Original Article

Hippocampal avoidance whole brain radiotherapy: developing a RapidPlan model

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Background: Hippocampal-avoidance whole brain radiotherapy (HA-WBRT) has emerged as an approach to retain intracranial tumour control while minimizing cognitive decline. However, the contouring and planning requirements are more complex and time consuming compared to standard WBRT. RapidPlan is an automated treatment planning software that is designed to increase planning efficiency whilst maintaining plan quality. Our group developed an automated HA-WBRT RapidPlan model (Auto) and compared it to a manually optimised standard template (Manual) to assess plan quality and planning efficiency.

Methods: A Radiation Oncologist first contoured the hippocampi on 31 patient CT brain data sets fused with MRI with a brain planning target volume (PTV) minus hippocampal avoidance structure, optic chiasm, optic nerve, and lens structures also created. Manual standard template plans were created by an experienced radiation therapist for the first 21 patients with all plans needing to achieve Radiation Therapy Oncology Group (RTOG) 0933 protocol requirements prior to inclusion for creation of the automated RapidPlan model. This Auto model was then tested on a set of 10 separate patients and compared with a Manual plan. The dosimetric parameters and number of optimisations required to achieve protocol requirements were recorded for both.

Results: Both the Auto and Manual plans achieved protocol requirements with Auto plans able to achieve these requirements on 1st optimisation for all 10 patients. In contrast, Manual plans were only able to produce acceptable plans in a single optimisation for 5 patients, with 4 patients requiring 2 optimisations and 1 patient requiring 3 optimisations. PTV coverage met RTOG recommendations for all plans but Auto plans were able to achieve lower doses to the organs at risk (OARs) compared to Manual plans, including significantly lower doses to the hippocampi. Independent dose calculation and patient specific dosimetry measurement had a greater than 99% pass rate.

Conclusions: A department-created automated HA-WBRT RapidPlan model is feasible and allows for more efficient plan creation with significantly better hippocampal doses compared manually optimised plans and physics check confirming deliverability. Auto plans were able to be created with reduced planning time and resource utilization compared to manual plan creation, allowing for streamlining of workflow and reduced time to treatment for patients.

Keywords: Radiotherapy; hippocampal avoidance; RapidPlan; knowledge-based planning; automated planning

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Introduction

It is estimated that 30% of all cancer patients will develop brain metastases with the rate of this likely to continue to increase with the ongoing improvements in systemic treatments in the palliative setting (1). Recent randomized evidence has now shown the treatment of multiple brain metastases to allow for better quality of life and memory outcomes when patients are given hippocampal-avoidance whole brain radiotherapy (HA-WBRT) with memantine as opposed to WBRT with memantine via simple opposed lateral photons (2,3). Furthermore, HA-WBRT has now been established to provide similar intracranial control and overall survival when utilised for prophylactic cranial irradiation in limited stage small cell lung cancer patients with better neurocognitive preservation as compared with WBRT (4). However, the workflow for this new standard is much more time-consuming, requiring inverse planning often delivered with arc therapy, acquisition and fusion of a diagnostic or simulation MRI, and contouring of additional at-risk structures including the hippocampi.

There is also difficulty in planning these more complex cases, requiring increased planning time due to conflicting objectives, potentially requiring several optimisations with the outcome dependent on the planner's experience and skills. The requirement that the maximum dose to the hippocampi be approximately 50% of the prescribed dose per Radiation Therapy Oncology Group (RTOG) 0933 constraints (3) is particularly challenging.

To alleviate these challenges, we explore the use of a knowledge-based automated optimisation engine, RapidPlan (Varian Medical Systems, Palo Alto, CA, USA), which is an addition into the Eclipse treatment planning system and aims to achieve improved plan quality and consistency leading to better efficiency in planning (5). The use of RapidPlan has been widely assessed for different anatomical sites (6-13) with this article outlining the creation and testing of an automated HA-WBRT RapidPlan model (Auto). We present the following article in accordance with the GRRAS reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-21-39/rc).

