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Original Research Article

Optimising tumour coverage and organ at risk sparing for hypofractionated re-irradiation in glioblastoma

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ABSTRACT

Background and purpose: Re-irradiation may be used for recurrent glioblastoma (GBM) patients. In some cases Planning Target Volume (PTV) under-coverage is necessary to meet organ at risk (OAR) constraints. This study aimed to develop a Volumetric Modulated Arc Therapy planning solution for GBM re-irradiation including a means of assessing if target coverage would be achievable and how much PTV 'cropping' would be required to meet OAR constraints, based on PTV volume and OAR proximity.
Materials and methods: For 10 PTVs, 360°, 180°, two coplanar 180° and 180° + non-coplanar 45° arc arrangements were compared using 35 Gy in 10 fractions. Using the preferred arrangement, dose fall-off was modelled to determine the separation required between PTV and OAR to ensure OAR dose constraints were met, with data presented graphically. To evaluate the graph as an aid to planning, seven cases with overlap were replanned in two treatment planning systems (TPSs).
Results: There were no significant dosimetric differences between arc arrangements. 180° was preferred due to shorter treatment times. The graph, which indicated if 95% PTV coverage would be achievable based on PTV volume and OAR proximity, was employed in seven cases to guide planning in two TPSs. Plans were deliverable.
Conclusions: Re-irradiation treatment planning can be challenging, especially when PTV under-coverage is necessary. 180° was considered optimal. To assist in the planning process, graphical guidance was produced to inform planners whether PTV under-coverage would be necessary and how much PTV 'cropping' would be required to meet constraints during optimisation.

1. Introduction

Glioblastoma (GBM) is the most common brain tumour in adults. Following initial treatment, most tumours recur after a median of seven months [1]. Re-irradiation may be employed at recurrence, although practice varies in terms of uptake, dose and fractionation and organ at risk (OAR) constraints. The most appropriate OAR constraints for re-irradiation are unknown, although overlap with the original target often means OARs have already received doses close to tolerance. As is typical with existing re-irradiation protocols [2], Planning Target Volume (PTV) under-coverage may be expected when the target lies close to or overlaps with an OAR that was previously irradiated to high dose. As well as respecting specific OAR constraints, it is also recognised that high cumulative doses to normal brain tissue should be minimised to reduce the risk of radionecrosis [3]. Previous recurrent GBM re-irradiation studies have focussed on the implementation of novel imaging and precision radiotherapy [4,5], while others have focussed on the overall survival and quality of life [6–8]. However, to date there has been little published regarding Volumetric Modulated Arc Therapy (VMAT) planning solutions for recurrent GBM.

Given the lack of existing literature, the aim of this study was to develop a solution for GBM re-irradiation planning, which included a means of assessment as to whether 95% coverage of the PTV was achievable and how much PTV 'cropping' for optimisation would be required to meet constraints, based on re-irradiation PTV size and location relative to OARs and OAR constraints. This will provide a useful aid to those planning GBM re-irradiation.

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2. Methods

2.1. Re-irradiation protocol

The prescription dose (P_x) was 35 Gy in 10 fractions, a commonly used schedule [2], using VMAT. The gross tumour volume (GTV) consisted of recurrent enhancing tumour. A 3 mm clinical target volume (CTV) margin was added and edited for anatomical barriers. A 5 mm isotropic PTV margin was used. The previous doses to OAR were used when determining optimal (rather than mandatory) OAR constraints for re-irradiation. To simplify this process, maximum doses (D0.1 cm^3) to each OAR were recorded from the previous plan and the 'doses remaining' in 10 fractions were read from local planning guidelines (supplementary material (SM), tables A-D). The optimal constraints allowed 25% repair between courses, while the mandatory constraints were from the RTOG1205 protocol (randomising between re-irradiation and bevacizumab and bevacizumab alone) [2], which used the same dose; SM, tables A-D. Mandatory constraints were independent of the dose received by the OAR during the original radiotherapy. Optimal dose coverage was considered as 95% of the PTV receiving 95% of the P_x (33.25 Gy). Mandatory constraints for brain OARs were prioritised over PTV coverage, which was prioritised over optimal optic nerves, chiasm and brainstem constraints, which, were prioritised over other OARs (SM, tables A-D).

