Physics and Imaging in Radiation Oncology 29 (2024) 100536

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

The impact of fluorine-18-fluoroethyltyrosine positron emission tomography scan timing on radiotherapy planning in newly diagnosed patients with glioblastoma

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ARTICLE INFO

Keywords:
Glioblastoma
PET
CTV
Radiation Therapy
Radiotherapy Planning

ABSTRACT

Background and purpose: Glioblastoma is one of the most common and aggressive primary brain tumours in adults. Though radiation therapy (RT) techniques have progressed significantly in recent decades, patient survival has seen little improvement. However, an area of promise is the use of fluorine-18-fluoroethyltyrosine positron-emission-tomography (^{18}F-FET PET) imaging to assist in RT target delineation. This retrospective study aims to assess the impact of ^{18}F-FET PET scan timing on the resultant RT target volumes and subsequent RT plans in post-operative glioblastoma patients.

Materials and Methods: The imaging and RT treatment data of eight patients diagnosed with glioblastoma and treated at a single institution were analysed. Before starting RT, each patient had two ^{18}F-FET-PET scans acquired within seven days of each other. The information from these ^{18}F-FET-PET scans aided in the creation of two novel target volume sets. The new volumes and plans were compared with each other and the originals.

Results: The median clinical target volume (CTV) 1 was statistically smaller than CTV 2. The median Dice score for the CTV1/CTV2 was 0.98 and, of the voxels that differ (median 6.5 cc), 99.7% were covered with a 5 mm expansion. Overall organs at risk (OAR) and target dosimetry were similar in the PTV1 and PTV2 plans.

Conclusion: Provided the ^{18}F-FET PET scan is acquired within two weeks of the RT planning and a comprehensive approach is taken to CTV delineation, the timing of scan acquisition has minimal impact on the resulting RT plan.

Abbreviations: ^{18}F-FET PET, fluorine 18 -fluoroethyltyrosine positron emission tomography; BTV, biological target volume; CT, computed tomography; CTV, clinical target volume; Dice, dice similarity coefficient; EORTC, European Organization for Research and Treatment of Cancer; ESTRO-EANO, European Society for Therapeutic Radiology and Oncology - European Association of Neuro Oncology; FET, fluoroethyltyrosine; FIGR, functional image-guided radiotherapy; GTV, gross tumour volume; ICRU, International Commission on Radiotherapy Units; MRI, magnetic resonance imaging; OAR, organs at risk; ORBIT-RT, Online Real-time Benchmarking Informatics Technology for RadioTherapy; PET, positron emission tomography; PTV, planning target volume; RT, radiation therapy; RTOG, Radiotherapy and Oncology Group; TMZ, temozolomide; TPS, treatment planning system; VMAT, volumetric modulated arc therapy.

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https://doi.org/10.1016/j.phro.2024.100536
Received 2 September 2023; Received in revised form 1 January 2024; Accepted 9 January 2024
Available online 17 January 2024

1. Introduction

Glioblastoma is a devastating disease, with 3.2 cases diagnosed per 100,000 people annually and patients experiencing a post-diagnosis survival of less than 7% at 5 years [1]. Current guidelines for glioblastoma recommend maximum safe surgical excision, followed by concurrent chemo-radiotherapy with temozolomide (TMZ), followed by adjuvant TMZ [2].

Outlining the target for glioblastoma radiation therapy (RT) treatment is a crucial step in the RT process and relies on image guidance. However, there are variations in the guidelines and institutional practice around clinical target volume (CTV) delineation. The main international bodies that guide RT practice for glioblastoma (European Society for Therapeutic Radiology and Oncology - European Association of Neuro Oncology (ESTRO-EANO) and, Radiotherapy and Oncology Group (RTOG)) recommend different guidelines from each other [3,4]. A single-phase approach of 60 Gy is recommended by ESTRO-EANO and, in contrast, RTOG recommends a two-phase approach of 54 Gy and 60 Gy. Further, a large proportion of radiation oncologists follow practitioner-specific local guidelines [5]. However, glioblastoma treatment with RT continues to evolve according to emerging technology [6], clinical knowledge [7] and professional expertise [8,9]. There is growing support to change the target outlining process by incorporating functional image-guided radiotherapy (FIGR) [10–12]. Fundamental to this new process is the concept of a biological target volume (BTV) [13]. The BTV may be used in combination with the anatomically derived gross tumour volume (GTV) to create an individualised CTV that is more specific and sensitive for disease overall [14].