Methods

Contouring and volume generation

Thirty-one consecutive patient datasets in which the whole brain was CT scanned with IV contrast and same-day MRI fusion were identified. Twenty-one patients were selected to create an Auto model and the remaining 10 patients were used to test the model. From these datasets, the hippocampi were contoured by an experienced Radiation Oncologist following the RTOG atlas (14). The hippocampal avoidance structure was formed using an isotropic 5 mm expansion of the volumed hippocampi and this was subtracted from the brain structure to create the planning target volume (PTV). The inferior level of the PTV volume was the inferior border of C1 if there were no posterior fossa metastases or C2 if there was MRI evidence of posterior fossa metastases. The other organs at risk (OARs) contoured include the optic chiasm and optic nerves and in accordance to RTOG guidelines (3).

The PTV was split into two structures, PTV-High (red) and PTV-Low (green), to allow for better optimisation control in the hippocampal region (*Figure 1*). PTV-Low is defined as the level of the PTV that encompassed the hippocampal region plus 1 slice superior and inferior to this region. This was then subtracted from the PTV to create PTV-High.

Planning parameters

Prescribed dose was 30 Gy in 10 fractions with PTV coverage requirements in accordance to RTOG 0933 and listed in the table below (*Table 1*).

OAR constraints were as per RTOG 0933 guidelines and listed in the table below (*Table 2*). The mean doses to lenses and maximum doses to the eyes were also recorded.

Standard template planning

Five arcs were utilised in the planning process with two full arcs at couch 0 degrees and three half arcs at couch 90 with beams eye views in *Figure 2* and field details in *Table 3*. The three half arcs at couch 90 were utilised for optimisation around the hippocampi specifically field 3 for dose optimisation between the hippocampi (*Figure 2C*), field 4 dose optimisation to the left hippocampi (*Figure 2D*) and field 5 for dose optimisation to the right hippocampi (*Figure 2E*). The isocentre was set at the centre of both hippocampi based on the beam's eye-view. Jaw tracking was also used to reduce the dose to the normal tissue. All plans were optimized with a 6-MV beams on a TrueBeam linac. The manually optimized plans were created for 21 patients and were optimized

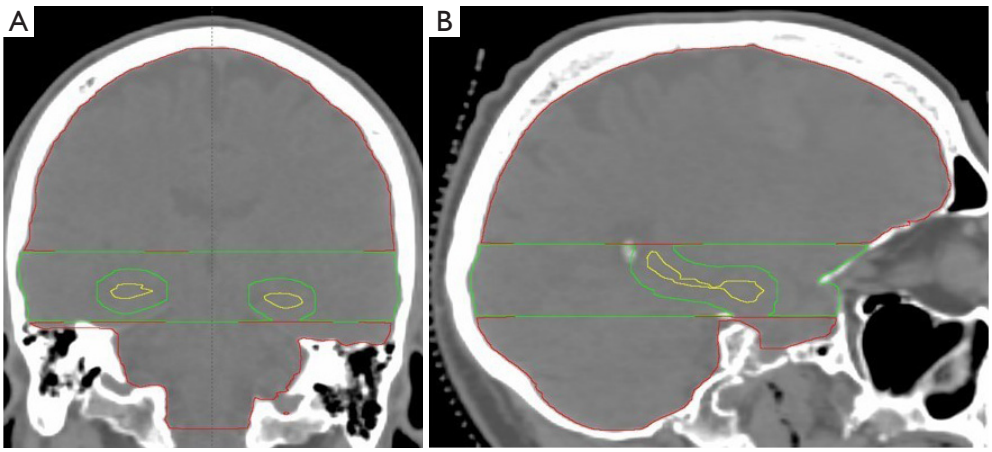

Figure 1 Split PTVs in axial (A) and coronal (B) views. The PTV-Low, PTV-High, and hippocampi are the in green, red and yellow structures, respectively. PTV, planning target volume.

