within our clinical team, it was decided to proceed with the D40% value of <12Gy in order to robustly challenge the planning systems to investigate the feasibility of this constraint.

VMAT plans with hippocampus sparing (VMAT_HS) consisted of two full arcs with a 30° complementary collimator tilt.

MCO planning process

MCO planning enables optimisation of treatment plans by allowing the planner to explore the Pareto surface of various dose objectives. The Pareto surface is explored using a slider bar, with visual dose volume histogram (DVH) information and selected dose objectives displayed to guide selection of an optimal solution. With the VMAT_HS plan acting as a starting point for the MCO process, highest priority was given to not compromising PTV coverage or OAR constraints and then minimising hippocampus dose, primarily D40%, to generate the MCO_HS plan retaining a two arc co-planar geometry. Within these criteria, the final determination of the optimal solution was left to the planner’s judgement.
HyperArc planning

HyperArc is an Eclipse TPS feature which is primarily designed to treat brain metastases in a highly conformal, efficient and automated manner. HyperArc beam arrangements are non-coplanar and designed to be collision risk free due to the use of a Q-Fix Encompass immobilisation device which is modelled in the Eclipse TPS. As these retrospective patients were scanned prior to the use of the Encompass immobilisation system, an Encompass structure set was inserted into the dataset to allow the use of HyperArc planning. HyperArc_HS plans were created using the HyperArc (v15) plan creation wizard to place the isocentre of the non-coplanar beams in a collision free zone. Beam arrangements varied based on the geometry of the PTV but typically 4-5 non-coplanar half arcs were used with the collimator angles optimized for MLC coverage of the target. Rapid plan was used to generate PTV and OAR optimisation objectives while planners manually attempted to spare hippocampus dose by prioritizing D40% during optimisation. For all plans, final dose distributions were calculated with Acuros 15.5.07 at a 2.5 mm grid size and were optimised and calculated on a TrueBeam STX at 6MV with HD-MLC. The TrueBeam STX was chosen because it is HyperArc enabled and would allow clinical delivery of all calculated plans for the purposes of quality assurance (QA).

Dosimetric and plan quality comparison analysis

For all patients, the prescription dose to the planning target volume (PTV) was 50.4 Gy in 28 fractions. All plans were normalized to a median PTV dose of 100%. PTV and OAR dose constraints are detailed in appendix 1. The PTV was given priority over OARs and PTV coverage was not compromised in any of the plans. With regards to hippocampal sparing, the following metrics were assessed: mean dose (Dmean), point max of hippocampus (Dmax) and
D40%. In cases where the ipsilateral hippocampus was within the PTV or adjacent to the PTV, the dosimetric criteria for the contralateral hippocampus was prioritised. The brain stem, optic chiasm, and optic apparatus were also delineated and these established organs at risk were prioritised over the hippocampal dose constraint. General plan quality was assessed by experienced operators. DVH data for all evaluated parameters were recorded and analysed.

**Statistical Analysis**

Each of the PTV target (D2, D5, D95, D99 and mean dose), hippocampus (D10, D20, D30, D40, mean and maximum dose) and other OAR indices were summarised using medians and interquartile ranges (IQR). Differences in patient index values between all planning techniques were assessed using the Friedman test (which is a nonparametric repeated measures ANOVA). A statistical significance level of 0.05 was used for this test. Differences between pairs of planning techniques were assessed using the Wilcoxon signed rank test. For these multiple pairwise comparisons, a Bonferroni-adjusted statistical significance level of 0.008 was used.

**Ethics approval and consent to participate**

This study was a retrospective radiotherapy planning study using anonymised patient data. Ethical approval was not required as per Beatson West of Scotland Cancer Centre Research & Development guidelines. This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This work did not require written patient consent.
Results

Of the 25 patients included, bilateral hippocampal sparing was deemed appropriate in 9. For the other 16 patients, only the contralateral hippocampus was contoured due to overlap of the ipsilateral hippocampus and the PTV. Dose statistics are quoted for contoured hippocampus volumes. In Table 2, the PTV target indices are shown for all planning techniques. These were achieved for all plans included in the study. No clinically significant differences in median values of PTV dose measures were observed between different planning techniques. For all 25 patients, there was no statistically significant difference between planning techniques in terms of the monitor units delivered.