A recent paper by ESTRO-EANO recommended fluorine 18 -fluoroethyltyrosine positron emission tomography (^{18}F-FET PET) as an additional tool to assist in glioblastoma target delineation, though they acknowledged financial barriers as an impediment to access [15]. In the ESTRO-EANO paper, the amino acid PET-aided studies used a 0–1.5 cm GTV-CTV margin [15]. This reduced GTV-CTV margin is based on the belief that (^{18}F-FET PET) in combination with magnetic resonance imaging (MRI) is more specific than MRI alone, when determining the extent of cerebral gliomas [16]. Additionally, Fleischmann and colleagues demonstrated that when technology-specific GTV-CTV margins are used with combined (^{18}F-FET PET)-MRI, the glioblastoma CTV decreased in size, the dose to the healthy brain tissue was reduced, and patients experienced a similar pattern and frequency of recurrence [14]. However, there is still uncertainty around the impact of (^{18}F-FET PET) scan timing on the resultant CTV [17].

This retrospective study aims to assess the impact of ^{18}F-FET PET scan timing on the CTV and subsequent RT plans, in newly diagnosed patients with glioblastoma.

Table 1
Patient Cohort, Imaging and Treatment Timeline Details.

Par #	Study	Age	Pathology	Location	Methylation	Primary Surgical	Progression	MRI Type	MRI Time	FET Time		RT CT Time	RT Start Time
										1st Scan	2nd Scan		
1	FGL005SP	53	Small Cell Glioma	Right frontotemporal	Unmethylated	Craniotomy stealth microsurgical technique	Local recurrence in right temporal region	T1 Ax & FLAIR Ax	Day + 44	Day + 49	Day + 56	Day + 40	Day + 66
2	FGL006RS	36	Astrocytoma	Left frontal	Methylated	Craniotomy and resection	New lesion left basal ganglia	T2 Ax & FLAIR Ax	Day −2	Day + 49	Day + 56	Day + 28	Day + 61
3	FGL009PB	60	Astrocytoma	Right frontotemporal	Methylated	Craniotomy and excision	Local recurrence in right temporal region	T1 Ax & FLAIR Ax	Day + 20	Day + 29	Day + 36	Day + 20	Day + 35
4	FGL013SW	58	Astrocytoma	Left frontal	Methylated	Stealth guided craniotomy	Local recurrence in left frontal region	T1 Ax & FLAIR Ax	Day + 24	Day + 33	Day + 40	Day + 24	Day + 40
5	FGL015SO	58	Astrocytoma	Right parietal	Unmethylated	Craniotomy and incomplete resection	No recurrence	T1 Ax & T2 Ax	Day + 15	Day + 28	Day + 35	Day + 21	Day + 40
6	FGL016LM	56	Astrocytoma	Right frontal	Unmethylated	Craniotomy and decompression	Local recurrence in right frontal region	T1 Ax	Day + 14	Day + 20	Day + 27	Day + 18	Day + 39
7	FGL019KM	43	Astrocytoma	Right temporal	Unmethylated	Lesionectomy	Local recurrence in right temporal region	T1 Ax & FLAIR Ax	Day + 1	Day + 29	Day + 35	Day + 22	Day + 48
8	FGL022DW	61	Astrocytoma	Left Parietal	Not available	Stealth guided craniotomy	New lesions corpus callosum and left parietal lobe	T1 Ax & T2 Ax	Day + 20	Day + 31	Day + 40	Day + 24	Day + 45
Average									Day + 17	Day + 34	Day + 41	Day + 25	Day + 47

Par # Participant Number, *MRI* Magnetic Resonance Imaging, *FET* Fluoroethyltyrosine, *RT* Radiation Therapy, *CT* Computed Tomography, *Ax* Axial and *FLAIR* Fluid Attenuated Inversion Recovery. Time measurements are relative to the primary surgical date.

2. Materials and Method

2.1. Study data

The imaging and RT treatment data of eight patients diagnosed with glioblastoma and treated at a single institution under a prospective study (Australian New Zealand Clinical Trials Registry number ACTRN12614001114639) [18] were analysed (RMIT Ethics 2020–23043-10513).

Inclusion criteria included a newly diagnosed glioblastoma and adjuvant post-operative radiation therapy (Table 1). Study participants underwent two RT planning (^{18}F-FET PET) scans post-surgery, in addition to the standard local RT treatment workup of MRI and computed tomography (CT) RT planning scans (Table 1). An RT planning CT scan, MRI scan/scans, two (^{18}F-FET PET)-CT scans and RT volumes were available for analyses (Table 1). The individual patient's timeline for imaging and treatment is provided in Table 1. The (^{18}F-FET PET) scan acquisition details and a comparison between the BTVs outlined has been reported elsewhere by Ferjančič and colleagues [17]. All RT planning scans were acquired in the supine position, with the patient's head immobilised using a mask, and using a slice separation of 2.5 mm.