Therefore, in order to meet mandatory constraints, PTV undercoverage was permitted in cases where there was overlap or close proximity between the PTV and an OAR that was previously irradiated to high dose. PTV coverage would not require to be compromised to meet optimal constraints, taking into account previous dose and repair.

2.2. Arc arrangements

All treatment planning in 2.2 to 2.3 was performed by one Medical Physicist (MP). Planning in 2.4 was performed by the same MP and two Dosimetrists.

Datasets for 14 re-irradiated GBM PTVs were used; 10 PTV volumes were those of previously treated patients and four were generated artificially to provide more cases where there was PTV-OAR overlap (SM, figure A). Artificial PTVs were manually created by an experienced Clinical Oncologist (LM). The locations of artificial PTVs were similar to those encountered clinically but with PTV-OAR overlap. Patients were previously treated on a Versa HD linac (Elekta AB, Sweden) with 6MV FFF. Of the fourteen PTVs, seven had PTV-OAR overlap (cases A, C, E, G, H, I, K).

Four arc arrangements were compared for the 10 clinical targets (i.e. excluding the artificial PTVs): one 360° arc (1FA); one 180° arc (1PA); two 180° arcs (2PA); one 180° arc and one non-coplanar 45° arc (2NPA).

For each plan, the following were assessed: CTV/PTV: D50%, D2%, D98%, D95% (PTV only); OAR: mean/max doses; Conformity Index (CI): volume 95% isodose/PTV volume; Homogeneity index (HI): (D2-D98%)/D50%; R50: volume of 50% isodose/PTV volume; maximum dose 1 cm from PTV (D_{max} 1 cm); MU per fraction; estimated delivery time (EDT).

In cases of OAR overlap, optimisation structures that excluded the region of PTV-OAR overlap were created for the purposes of planning (labelled PTV_Opt). All reported doses, however, reflect the whole structure [9]. PTV_Opt is created by subtracting the OAR(s) that overlap with the PTV *plus* a margin from the OAR(s), determined in 2.3. Plans were generated using RayStation version 8B (TPS1) (RaySearch Laboratories, Stockholm, Sweden).

2.3. Achievability of 95% PTV coverage

During plan generation in 2.2, the ability to cover the PTV was influenced by the dose difference between the P_x and the OAR dose constraint. The greater the dose difference, the greater the distance required between PTV and OAR to allow adequate dose fall-off. To generate a guide as to the distance required between an OAR with a dose constraint and the PTV, in order to achieve 95% PTV coverage, and to give an indication the minimum amount of PTV 'cropping' that would be required in order to meet constraints during the optimisation process, dummy spherical PTVs ('spheres') were generated using the same isocentres as the 10 clinical plans (cases A, B, D, F, I, J, K, L, M, N). These were grown from 10 cm^3-90 cm^3 in 20 cm^3 increments to represent the range of typical GBM PTV volumes, Fig. 1, i.e. 5 'spheres' generated per isocentre. Despite being created as spheres, the 'sphere' was never extended by more than 5 mm into an OAR to reflect CTV trimming to anatomical boundaries prior to PTV formation. This approach was used for simplicity to produce nearly isotropic dose distributions that could be used for modelling while maintaining clinically representative PTVs

A clinical plan was generated for each sphere using the 1PA arrangement. During planning, no dose constraints were applied and 'sphere' coverage was prioritised. This generated a dose gradient falling from the D95% level (Fig. 1). The volumes of isodoses were calculated using the Treatment Planning System (TPS) and assumed to be spherical. Therefore, the radius of each isodose was approximated. This assumption became more inaccurate at lower doses, so no isodoses < 12 Gy were included. Distances between the D95% isodose and different isodose levels (i.e. potential OAR constraints) were calculated for each 'sphere' and median distances (cm) were plotted.