Table 1 RTOG 0933 PTV 30 coverage requirements

Site	Coverage	Max	Unacceptable
PTV 30	D98% ≥25 Gy (ideal)	D2% ≤37.5 Gy (ideal)	V30 <90%
	D98% <25 Gy (acceptable)	D2% ≤40 Gy (acceptable)	D2% >40 Gy

PTV, planning target volume.

Table 2 RTOG 0933 OAR constraints

Structure	Optimal	Acceptable
Hippocampus	D100% ≤9 Gy	D100% ≤10 Gy
	Maximum ≤16 Gy	Maximum ≤17 Gy
Optic chiasm	Maximum ≤37.5 Gy	–
Optic nerve	Maximum ≤37.5 Gy	–

OAR, organ at risk.

through the Eclipse™ (Varian Medical Systems, Palo Alto, CA, USA) Photon Optimizer v15.6 engine with the final calculations performed with the Anistropic Analytical Algorithm v15.6 at a 2.5 mm dose grid sizes.

The order of optimisation priority of the structures was hippocampi as the top priority followed by PTV coverage constraints, lenses and finally the remaining optic apparati. Once all plans achieved the RTOG 0933 PTV coverage requirements and OAR constraints, the plans were assessed by a Radiation Oncologist with the final approved plans for the 21 patients used to create the Auto model. The same standard template planning with manual optimisation approach (Manual) was then applied to the 10 test patients by the same experienced radiation therapist for comparison with RapidPlan produced Auto plans. All plans to create the RapidPlan model as well as all Manual plans were created by the same experienced senior radiation therapist.

Automated RapidPlan model creation

The 21 manually-optimised plans were used to create a v15.6 RapidPlan model by importing 21 Radiation Oncologist approved plans into the dose volume histogram (DVH) estimation model configuration module within Eclipse (Varian Medical Systems, Palo Alto, CA, USA). The software extracts treatment planning information from the imported plans and establishes correlations between plan DVHs, patient anatomy and beam geometry features (15). From the extracted information, the Auto model is trained for each OAR to estimate of DVH curves for new patients.