2.2. Image Processing

The MRI and (^{18}F-FET PET) CT scans were co-registered to the RT planning CT scan with a six-degrees-of-freedom rigid-registration in Eclipse® Version 16.1 (Varian Medical Systems, Palo Alto, California, USA). Cranial bones and ventricular surfaces were used as landmarks for matching. The (^{18}F-FET PET) thresholding volumes created as part of the Ferjančič 2021 study [17] were imported into Eclipse to aid BTV outlining.

Target volumes and OAR were outlined by an experienced radiation therapist/clinical medical dosimetrist (10 + years) with advice from two radiation oncologists with specialisations in neuro-oncology (Fig. 1 and Table 2). This advice was provided over three hours and across three online sessions, while screen sharing. Discussions focused on methods and reviewing the delineated volumes.

2.3. Treatment planning

Radiation therapy treatment plans were subsequently generated in Eclipse® Version 16.1 (Varian Medical Systems, Palo Alto, California, USA) using beam data based on a Varian Truebeam® machine with a Millennium-120 multi-leaf collimator. A consistent approach to planning was applied for each patient. An individual RT plan was created for each patient's PTV1 and PTV2 with a prescription of 60 Gy in 30 fractions to the PTV, and at least 98% of PTV covered by 58.2 Gy and less than 2% of PTV covered by 64.2 Gy. Each plan consisted of two 360-degree 6 MV volumetric modulated arcs with opposing collimators (30% and 330%). The Online Real-time Benchmarking Informatics

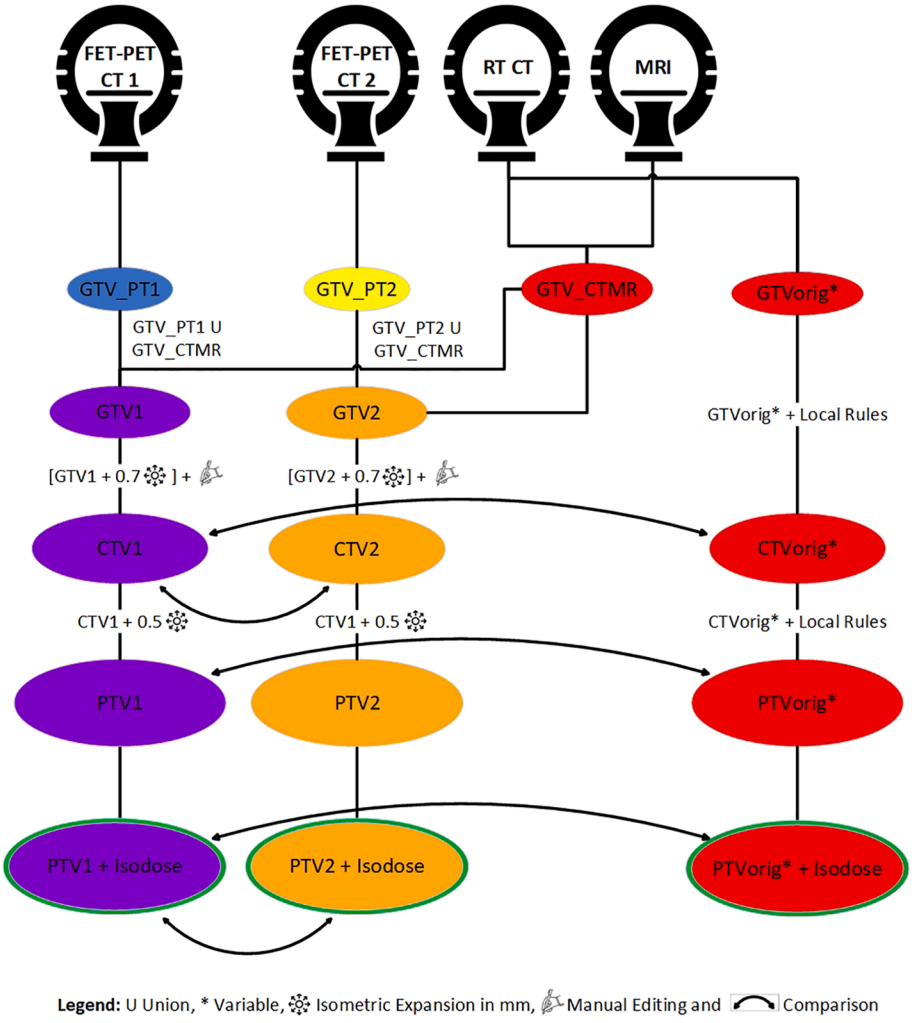

Fig. 1. An overview of the target outlining process and volume comparisons.The CTV1 was compared with the CTV2 and the CTVorig. The PTV1 was compared with the PTVorig. The PTV1 plan 95% dose distribution was compared to the PTV2 and PTVorig. The PTV2 plan 95% dose distribution was compared to the PTV1.