2.4. Re-planning and generalisability between TPSs

VMAT plans were generated for seven of the above cases (A, C, E, G, H, I, K, i.e. those with PTV-OAR overlap; three clinical PTVs and four artificial PTVs) in both TPS1 and Monaco (TPS2) (Elekta AB, Sweden) using 1PA arc and the graph generated from 2.3 to guide coverage. The isocentres of the three clinical cases used here were shared with those used to generate the model in 2.3, but the PTVs were different. Plan metrics were compared with those of the 1PA arc from 2.2 (for the seven overlap cases) to investigate if an improvement had been made in the same TPS, using the updated planning method. Replanning was performed by a MP who subsequently trained two dosimetrists who planned case A in TPS1 using the graph from 2.3. The time taken to optimise the plans was recorded and compared to average time taken to create GBM re-irradiation plans on TPS2 over the past 12 months. The following dose volume statistics were evaluated for PTV/PTV_Opt: D99%, D98%, D95%, D50%, D2% and D1%.

The purpose of training dosimetrists was not to validate the use of the graph, as the sample size is too small, but was to provide an initial indication that the graph could be used to successfully guide planning. In addition, the dosimetrists completed a questionnaire (SM, dosimetrist questionnaire).

Although designed with the intention of assisting the planner in determining if 95% coverage would be achievable and the degree of PTV 'cropping' that would be required for optimisation, the graph was also evaluated with reference to the optimal constraints in seven cases (cases A, B, C, D, E, H, J; 38 OARs). Not all cases were included because for 3/7, all the OARs were outside the predictive capacity of the graph and for 4/7, the dose received was minimal, so further optimisation was unnecessary.

2.5. Plan deliverability

The seven plans generated in TPS1 in 2.4 were delivered on a Versa HD linac and measured using the Delta4 detector array (Scandidos, Uppsala, Sweden). The tolerance for the gamma analysis was 3%/3mm overall. The global gamma was calculated with a 20% threshold [10].

2.6. Statistics

The Wilcoxon signed-rank test was performed to compare the four

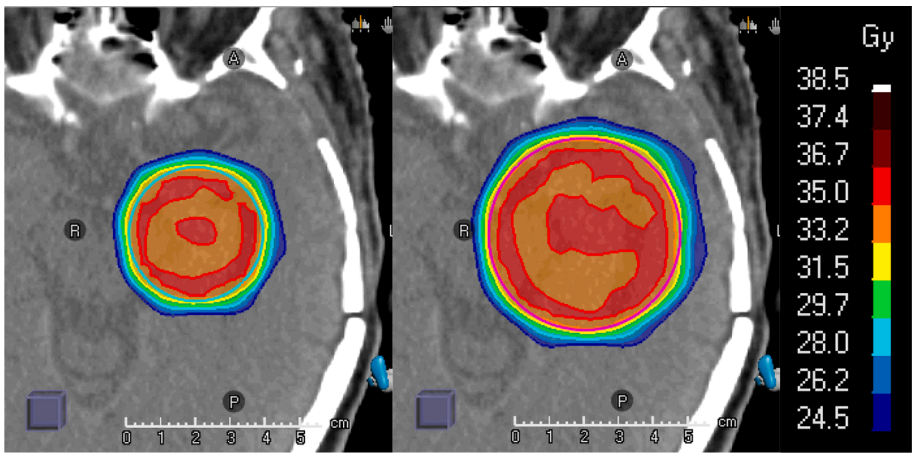

Fig. 1. Example of dummy 'PTV spheres' with different volumes: 30 cm^3 (left) and 90 cm^3 (right), with enlarged dose scale. It can be seen that lower isodose levels are associated with less symmetrical isodose lines and so 12 Gy was chosen as a lower limit for modelling (see text).