Automated RapidPlan model validation

This Auto model, without user intervention, was then

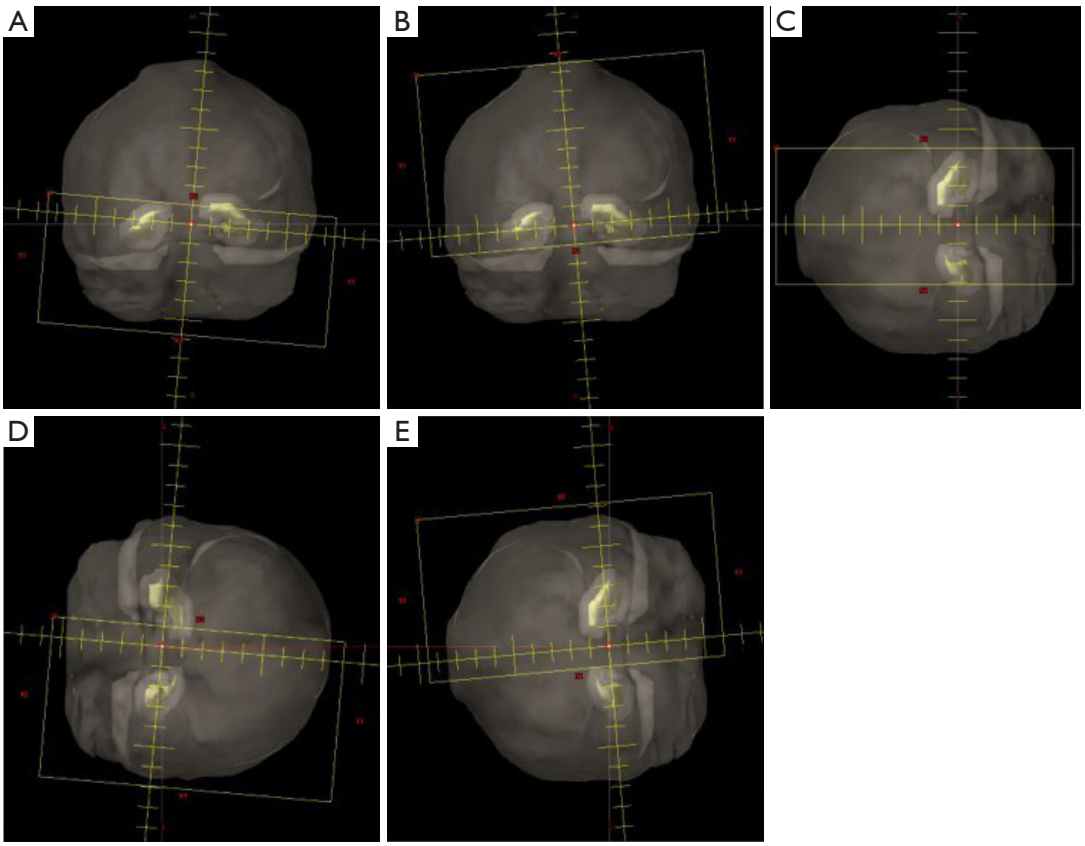

Figure 2 Beams eye view of fields 2 full co-planar arcs (A,B) and 3 half arcs at couch 90 degrees (C-E) with the hippocampi highlighted in yellow.

Table 3 Field parameters used for both Auto and Manual plans

Field	Gantry rotation (degrees)	Direction	Collimator rotation (degrees)	Couch rotation (degrees)
1	179–181	CCW	85	0
2	181–179	CW	95	0
3	179–0	CCW	90	90
4	0–179	CW	85	90
5	179–0	CCW	95	90

Auto, an automated HA-WBRT RapidPlan model; Manual, a manually optimised standard template; CCW, counterclockwise; CW, clockwise.

applied to the 10 test patients to create HA-WBRT plans. For the Auto and Manual plans created on the 10 test patients, DVH data were extracted using the Eclipse Scripting API and compared using the PTV coverage requirements and OAR constraints in *Tables 1,2*. All plans were normalized to achieve V30 Gy target coverage of 90%. Dose homogeneity was assessed using the homogeneity index (HI), calculated as follows:

$$HI = D2\% - D98\% / Dmedian \quad [1]$$

A value close to 0 indicates better dose homogeneity within the target volume.

Conformality index (CI) was also calculated as per

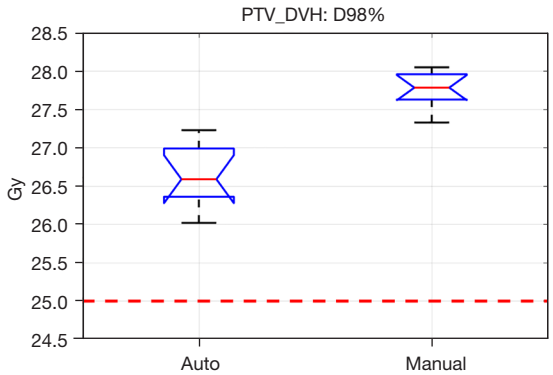

Figure 3 The D98% dose for PTV. The Manual plans D98% value is significantly higher than the Auto plans (P<0.001) but all plans achieved the ideal dose coverage parameter of D98% >25 Gy as per RTOG guidelines. PTV, planning target volume; DVH, dose volume histogram; Auto, an automated HA-WBRT RapidPlan model; Manual, a manually optimised standard template.

Paddick *et al.* (16):

$$CI = TV_{PTV}{}^2 / TV \times V_{RI} \quad [2]$$

where TV is the target volume, TV_{PTV} is the target volume covered by the prescription isodose, and V_{RI} is the total volume covered by the prescription isodose with a CI close to 1 indicating better dose conformity to the target volume size and shape.