Table 2
Targets and Organs at Risk Outlining Process.

Targets	Description and Outlining Process
GTVorig	The gross tumour volume as delineated on the original RT treatment plan. Practitioner-specific approaches were used across the cohort.
GTV_PTx	The gross tumour volume as delineated on a (^{18}F-FET PET) CT scan. A normal background FET standardised uptake value was calculated by creating a spherical volume (1.9 cm^3) in the contra-lateral hemisphere of the brain at approximately the same location as the malignancy. The standardised uptake value average (SUVaverage) of this volume was recorded. A volume that was 1.6 times the SUVaverage was outlined using the Eclipse thresholding tool. Areas of the scalp or cranium bone were subsequently manually removed along with any high uptake that was distal and not connected to the volume.
GTV_MRCT	The gross tumour volume as delineated on the fused RT planning CT and MRI images following the guidelines by Niyazi et al. 2016 [19]. All high-intensity signal on the post-surgery MRI images were included.
GTVx	The gross tumour volume as delineated on a (^{18}F-FET PET) CT, MRI and RT planning CT scan. A boolean union of the GTV_MRCT and GTVPTx created the GTVx.
CTVorig	The clinical target volume as delineated on the original RT treatment plan delivered. There were practitioner-specific
approaches were used across the cohort.	
CTVx	The clinical target volume as delineated on the GTVx with an isometric expansion of 0.7 cm and manually edited for known barriers to tumour invasion, as per the guidelines by Niyazi et al. 2016 [19].
PTVorig	The planning target volume as delineated on the original RT treatment plan delivered. Pactitioner-specific approaches were used across the cohort.
PTVx	The planning target volume as delineated on the CTVx with a 0.5 cm expansion and following the guidelines by Niyazi et al. 2016 [19].
Organs at Risk	Bones were auto-contoured using the density segmentation wizard. The brain, brainstem, Cochlea_L/R, Gland_Lacrimal_L/R, Hippocampus_L/R, Lens_L/R, OpticChiasm, OpticNrv_L/R, Pituitary, Retina_L/R were contoured as per guidelines by Eekers et al. [20]. The Spinal Cord, Eye_L/R_Ant, Eyes_L/R_Post and Glnd_Lacrimal_L/R were contoured as per guidelines by Brouwer et al. [21].

RT Radiation Therapy, *CT* Computer Tomography, *MR* Magnetic Resonance, *FET* Fluoroethyltyrosine, *PET* Positron Emission Tomography and *x* FET Scan Number 1 or 2

Technology for RadioTherapy (ORBIT-RT) [22] glioblastoma rapid plan model was imported to reduce doses to OAR. If a particular OAR (i.e. hippocampi and pituitary) was not included in the ORBIT-RT rapid plan model the local hospital's clinical protocol was used to guide optimisation for that OAR. OAR optimisation objectives were patient-specific and OAR goals were secondary to target coverage goals in this study, therefore if an optimisation objective was adjusted in the PTV1 plan on a patient it was also adjusted in the PTV2 plan. The OAR goals used were, brain V33/66/100 less than 60/50/45 Gy [23], brainstem max dose less than 54 Gy [24], cochlea mean dose less than 45 Gy [25], hippocampus mean dose less than 10 Gy (local practice), lens max dose less than 10 Gy [26], optic-chiasm max dose less than 54 Gy [26], optic nerve max dose less than 56 Gy (local practice) and the pituitary mean dose less than 40 Gy [27]. No plan normalisation was used post-optimisation. The "RATING" guideline [28] was used to guide plan reporting (Appendix A: RATING Scorecard).

2.4. Analyses

After planning, the 95% isodose line was converted into a structure in each plan. The plans were then exported to ProKnow DS® (Elekta AB, Stockholm, Sweden) to facilitate two types of analyses. Firstly, individual plans were grouped into collections in ProKnow DS® to facilitate grouped dosimetric analyses. Secondly, ProKnow DS® and Golden Rule® [29] were used to analyse the relationship between the volumes specifically.

The dosimetric analyses consisted of extracting dose-volume histogram data from plans that were grouped based on the optimisation target. The extracted plan metrics included the D2%, D98%, D95% for the PTV1, PTV2, PTVorig, and all OAR metrics listed previously.