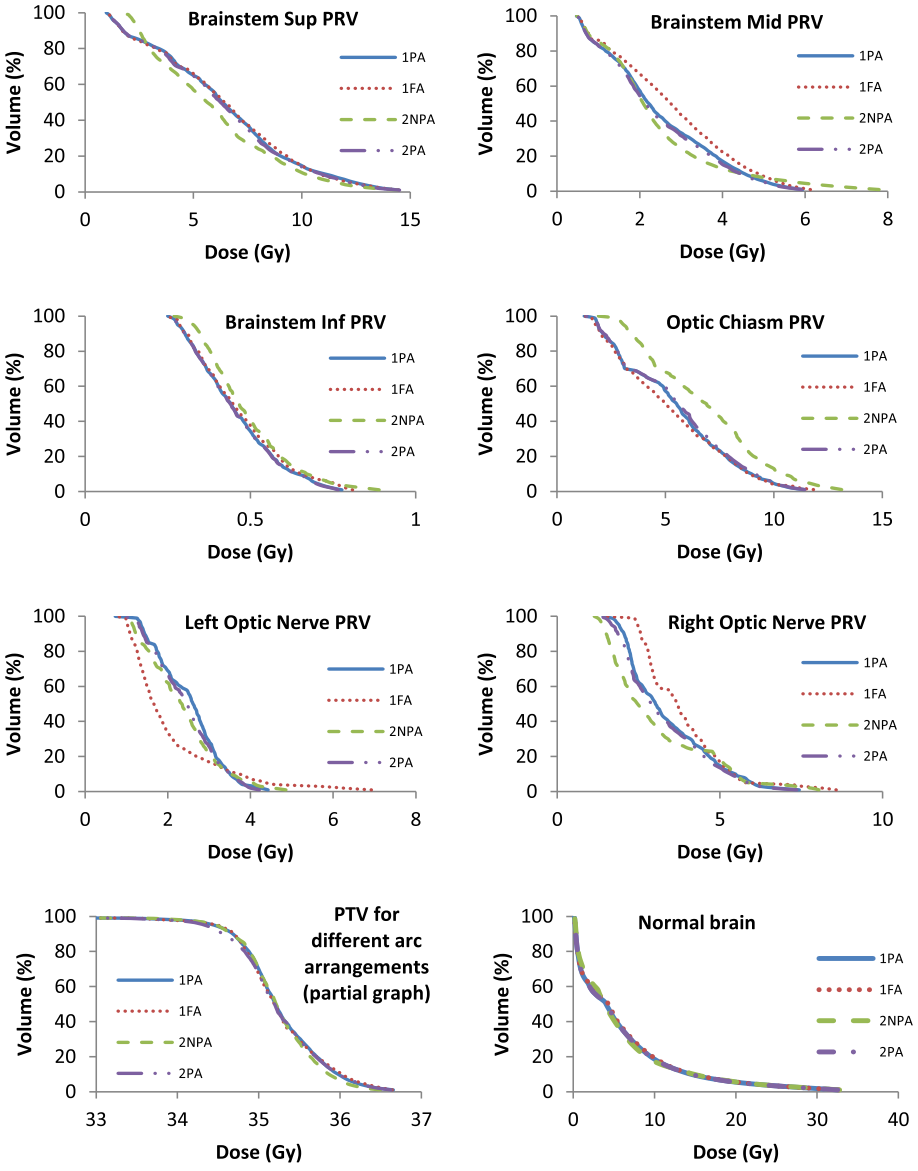

Fig. 2. Dose volume histogram s for different structures using median values across the 10 cases. Vertical axis volume (%), horizontal axis dose (Gy). No statistically significant differences observed between different beam arrangements.

arc arrangements (using 1PA data as base values). $p \leq 0.05$ was considered statistically significant. Statistics were performed using Microsoft Excel.

3. Results

3.1. Arc arrangement

All mandatory OAR tolerances were met using all four arc arrangements in all cases. PTV under-coverage was required in 3 cases as a result of PTV-OAR overlap. Median PTV D95% for 1PA was 34.4 Gy, for 1FA was 34.5 Gy, for 2NPA was 34.3 Gy and for 2PA was 34.5 Gy. Plans were highly conformal with CI $\leq$ 1.2 and homogeneous, HI = 0.1.

There was no significant difference between arc arrangements (Fig. 2) except for EDT, which was significantly lower for 1PA ($p = 0.005$; SM, table E). However all EDT were <2.5 min and thus considered clinically acceptable. The faster delivery time for 1PA made this the preferred arc arrangement.