Dose to bilateral hippocampus – 9 cases

The calculated parameters for the bilateral hippocampus are shown in Table 3. Left and right hippocampal volumes were considered as a single overall structure. All three HS planning techniques showed dose reductions compared to VMAT_noHS, but only MCO_HS achieved a statistically significant difference (p<0.008) across all measured parameters (figure 1). There were statistically significant differences between hippocampal sparing techniques VMAT_HS and MCO_HS, but no statistically significant difference between these techniques and HyperArc_HS, even though HyperArc_HS tended to achieve the lowest mean dose. When compared to VMAT_noHS, there was a median decrease in D40% of 5 Gy (IQR 0.5-10.4) for VMAT_HS, 7.4 Gy (IQR 1.5-13.7) for MCO_HS, and 6.9 Gy (IQR -1.1-11.3) for HyperArc_HS. The median mean dose to the bilateral hippocampi with VMAT_noHS was 12.1Gy (IQR 5.0-20.5). This value was reduced by 4.6 Gy (IQR 2.3-12.4), 6.1 Gy (IQR 1.9-10.6)
and 6.5 Gy (IQR -0.4-12.9) by VMAT_HS, MCO_HS, and HyperARC_HS respectively.

HyperArc_HS showed the lowest median maximum dose to bilateral hippocampi of 9.1 Gy (IQR 7.8-16.8). Considering the hippocampal sparing techniques used for these 9 cases, the target D40% of <12Gy was achieved by 8 VMAT_HS, 8 MCO_HS and 8 HyperArc_HS plans (Appendix 2), whereas only 3 of the 9 VMAT_noHS plans achieved the target D40% constraint.

Dose to contralateral hippocampus – 16 cases

Table 4 shows all the calculated parameters for the contralateral hippocampus. All three HS planning techniques showed significant dose reductions to the spared contralateral hippocampus (figure 2). MCO_HS achieved the lowest median hippocampal mean dose and median D40%.

The median mean dose was 23.2Gy (IQR 19.0-29.3) with VMAT_noHS; this was reduced to 10.2Gy (IQR 8.6-12.4) by VMAT_HS, 9.1 Gy (IQR 6.6-11.5) by MCO_HS and 10.0 Gy (IQR 5.0-11.3) by HyperArc_HS. The median D40% dose of 23.3Gy (IQR 20.0-28.8) achieved by VMAT_noHS was reduced to 9.8 Gy (IQR 7.8-11.1) by VMAT_HS, 7.8 Gy (IQR 6.6-11.5) by MCO_HS and 8.9 Gy (IQR 5.0-11.3) by HyperArc_HS. The median reduction in D40% dose was greatest with MCO_HS (15.5 Gy) compared to median reductions of 13.5 Gy and 14.4 Gy with VMAT_HS and HyperArc_HS respectively. HyperArc_HS achieved the lowest median maximum dose to the contralateral hippocampus (18.4Gy - IQR 7.0-42.7). Amongst the 16 contralateral hippocampal cases, only one of the VMAT_noHS plans met the D40% <12Gy constraint. Amongst the HS techniques this number increased to 13 for VMAT_HS, 14 for MCO_HS and 15 for Hyperarc_HS (Appendix 2).
Dose to normal brain and OARs

The difference between the brain (-PTV) doses for the four techniques was small but statistically significant (p<0.0001) (Appendix 3 & 4). All planning techniques achieved dose constraints for orbit, optic nerve, and brainstem but not the lens. MCO_HS delivered the lowest median doses to the brainstem, optic chiasm and lens. For contralateral sparing plans, the differences between the median brain (-PTV) dose for the four techniques were small and non-significant. All other OAR dose constraints were achieved by all four planning techniques.

Correlation between PTV size and dose to hippocampus

Spearman correlation coefficients for the association between PTV size and dose to hippocampus are shown in the Appendix 5. For bilateral cases, no significant correlation between the size of the PTV and the hippocampal dose (mean and D40) was observed in any of the planning techniques. For contralateral cases, statistically significant strong correlations (p < 0.01) were found between PTV size and hippocampal D40 for VMAT_HS, MCO_HS and HyperArc_HS (rho = 0.724, 0.638, 0.698 respectively). However no statistically significant correlation was observed with the contralateral mean dose.
Influence of PTV localisation on hippocampal dose

No significant influence of tumour localisation was observed for hippocampal mean and D40 doses for both unilateral and bilateral cases. For temporal lesions, the hippocampal sparing techniques were associated with higher D40 doses compared to lesions without temporal involvement but this was not statistically significant (Appendix 6).