Patient specific quality assurance measurements were then performed on the 10 Auto plans to ensure accuracy and deliverability.

Statistical analysis

Statistical comparisons and graphs of the results were performed using Matlab™ with an unpaired two-sample *t*-test used where P<0.05 indicates significance in the difference of the mean values. Boxplots were produced to compare results. These display the interquartile range as a blue box with the median indicated by a red line and outliers shown as red '+' symbols.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Sydney Local Health District-Royal Prince Alfred Ethics Review Committee (reference: X20-0304 & 2020/ETH01446). Consent from patients was not required as datasets and plans were not for clinical use for these patients nor did they affect their management and solely for the creation and validation of the department-specific RapidPlan model.

Results

Both the Auto and Manual approach were able to produce plans that achieved protocol requirements. However, the Auto approach was able to achieve these requirements in its 1st optimisation for all 10 patients whereas the Manual was only able to produce acceptable plans in a single optimisation for 5 patients, with 4 patients requiring 2 optimisations and 1 patient requiring 3 optimisations to achieve protocol requirements. Regarding the Manual plan which required 3 optimisations, the main conflict was in balancing mean lens dose with hippocampi dose constraints.

The PTV coverages for the Auto plans were slightly lower than for the Manual plans but all plans easily achieved the ideal coverage level (*Figure 3*), with D98% greater than 25 Gy for all plans and V30 Gy coverage 90.2% for Manual plans, V30 Gy coverage 90.0% for Auto plans (P=0.405).

Importantly, the Auto plans achieved significantly lower hippocampal doses, with mean D100% for the right hippocampus at 8.51 Gy for and 9.22 Gy for the Manual plans (P<0.001) (*Figure 4*). Mean D100% for the left hippocampus was 8.56 Gy for the Auto planning and 9.24 Gy for the Manual plans with only the Auto plans meeting the ideal RTOG constraint of D100% ≤9 Gy for both hippocampi. The maximum hippocampal dose was also significantly better with Auto planning, at 14.1 and 16.2 Gy respectively for Auto and Manual for the right, and 14.0 and 16.1 Gy for the left (P<0.001) with Auto plans of the two meeting ideal maximal dose constraints for both hippocampi.

As an example, *Figure 5* is a dose colour wash distribution showing the 16 Gy isodose wrapping around the hippocampi for the Auto plan whereas the 16 Gy isodose is within the hippocampal region for the Manual plan.

In terms of the other OARs, maximum dose was less than 37.5 Gy for the optic chiasm and optic nerves for all plans, meeting the optimal dose constraints for RTOG 0933 in both Auto and Manual plans. A mean lens dose of less than 6 Gy was achieved for all Auto plans while the Manual planning failed to achieve this for 1 patient.