In the volume comparisons, the reference volume has been labelled as the first volume, and the comparison volume as the second volume. In this study CTV1 was compared to CTV2, CTV1 was compared to CTVorig, PTVorig was compared to PTV1, PTV1 was compared to the PTV2 plan 98% and 95% isodose, PTV2 was compared to the PTV1 plan 98% and 95% isodose, and PTVorig was compared to the PTV1 95% isodose (Fig. 1). Quantitative volume comparison metrics were computed in GoldenRule®. Appendix B shows the structure comparison parameters on which GoldenRule® extracted the data. Basic descriptive volume comparison metrics were reported, including total volume, total volume overlap, total missing volume, total extra volume, total different volume and Dice score. The more novel descriptive volume comparison metrics reported include the max distance to the matching of either extra or missing voxels, and the percentage of voxels that are either missing or extra but would be within 5 mm of the alternate volume.

To test the impact on target coverage if the alternate (^{18}F-FET PET) scan was used for planning, dosimetric and volume comparisons were completed for both the PTV and CTV. The coverage of the CTV2/PTV2 target was assessed dosimetrically in the PTV1-optimised plan at the D98% and D95% dose levels, and the CTV1/PTV1 target at PTV2 plans' D98% and D95% dose levels. The PTV1 target was also compared to the 95% isodose line volume from the PTV2 plan, and PTV2 target was compared to the 95% isodose line volume from the PTV1 plan. Further analyses compared the missing volume of the PTV outside the alternate plan's 95% isodose line volume.

The median and range of the volume and dosimetric metrics were calculated, and a 2-tailed Wilcoxon signed-rank test was used when testing for statistical significance using Microsoft Excel® [30].

3. Results

3.1. Volume comparisons

All volume and dosimetry metrics extracted from the RT plans are available in Appendix C and D. It was found that the CTV1 was very similar to CTV2 with a median Dice score of 0.98 (volumes 130 cm^3 and 143 cm^3) and less than five percent of the voxels demonstrating a difference. However, the CTV1 was statistically smaller than CTV2 (Appendix C). The missing and extra voxels between CTV1 and CTV2 were mostly (99.7%) within 5 mm of each other and are therefore likely covered by the alternate RT plans' high-dose-region (Fig. 2).

A comparison of the original targets and the novel targets (CTV1 and PTV1) was impossible for two patients, as a two-phase RTOG approach was used in their original plans. There was no significant difference in the other patients' total volumes of either CTV1 and CTVorig or PTV1 and PTVorig ($N = 6$). The median total volume for PTV1 (238 cm^3), PTV2 (204 cm^3) and PTVorig (239 cm^3) were very similar (Fig. 2 and Appendix C). However, the Dice score of 0.76 shows relatively high agreement between PTVorig and PTV1 (volumes 239 cm^3 and 238 cm^3), but only 66% of voxels that differed were within 5 mm of each other, and are therefore unlikely to be covered by the alternate RT plans' high-dose-region.

The median matching volume in Fig. 3 indicates that the PTV2 95% isodose line volume covers the PTV1 target by 100% but the PTV1 95% isodose line volume covers the PTV2 target by only 95% (Fig. 2 and Appendix C). There was also a significantly larger volume of voxels of