Discussion

The purpose of this dosimetric study was to investigate the feasibility of hippocampal sparing (HS) for LGG patients and to compare the ability of different photon planning methods to achieve it. We found that VMAT plans with hippocampal sparing could significantly reduce the dose to either contralateral or bilateral hippocampi, the latter being dependent on the proximity of the ipsilateral hippocampus to the PTV, while maintaining PTV coverage and other OAR constraints. No attempt was made to preserve the ipsilateral hippocampus when within or in close proximity to the PTV given the possibility of infiltration by the tumour (16 cases). For the 9 cases where both delineated hippocampal structures were distant to the PTV, bilateral sparing was carried out and the average distance from the inferior slice of the PTV to the superior slice of the delineated hippocampal volume was 2.3cm (0.7-3.5cm).

In our study, for both bilateral and contralateral sparing cases, only MCO_HS achieved statistically significant reductions in hippocampal dose parameters compared to the original VMAT and VMAT_HS plans. MCO_HS showed a statistically significant dose reductions across all parameters compared to VMAT_noHS for bilateral hippocampal sparing plans. VMAT_HS achieved statistically significant reductions in mean and maximum hippocampal doses.
compared to the original plan. HyperArc_HS only achieved a statistically significant reduction in maximum hippocampal dose when compared to VMAT_noHS.

Comparing the 3 HS techniques, only MCO_HS showed a consistent statistically significant difference (p<0.008) across all measured parameters when bilateral HS was attempted. This highlights potential benefits of the MCO planning process, which allows planners to minimize hippocampal dose, primarily D40%, with two arc co-planar geometry. The range in of dose sparing metrics for the bilateral hippocampi is indicative of the large variations in PTV and hippocampus geometry that are commonly observed. This may also account for the higher dose sparing metrics achieved by Hyperarc when delivering non co-planar beams.

For contralateral hippocampus sparing, all 3 techniques were statistically superior to the original VMAT_noHS plans. Of the three planning methods studied, MCO_HS generally achieved the lowest contralateral hippocampus dose and was the only technique that showed significant reductions compared to VMAT_HS. HyperArc_HS showed consistently lower Dmax for contralateral hippocampal sparing compared to the other two techniques. This reflects the benefits of a non-coplanar treatment approach that allows the opportunity to limit lateral entry and exit doses to a greater degree than co-planar planning techniques.

To our knowledge, this study is the first to compare VMAT_HS with multi-criteria optimiser (MCO) and HyperArc planning technology in this patient group. However, previous studies have investigated hippocampal sparing using VMAT and IMRT in low and high grade glioma. In a dosimetric study evaluating hippocampal-sparing radiotherapy for 18 patients with grade II and III gliomas using IMRT, a mean hippocampal dose of less than 30Gy was achieved in 14 out
of 18 patients, with mean dose to contralateral hippocampus of 24.9Gy. The authors identified that a PTV volume of less than 420.5 cm$^3$ was the only predictive factor in achieving hippocampal sparing. In another dosimetric study comparing 3D conformal radiotherapy and VMAT planning in high grade gliomas\textsuperscript{27}, a 36\% reduction to the contralateral HCP was achieved with VMAT (mean dose 14.7Gy). This study observed that, for VMAT planning, parietal lobe tumour location and larger PTV size (median volume 393.8 cm$^3$) were predictors of higher hippocampal dose ($p < 0.05$). A dosimetric case study of a left frontal grade II astrocytoma showed that VMAT planning with hippocampal sparing (standard coplanar) reduced the mean dose to the contralateral hippocampus from 29.9Gy to 12.6Gy\textsuperscript{28}. An IMRT planning study to assess the feasibility of sparing the hippocampus and limbic circuit during partial brain radiotherapy for five hemispheric low-grade gliomas reduced the mean dose from 32.6Gy to 12 Gy\textsuperscript{29}. Other studies have identified significant correlations between PTV size and mean dose to the contralateral hippocampus\textsuperscript{27,28}. In our study, a significant dose correlation was observed between PTV size and dose to the contralateral D40\% for VMAT_HS, MCO_HS, and HyperArc_HS, but no correlation was found for the contralateral mean dose. No correlation was observed for bilateral plans, suggesting that larger PTV’s do not influence D40\% or mean dose when distant (superior) to the hippocampi.

The hippocampus median dose values achieved in our study were lower than those reported in other studies\textsuperscript{27-29}. These studies (previously discussed) included a variety of pathologies, target volumes, doses and fractionation which may have resulted in higher doses to the hippocampus. Our study involved only grade II gliomas treated with a dose of 50.4 Gy at 1.8 Gy per fraction with the HC D40\% constraint of $<12$ Gy. The equivalent EQD2 for 1.8 Gy per fraction for the
7.3 Gy threshold identified in the Gondi paper (alpha beta normal brain tissue =2) was 7.7 Gy. With bilateral HS plans the D40% achieved was 7.7 Gy for VMAT_HS, 5.3 Gy for MCO_HS and 5.8 Gy for Hyperarc_HS. For contralateral only plans, MCO_HS achieved median D40% of 7.8 Gy compared with 9.8 Gy and 8.9 Gy for VMAT_HS and HyperArc_HS respectively. This indicates that it is possible to achieve EQD2 D40% values of 7.7 Gy with all three hippocampal sparing techniques when bilateral hippocampal sparing is possible, and with MCO when contralateral hippocampal sparing is attempted.