In assessing HI and CI between the Auto and Manual

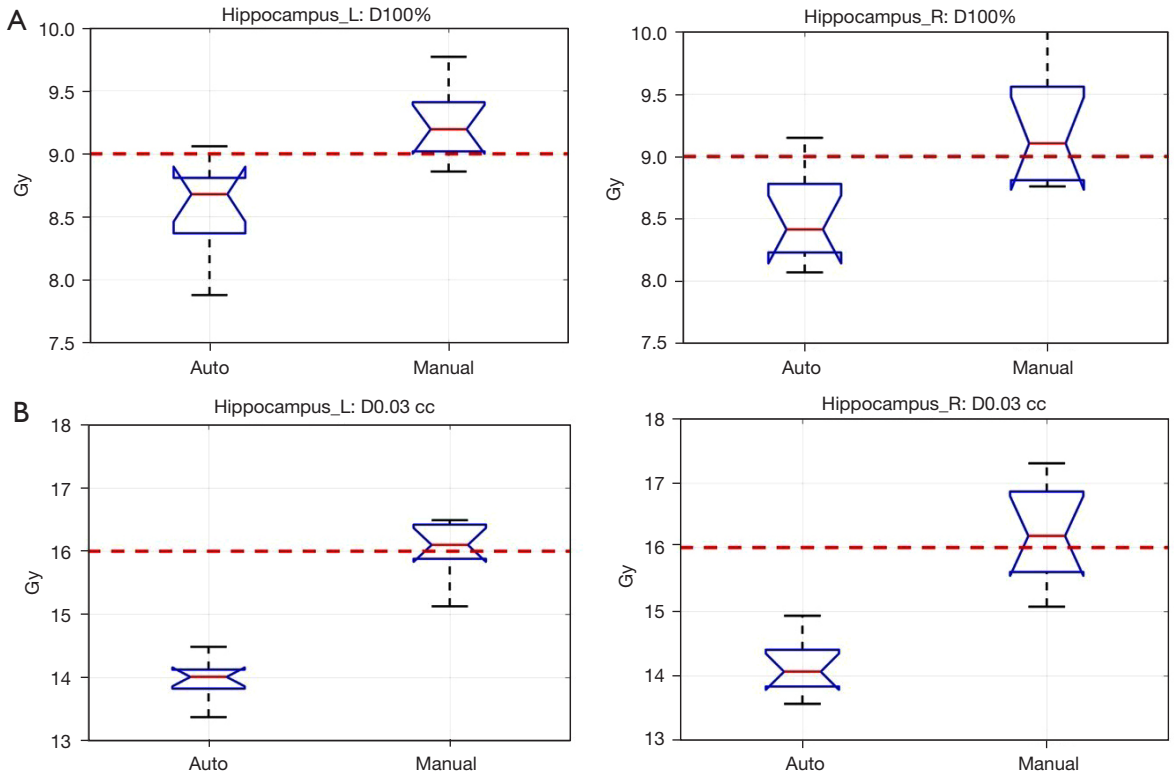

Figure 4 The D100% (A) and D0.03 cc (B) for the left and right hippocampus with the RTOG optimal dose levels displayed as a red dashed line. The Auto dosimetric values are significantly lower than the Manual plans in all cases (P<0.001). Auto, an automated HA-WBRT RapidPlan model; Manual, a manually optimised standard template.

plans, the values were all comparable to each other with low HI and high CI (*Table 4*). The monitor units and complexity of the auto and manual plans were compared using a complexity analysis (17). The Auto plans were found to be more complex (P=0.02) as would be expected. However, as the fluences were simple in both plan sets this did not lead to reduced deliverability. The Auto plans had higher monitor units but this was not significant (P=0.76).

An independent dose calculation and patient specific dosimetry measurement were performed for all 10 Auto plans with all easily achieving the required tolerance levels. The independent dose calculation was performed using SunCHECK™ with point doses for each field agreeing within 3% and PTV gamma pass rates greater than 99% with a 3%/2 mm tolerance.

Patient specific dosimetry measurements were performed using an ArcCheck™ device with pass rates using a 3%/2 mm gamma assessment of 98.8% or above for all fields. In addition, Portal Dosimetry™ measurements were performed and all arc fields passed a 3%/3 mm tolerance at greater than 99% in relative mode. Based on the high pass rates observed and the consistency of the plans produced, ongoing patient specific quality assurance has been streamlined to include only an independent dose check with SunCheck and a Portal Dosimetry fluence check.