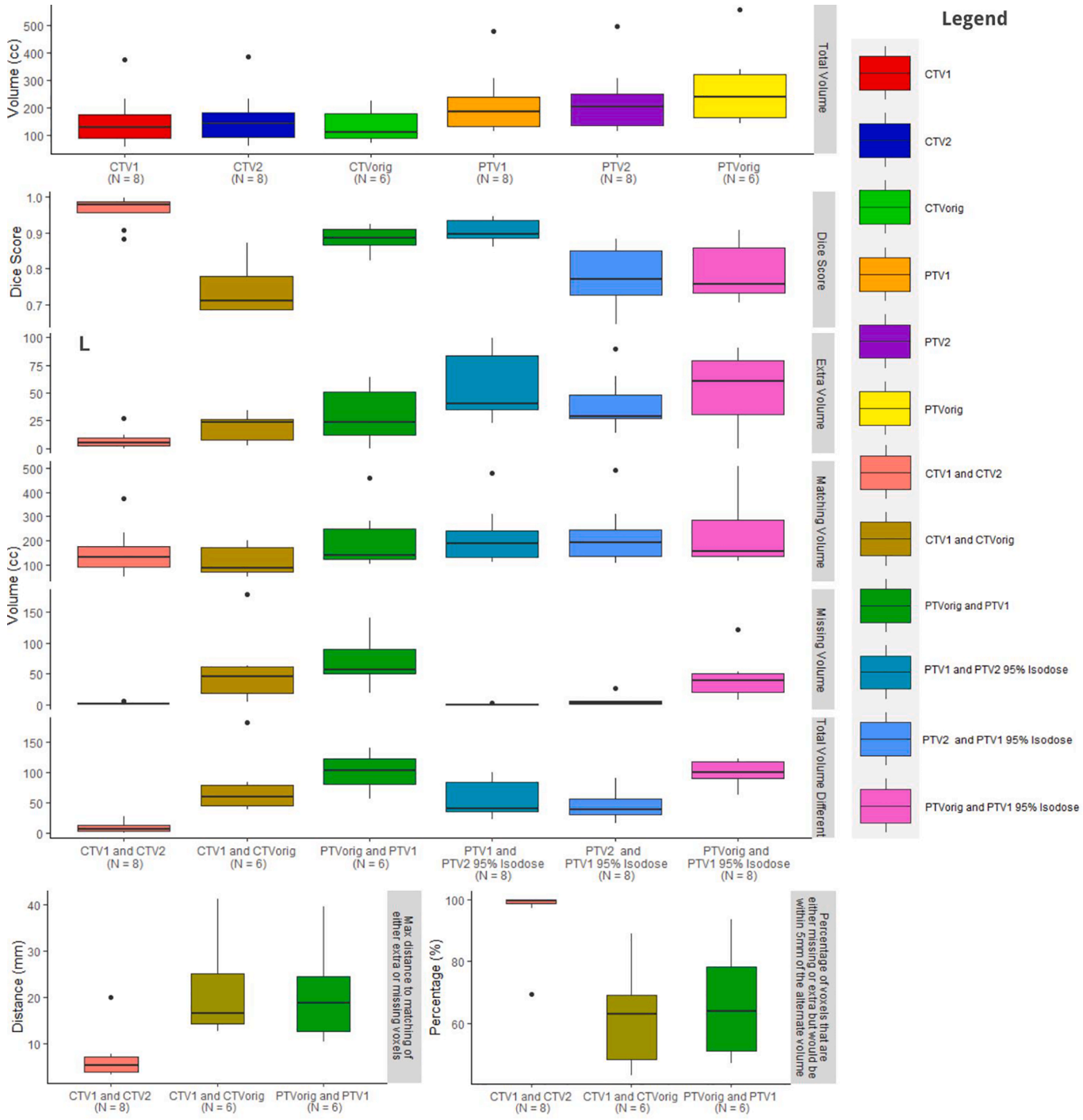

Fig. 2. The quantitative comparisons of target and dosimetry volumes including the Total Volume, Dice Score, Extra Volume, Matching Volume, Missing Volume, Total Volume Different, Max Distance to Matching of either Extra or Missing Voxels, and the Percentage of Voxels that are within 5 mm of the Alternate Volume.

novel PTV2 (median 2.5 cm^3) outside the PTV1 95% isodose line volume, compared to the PTV1 (median 0.3 cm^3) outside the PTV2 95% isodose line volume (Appendix C, $p < .05$ and $N = 8$). Table replace figure as recommended by Reviewer 2

3.2. Radiation therapy planning

When comparing the dosimetry of the PTV1 plans with the PTV2 plans, target coverage and OAR doses were similar. The median increase in the right hippocampus and right optic nerve doses in the PTV2 plan were not statistically significant (Fig. 3). However, when comparing the D98% and D95% coverage of the PTV2 target in plans that were optimised for the PTV1 target and vice versa, there are statistically significant differences (Fig. 3, $p < .05$ and $N = 8$ and Appendix D). The D98% and D95% of the PTV1 plans do not cover the PTV2 target as well as the D98% and D95% of the PTV2 optimised plan on the PTV1 target. The CTV coverage by the alternate plan was not different.

Direct comparisons between the novel and treated plans were completed for five of the eight patients as two patients were treated with a two-phase approach and original dosimetry was not available for one patient (Appendix D). The median volume of normal brain tissue receiving 60, 50 and 45 Gy was reduced in the novel PTV1 and PTV2