The major shortcoming of any retrospective planning study is the inherent plan bias. Planner experience is crucial because the plan optimisation process is user dependent. We used various strategies to mitigate this bias: Rapid Plan (RP) model knowledge-based planning was used as a planning aid for HS co-planar techniques, two experienced planners were involved, dose objective documentation was created and planners verified that all dose constraints were met. High-quality RP models result in improved plan quality, optimal target coverage, reduced OAR doses and substantially reduced planning times. The RP model utilised for this study is built from a dataset of 79 patients, has been internally validated and is routinely used for clinical patients. It is also worth noting that a larger cohort of patients would be beneficial to validate the findings of this study but this is challenging due to the rare nature of this disease. Planning time was not captured for this study. Therefore, we have no insight into the time taken to plan a patient with each of the 4 planning methods. This would be helpful information for radiotherapy departments considering the implementation of hippocampal sparing with limited resources.
The prospective study by Gondi et al\textsuperscript{13}, which included benign and low-grade brain tumours treated with fractionated radiotherapy, observed a relationship between EQD2 to the bilateral hippocampi and likelihood of long-term memory impairment at 18-month follow-up. A normal tissue complication probability (NTCP) of 66.7\% was observed when the D40\% exceeded an EQD2 of 7.3Gy. Other studies have attempted to quantify the hippocampal NTCP model within a group of LGG patients. Analysis of data from the EORTC 22033-26033 trial\textsuperscript{31} revealed no difference in incidence of a cognitive event between patients receiving D40\% above vs. below the median (47.2 Gy) (14 vs. 25\%, $p = 0.68$)\textsuperscript{32}. Median follow up in the EORTC 22033-26033 trial was 18 months, which may be considered short in the context of late neuro-cognitive toxicity. Previous studies have identified neurocognitive deficits occurring 5 years or more after fractionated radiotherapy\textsuperscript{33,34}. Further studies are required in low grade gliomas to elucidate the relationship between dose received by the hippocampus during photon radiotherapy and neurocognitive dysfunctions. A prospective longitudinal study utilising hippocampal sparing with MCO and neurocognitive assessment in grade 2 oligodendroglioma and astrocytoma patients is in development within our local centre. The authors have identified the benign tumour type meningioma as another disease indication that could benefit from the use of hippocampal sparing. A dosimetric study is planned for this patient group.
Conclusion

This retrospective dosimetric study performed in 25 patients demonstrates the feasibility of hippocampal sparing for low-grade glioma using different photon planning techniques without compromising PTV or other OAR’s. All three HS planning techniques showed significant benefits when contralateral hippocampus sparing was suitable, but only MCO_HS and VMAT_HS showed benefit when bilateral hippocampal sparing was attempted. MCO_HS showed the largest reduction in median hippocampal D40% in both unilateral and bilateral cases, which could potentially lead to a clinically relevant reduction of late neurocognitive side effects, although further research would be required to confirm this.
References


Figure 1: BiLateral hippocampal sparing (images V12 Gy colour wash)
From left to right: VMAT_noHS mean dose 12.7Gy, VMAT_HS mean dose 5.1Gy, MCO_HS mean dose 3.3 Gy, HyperArc_HS mean dose 4.3 Gy

Figure 2: Contralateral hippocampal sparing (images V12 Gy colour wash)
From left to right: VMAT_noHS mean dose 20.5Gy, VMAT_HS mean dose 7.0 Gy, MCO_HS mean dose 4.5 Gy, HyperArc_HS mean dose 5.5 Gy
### Table1. Patient Characteristics

<table>
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<th>Characteristics</th>
<th>Number (%) or median (range)</th>
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<tr>
<td><strong>Age (years)</strong></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
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<td><strong>PTV (cm³)</strong></td>
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<td><strong>Hippocampal volume (cm³)</strong></td>
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Table 2: Median (IQR) D2, D5, D95, D99, mean dose and MU for PTV

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<td>99.9 (99.8-100.0)</td>
<td>99.9 (99.9-100.0)</td>
</tr>
<tr>
<td>MU</td>
<td>378 (341-395)</td>
<td>382 (352-407)</td>
<td>364 (338-401)</td>
</tr>
</tbody>
</table>