Discussion

The Phase III NRG CC001 randomised trial results recently confirmed HA-WBRT with memantine to be superior to WBRT with memantine in diffuse cognitive parameters as well as quality of life with no difference in overall or intracranial progression free survival (2). This new standard of care treatment for multiple brain metastases is of great importance as neurocognitive toxicity has been a major contributor in the diminishing use of traditional WBRT. The PREMER randomized study this year also provided evidence for neurocognitive preservation in prophylactic cranial irradiation with hippocampal avoidance in small cell lung cancer (4), further increasing the utility

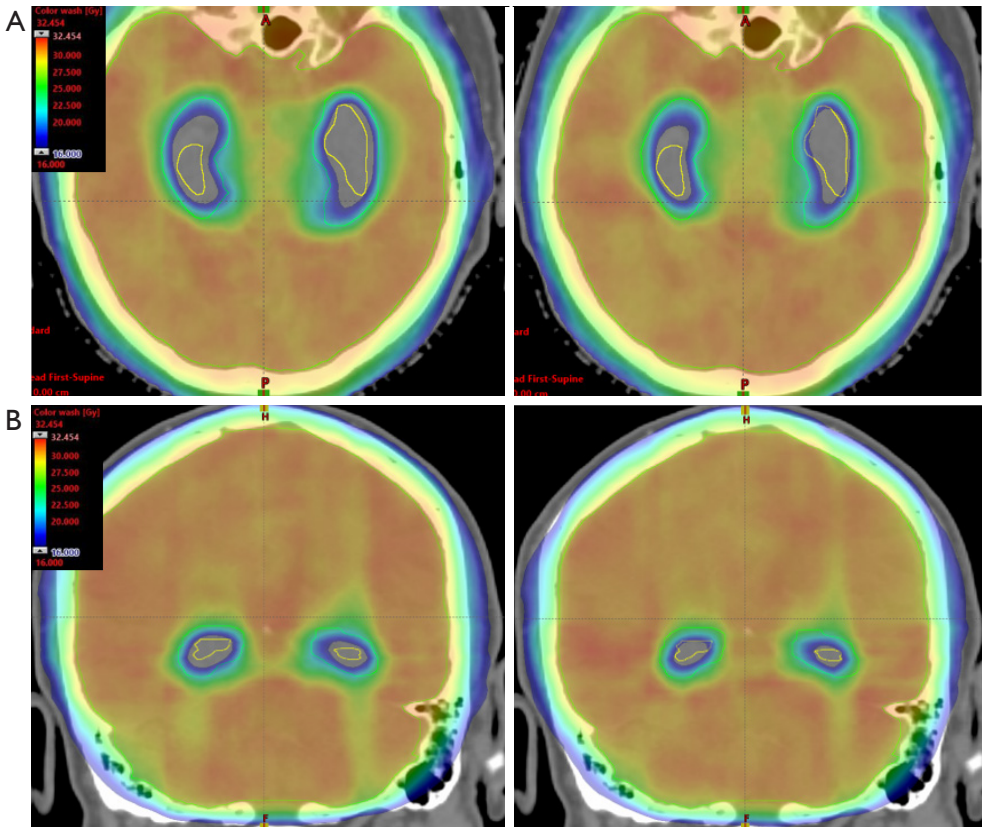

Figure 5 Dose colour wash distribution in axial (A) and coronal (B) views at the level of the hippocampi for Auto (left) and Manual (right). Auto, an automated HA-WBRT RapidPlan model; Manual, a manually optimised standard template.

Table 4 HI and CI for Auto and Manual plans

	Auto		Manual	
	HI	CI	HI	CI
Mean	0.16	0.83	0.13	0.83
SD	0.02	0.02	0.01	0.01

HI, homogeneity index; CI, conformality index; Auto, an automated HA-WBRT RapidPlan model; Manual, a manually optimised standard template; SD, standard deviation.

of HA-WBRT. However, workflow for HA-WBRT is significantly more complicated, requiring up-to-date MRI brain acquisition and fusion, OAR contouring, and complex planning.

To streamline workflow, our prior study assessed whether auto-contouring of the hippocampi via Elements Treatment Planning System had reasonable conformality to clinician manual contours using the RTOG atlas (18). This paper outlines the creation of a department-specific HA-WBRT Auto RapidPlan model and its validation using RTOG 0933 dosimetric parameters and Radiation Oncologist final approval to allow for further downstream efficiency.