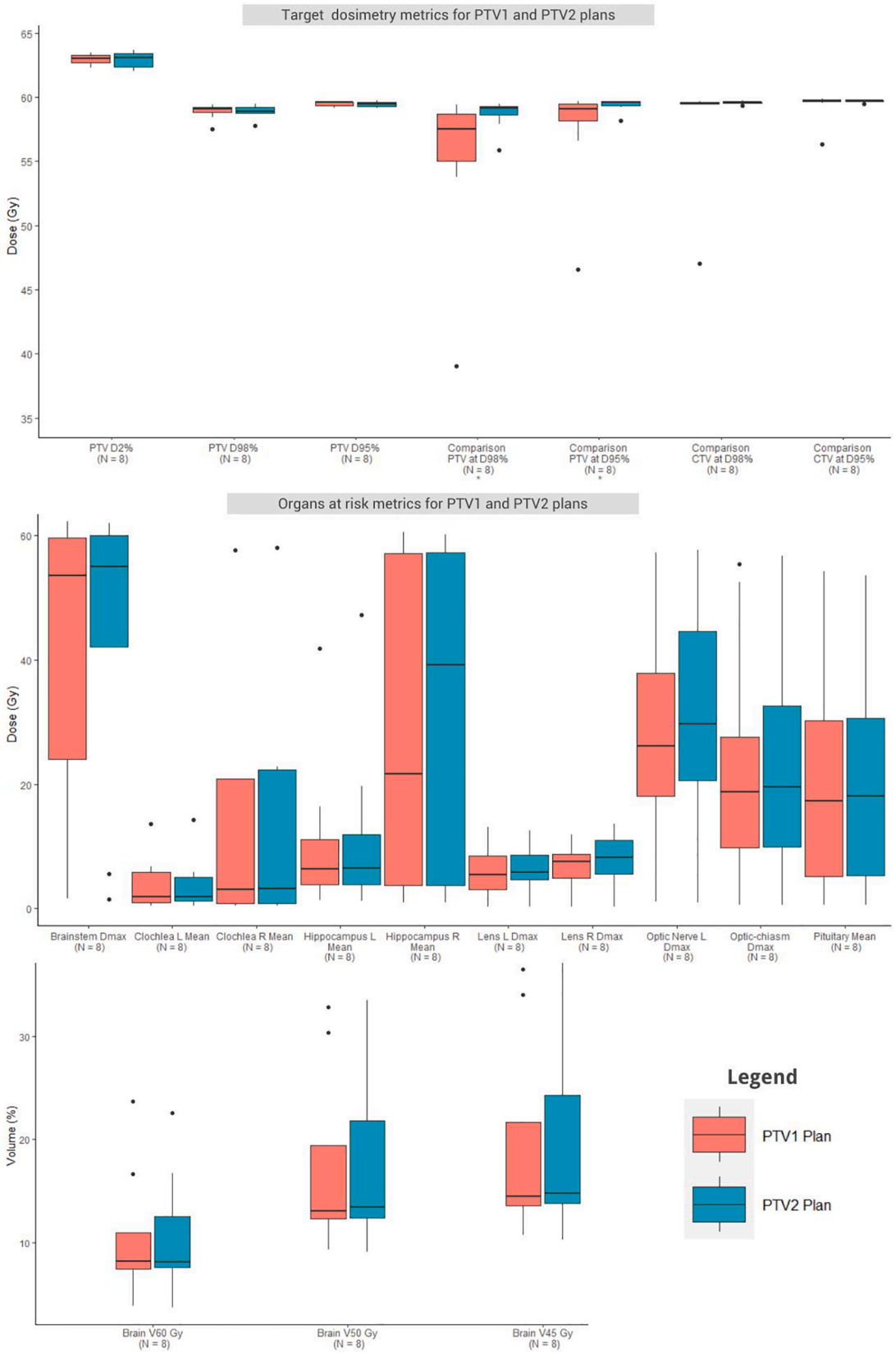

Fig. 3. Target and organ at risk dosimetry metrics for PTV1 and PTV2 plans. * Statistically significant using a p-value of $<.05$ on a Wilcoxon 2-tailed signed-rank test to indicate significance.

plans compared to the PTVorig plan (N = 5). The median mean dose to the left and right hippocampus and pituitary were also lower in the novel plans (N = 5). Overall OAR doses are similar if not generally improved in the novel plans (Appendix D).

4. Discussion

To the authors' knowledge, this is the first time-dependent volume comparison and RT planning study with a (^{18}F-FET PET) customised targets for patients with newly diagnosed glioblastoma. This study adds to previous work [17,12] and was conducted in the context of a larger Phase II prospective trial involving (^{18}F-FET PET) in glioblastoma treatment [31], and the changing attitude towards the value of (^{18}F-FET PET) in glioblastoma patient care [15].

Ferjančič and colleagues demonstrated substantial variation in the BTV outlined based on fluoroethyltyrosine (FET). In Ferjančič's study, the BTVs outlined had mean volume sizes of 31.5 cm^3 and 35.0 cm^3 and a mean dice similarity coefficient (Dice) score of 0.66 [17]. This study assessed whether this variation in the BTVs due to (^{18}F-FET PET) scan timing impacts the resultant CTVs and plans.

The eight patient datasets used in this study are representative of the typical glioblastoma patient profile in terms of age profile, tumour location and methylation status (Table 1). The (^{18}F-FET PET) scans were acquired systematically but MRI scans and original RT planning varied between patients (Table 1). The MRI scans to support RT planning were not ideal with one MRI scan acquired 30 days before the RT planning scan (Participant 2). Current guidelines recommend that MRI scans are acquired no more than 14 days before the RT planning scan [15]. The original RT plans used a mixture of practitioner-specific techniques with ESTRO-EANO, RTOG and unique local practices followed. Therefore, the nomenclature, expansion margins and manual editing processes varied between patients within the original RT plans and made direct comparisons between new volumes and treated volumes impossible for participants six and seven, as a two-phase approach was used in their original plan.