Pairwise comparisons Wilcoxon sign rank test - p<0.008 compared to 1 VMAT_noHS, 2 VMAT_HS, 3 MCO, 4 HyperArc
<table>
<thead>
<tr>
<th></th>
<th>VMAT_noHS</th>
<th>VMAT_HS</th>
<th>MCO_HS</th>
<th>HyperArc_HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>12.1</td>
<td>7.5</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>(5.0-20.5)</td>
<td>(3.1-7.9)</td>
<td>(2.7-7.3)</td>
<td>(5.3-8.0)</td>
</tr>
<tr>
<td>D10</td>
<td>14.9</td>
<td>8.4</td>
<td>8.2</td>
<td>7.0</td>
</tr>
<tr>
<td></td>
<td>(10.0-25.7)</td>
<td>(4.3-10.2)</td>
<td>(3.6-9.1)</td>
<td>(6.3-10.0)</td>
</tr>
<tr>
<td>D20</td>
<td>14.1</td>
<td>8.2</td>
<td>7.7</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>(7.6-23.8)</td>
<td>(3.8-9.1)</td>
<td>(3.2-8.4)</td>
<td>(6.1-9.1)</td>
</tr>
<tr>
<td>D30</td>
<td>13.4</td>
<td>8.0</td>
<td>6.8</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>(5.6-22.4)</td>
<td>(3.5-7.7)</td>
<td>(3.0-7.7)</td>
<td>(5.8-8.5)</td>
</tr>
<tr>
<td>D40</td>
<td>12.7</td>
<td>7.7</td>
<td>5.3</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>(4.3-21.3)</td>
<td>(3.2-8.1)</td>
<td>(2.8-7.5)</td>
<td>(5.5-7.7)</td>
</tr>
<tr>
<td>Max</td>
<td>22.4</td>
<td>9.8</td>
<td>9.8</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>(16.8-32.6)</td>
<td>(7.3-16.5)</td>
<td>(5.5-14.2)</td>
<td>(7.8-16.8)</td>
</tr>
</tbody>
</table>

Pairwise comparisons Wilcoxon sign rank test - p<0.008 compared to ¹ VMAT_noHS, ² VMAT_HS, ³ MCO, ⁴ HyperArc
Table 4: Contralateral hippocampus median (IQR) mean dose, D10, D20, D30, D40 and max dose

<table>
<thead>
<tr>
<th></th>
<th>VMAT_noHS</th>
<th>VMAT_HS</th>
<th>MCO_HS</th>
<th>HyperArc_HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean</td>
<td>23.2 (19.0-29.3)²,³,⁴</td>
<td>10.2 (8.6-12.4)¹,³</td>
<td>9.1 (6.6-11.5)¹,²</td>
<td>10.0 (5.0-11.3)¹</td>
</tr>
<tr>
<td>D10</td>
<td>28.3 (22.8-37.9)²,³,⁴</td>
<td>14.2 (10.3-24.2)¹,³</td>
<td>12.9 (8.0-20.1)¹,²</td>
<td>11.8 (5.6-20.8)¹</td>
</tr>
<tr>
<td>D20</td>
<td>24.8 (21.9-32.4)²,³,⁴</td>
<td>12.3 (9.5-17.2)¹,³</td>
<td>10.6 (7.5-15.6)¹,²</td>
<td>10.8 (5.4-13.8)¹</td>
</tr>
<tr>
<td>D30</td>
<td>24.0 (20.5-30.7)²,³,⁴</td>
<td>10.9 (9.1-12.6)¹,³</td>
<td>9.0 (7.0-11.5)¹,²</td>
<td>9.5 (5.3-11.9)¹</td>
</tr>
<tr>
<td>D40</td>
<td>23.3 (20.0-28.8)²,³,⁴</td>
<td>9.8 (7.8-11.1)¹,³</td>
<td>7.8 (6.4-10.6)¹,²</td>
<td>8.9 (5.2-10.8)¹</td>
</tr>
<tr>
<td>Max</td>
<td>33.8 (26.9-47.1)²,³,⁴</td>
<td>24.9 (13.2-41.1)¹,³</td>
<td>20.7 (7.0-42.7)¹,²</td>
<td>18.4 (7.0-42.7)¹</td>
</tr>
</tbody>
</table>

Pairwise comparisons Wilcoxon sign rank test - p<0.008 compared to ¹ VMAT_noHS, ² VMAT_HS, ³ MCO, ⁴ HyperArc