Our results first showed that creation of an Auto model from our manually optimised plans using 21 patient plans is feasible. Historically, the number of cases required to create an automated RapidPlan model varied, ranging from 20 to almost 200 (11,19-24), with number of cases likely at least partially dependent on the subsite being assessed. Ueda *et al.* (20) suggested that only 20 cases might be enough to create a model if large variations existed in the

registered cases. This was evident in our study, with our Auto model containing 21 patients able to achieve a single optimisation plan meeting all plan requirements for the 10 study patients. Similarly, Rusu *et al.* (19) utilised an outside-sourced RapidPlan model for HA-WBRT created with 20 patients and were able to produce plans which achieved RTOG 0933 requirements in a single optimization. The fewer cases required is at least partly due to the brain being a relatively stable structure with less variation in anatomy than other sites and the standardized beam arrangement used. This allows for a more expedited process for creation of a department-specific automated RapidPlan model.

A point of difference with Rusu *et al.* (19) was their utilisation of an outside RapidPlan model which they then validated. Our group built our own model which can be invaluable in creating a local model as it considers local planning practices, included contouring, treatment technique and planning goals (25). Schubert *et al.* (26) explored model sharing amongst multiple centres finding that although all cases of RapidPlan plans were clinically acceptable some OARs were better spared in some centres compared to others. This was due to different contouring protocols or emphasis in structures for optimisation priority and certainly we have previously interrogated adherence of our in-house hippocampi contouring to the RTOG atlas (18). Additionally, Ueda *et al.* (20) suggest that for models to be shared successfully that plan design should match between institutions as values created with RapidPlan are influenced by plans contained in the model. A further point of consideration include departmental machine capabilities which may not be considered by an external model.

Our automated RapidPlan model was validated on 10 further patients in comparison with radiation therapist-created manual standard template minimal optimisations required for plan generation that met or exceeded RTOG 0933 plan requirements, thus reducing time and staffing demands for plan creation. Auto plans also had significantly lower hippocampal doses, optimizing neurocognitive preservation with this memory-critical structure. Doses to optic nerves, chiasm and lenses were also lower with Auto plans, again potentially further reducing toxicity. The results did show a slightly lower dose to the PTV D98 in the Auto plans compared to the Manual plans and this was because our top priority was to minimise the dose to the hippocampi while still meeting optimal dose coverage requirements, the goal of which was met.

The dosimetric verification of the plans prior to implementation of the model clinically demonstrates that the plans created are deliverable but also reduces the chance of patient delays due to failing dosimetric measurements. The simplification of patient specific quality assurance based on a standardized and reproducible planning method reduces the physics resource requirements and expedites the physics checking process contributing to a streamlined workflow and efficiency of clinical implementation.

Conclusions

This paper has shown the feasibility of an automated HA-WBRT RapidPlan model created from 21 standard template plans with department-specific prioritizations. The department specific automated RapidPlan model was then validated in comparison with plans optimized by a standard template of objectives with plans generated meeting RTOG 0933 constraints on first optimization and with significantly better hippocampal doses as well as lower optic apparati and lens doses. The plans were also all dosimetrically verified for clinical implementation, mimicking clinical practice and ensuring deliverability. This paves the way for true clinical implementation and real world streamlining of HA-WBRT treatment with quicker plan turnaround and minimized resource utilisation.

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Footnote

Reporting Checklist: The authors have completed the GRRAS reporting checklist. Available at https://tro.amegroups.com/article/view/10.21037/tro-21-39/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-21-39/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Sydney

Local Health District-Royal Prince Alfred Ethics Review Committee (reference: X20-0304 & 2020/ETH01446). Consent from patients was not required as datasets and plans were not for clinical use for these patients nor did they affect their management and solely for the creation and validation of the department-specific RapidPlan model.

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