3.2. Achievability of 95% PTV coverage

The distance required for dose fall-off between the PTV and an OAR with a specific constraint, while achieving 95% coverage, varied with PTV volume (Fig. 3): larger PTV volumes required greater distances for the same dose level. The required distance increased with a decreasing dose level. Where the distance between the PTV and OAR was below the required distance as indicated by the graph, PTV under-coverage was anticipated.

3.3. Re-planning and generalisability between TPSs

Median PTV D95% for seven TPS1 plans, generated without the guidance graph was 19.7 Gy (2.2). For the seven TPS1 replans, generated with the guidance graph (2.4), it was 26.7 Gy and for TPS2 plans, generated with the guidance graph, 23.6 Gy (Fig. 4, SM, table F). These values are lower than in 2.2 because only cases with PTV-OAR overlap were included in this analysis.

Due to the low sample size, it was not possible to perform statistical comparisons between approaches; however, the plans generated using the graph result in visually improved PTV coverage at the low dose end, without clear detriment in OAR doses at the high dose end (Fig. 4).

The times for the dosimetrists to optimise case A were approximately A: one hour and B: two hours. The average time to optimise GBM re-irradiation plans over the last year was approximately two hours.

Dose-volume statistics were similar between the plans produced by both dosimetrists and the MP (SM, table G). All mandatory OAR constraints remained within tolerance.

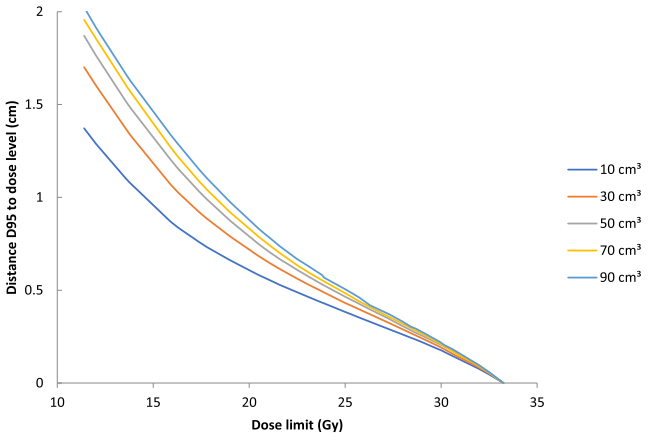

Fig. 3. Distance from D95% to dose level (cm) against OAR dose limit (Gy) for different PTV volumes (cm^3). The larger the PTV volume or the lower the dose limit, the greater the distance required for sufficient dose fall-off.

In all cases, for any optimal constraint, where the relevant OAR was positioned further from the PTV than the distance specified on the graph (31 OARs), the optimal constraint was met. For the remaining seven OARs (six cases), it was also possible to achieve coverage and respect the optimal constraint, as a result of a different OAR in each case requiring a mandatory constraint to be met with PTV under-coverage, such that dose fall off began before the edge of the PTV and thus at a lesser distance than predicted by the graph (SM, figure B).

3.4. Plan deliverability

All seven plans passed the gamma analysis (SM, table H). The average MU delivered by 1PA was 970.2. Mean actual delivery time for 1PA was 61 s, higher than the EDT for 1PA.

4. Discussion

This paper aimed to develop a solution for GBM re-irradiation planning, including a means of assessing achievability of 95% PTV coverage. A 1PA arc arrangement was preferred because of reduced EDT (2.2). A model was developed to indicate the minimum amount of PTV 'cropping' from an overlap region required to meet constraints during optimisation, based on PTV size and location relative to OARs (2.3). This model was employed by a MP and two dosimetrists (2.4). All the plans were deliverable (2.5).

In recurrent GBM re-irradiation, optimal OAR constraints are unknown so a balance is struck between delivering meaningful dose while minimising toxicity. While data on normal tissue recovery in brain OARs are lacking, recovery data for the spinal cord suggests that after six months, at least 25% repair may be assumed [11]. As such, in this study only 75% of the previous OAR dose is used when determining remaining dose for re-irradiation. Despite this, it may still be challenging to achieve coverage in instances of PTV-OAR overlap. As such, a set of mandatory constraints were included, based on RTOG1205 [2]. These constraints were prioritised over PTV and could necessitate PTV under-coverage. Both differing OAR constraints on a per-patient basis and the likelihood of PTV under-coverage can pose challenges.

For PTV-OAR overlap, PTV coverage may be compromised [2]. However, the degree of compromise will be variable because of variation in PTV volume, OAR proximity and individual OARs constraints. We aimed to provide a means of assessing the minimum amount of PTV 'cropping' from a region of PTV-OAR overlap required to meet constraints, by producing a graph that was used as a starting point for planning. The purpose of the graph is to minimise planner testing and to provide perspective of what is possible based on the mandatory constraints. For larger PTV volumes, a greater distance was required for a specific OAR dose limit because the dose required a greater distance to fall-off to the same level. Further challenges with larger PTVs result from these occupying a larger proportion of the brain, increasing OAR proximity likelihood. Also, the higher the dose limit, the easier it was to achieve dose constraints because the distance required for the dose to fall-off from the level of the PTV was less. In cases where there is PTV-OAR overlap, as often occurs [11], then mandatory constraints will invariably be employed and the PTV compromised, as the PTV P_x exceeds the mandatory dose limits of the OARs. A limitation of the model is that it is not representative for a relatively smaller PTV situated close by an OAR and thus with relatively more overlap, as this was not modelled.

As only two dosimetrists were trained in planning using the graph, no meaningful comparison between the optimisation times with and without the graph can be made. Furthermore, the average time of the pre-graph technique came from plans of variable complexity over a one year period. In addition, time differences could be attributed to differences in TPS calculation times. Despite these issues, it must be acknowledged that the dosimetrists had less training and experience

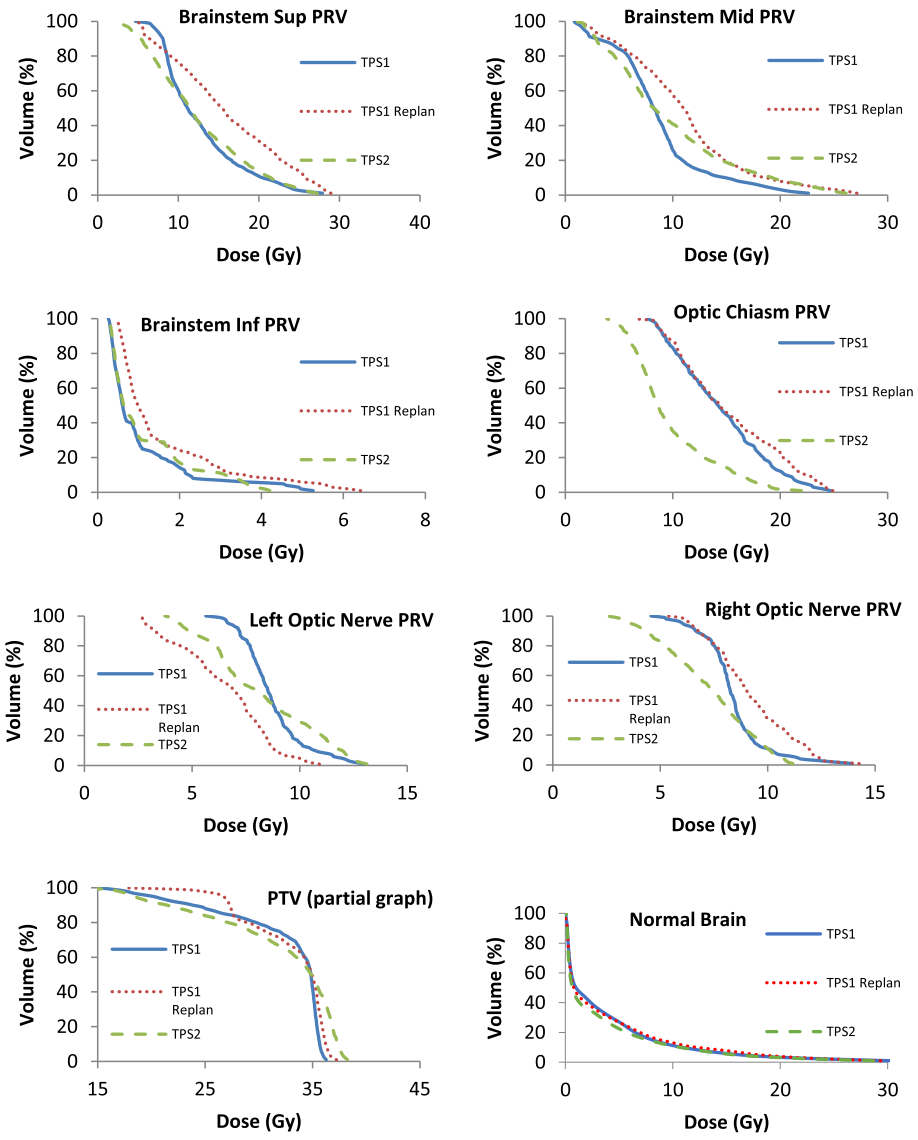

Fig. 4. Dose volume histograms for different structures using median values across 7 overlap cases. TPS1 used the results from 2.2, TPS1 Replan and TPS2 followed the methodology in 2.3. Vertical axis volume (%), horizontal axis dose (Gy).

using the new technique in TPS1 than the previous technique, and so the preliminary results could be considered encouraging. Variability of the PTV dose statistics were low between dosimetrists and the MP, which is also encouraging

We have confirmed the generalisability of our approach across two TPSs and have demonstrated that plans are deliverable.

Multiple series regarding brain re-irradiation in patients with relapsed high grade glioma (HGG) have been published [12–14]. The amount of detail provided regarding planning techniques for external beam radiotherapy (EBRT) is highly variable and often brief. The use of non-coplanar arcs have been described (e.g. [4,6,15,16]). The RTOG1205 trial permits re-irradiation delivery by any FDA cleared EBRT system and advises multiple non-coplanar arcs. Further details are not provided [2]. Other series also provide little detail regarding OAR constraints for re-irradiation and cumulative radiobiological approaches are infrequently described [17]. Attempts to determine normal tissue complications based on retrospective cumulative doses have, however, been made [18]. Similar arc arrangements to those used in this study have been investigated in regard to PTV-OAR overlap [19], showing significant reductions in treatment times and critical OAR doses for single vs. double arc arrangements, which further justifies the choice of 1PA in the current study; however, this study investigated primary HGG rather than recurrent GBM. Furthermore, previous studies have acknowledged PTV coverage is sub-optimal when dealing with PTV-OAR overlap [20] but we are not aware of any other studies assessing if 95% coverage was achievable in the setting of brain re-irradiation.

One limitation of this work is the sample size which limited statistical analysis such that it was not possible to correct for multiple hypothesis testing. Furthermore, the locations of the PTVs were similar in some cases, which could limit the generalisability of our results, although the cases represent locations encountered in practice. Including a greater number of cases would overcome these limitations, although the numbers here are not dissimilar to those in other studies [21–23]. Our work is limited by using artificial GTVs in four cases, in order to increase the number of cases with PTV-OAR overlap. Further work in a larger number of patient cases would confirm the validity of our solution. Despite these limitations, this study describes a pragmatic approach to re-irradiation planning. We chose not to investigate using more than two arcs, as limiting the time the patient spends on the couch was preferred to reducing dose spill into normal brain. The addition of more arcs could be investigated as further work, to establish the degree to which plans would improve versus delivery time. Lastly, only two dosimetrists

performed re-irradiation planning using the graph. Clearly, additional treatment planners would need to be trained to draw conclusions.

Re-irradiation planning can be challenging because of the use of individualised constraints and the need to accept under-coverage in order to respect mandatory OAR constraints. For brain re-irradiation we found a 1PA arrangement to be preferable and have created a means of assessing if 95% coverage is achievable and what degree of PTV 'cropping' of a region of PTV-OAR overlap is required, during the early stages of optimisation, based on tumour size, OAR distance from the re-irradiation PTV and OAR constraints.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2022.02.012.

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