Core to this research was the creation of a novel outlining method that used functional and anatomical information from the CT, MRI and PET scans and clinical practice knowledge to create realistic target volumes. Given the variation between institutions and clinicians, this approach may not be consistent with future recommendations. As no formal guidelines currently exist to guide this process, the method described in Table 2 and Fig. 1 will likely require refinement. Future work may consider a Delphi and a prospective study to inform clinical guidelines. A 0.7 cm GTV-CTV margin was used in this study for the (^{18}F-FET PET) aided GTV-CTV margin, amino acid-PET studies have used between 0–1.5 cm GTV-CTV margins [15]. Based on the results of this study and the work of Fleischmann et al. 2020 [14], it is recommended that future studies test a 1–1.5 cm GTV-CTV margin with FET-PET aid CTV outlining.

The total volume metrics used in the comparisons of the target volumes in this study indicate that the new outlining pathway produces reasonable targets in terms of overall size, which is important in terms of the deliverability of resultant RT plans and their toxicity profile (Fig. 2 and Appendix C). The median total volume size of the novel volumes (CTVx and PTVx) are smaller than similar volumes reported previously [32,33,14] though comparing different populations between studies is not recommended given the small number of participants in the current study.

The maximum distance to the matching of either extra or missing voxels is a useful metric as it indicates the suitability of a plan when overlayed on an alternate volume, in terms of under or over-coverage. It is clear from Fig. 2 that the voxels that differ between CTV1 and CTV2 are relatively close to the corresponding volume and would therefore most likely be in the corresponding plan's high-dose-region. However, the median difference between the new and original target volumes (CTV1/CTVorig and PTV1/PTVorig) is 16 and 19 mm and would therefore be outside the standard high-dose-region.

The novel target volume pair (CTV1 and CTV2) are very similar, the median Dice score between the pair was high (median Dice 0.98, median volumes 130 cm^3 and 143 cm^3) and the median max distance to matching was low (0.52 cm, Fig. 2). Furthermore, the majority of any differences between the CTVs (99.7%) are within the resultant PTV plan's high dose region (Fig. 2). However, the variation in the BTV pair described by Ferjančič and colleagues [17] (median Dice score 0.74, median volumes 21.41 cm^3 and 16.71 cm^3 and median Hausdorff distance 0.27 cm^3) needs to be accounted for if glioblastoma RT practice changes to incorporate a boost or use a heterogeneous dose prescription based on the BTV.

The dosimetry comparison between the PTV1 and PTV2 plans demonstrated that changes in PTV size due to (^{18}F-FET PET) scan timing had a minimal impact on individual plan dosimetry. However, the PTV2 optimised plans cover the PTV1 targets more efficiently than the PTV1 optimised plans cover the PTV2 target (Fig. 2 and 3). There were significant differences in terms of coverage by the alternate plans', with PTV2 coverage at D98% and D95% reducing ($p < .05$ and N = 8). Therefore, as the time between (^{18}F-FET PET) scanning and RT treatment starting increases, the GTV-CTV margin may have to be increased by 1–2 extra mm to ensure coverage. These findings indicate that once the (^{18}F-FET PET) is acquired relatively close to the start of RT, one week's difference in scanning has minimal effects on the efficacy of the RT plan.

Our study has several limitations. Firstly, as it is retrospective with limited patient numbers, the clinical implications of the novel target outlining pathway and, individual patient differences due to the timing of surgery and RT starting, are untested. Secondly, the heterogeneous nature of the original planning techniques used makes direct comparisons between patient outcomes and delivered plans impossible. Thirdly, there were resource limitations as this work extends across multiple areas of rapidly evolving RT professional group practice. Finally, the margin recipe used to create the novel CTV1 and CTV2 is based on literature, clinical experience, testing, consultation and was created with only one main observer who was not fully blinded to the comparison volumes or original planning volumes.

This work showed that the variation in (^{18}F-FET PET) scan timing had minimal impact on the new CTVs produced. Therefore, provided the (^{18}F-FET PET) scan is acquired within two weeks of the RT starting, the specific period of the scan acquisition has minimal impact on the resultant dosimetry.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

Generative artificial intelligence has not been used by the authors during this study or creating this manuscript.

Funding

John Ryan was supported by an Australian Government Research Training Program Fee-Offset Scholarship.

The 2020 Victorian Medical Radiation Practitioners Education Trust Award supported this research.

Ethical Declaration

Consent for publication

All the authors have approved the manuscript and agree with submission to your journal.

Author's contributions

John Ryan researched the topic, drafted the study protocol, carried out the study, analysed the results, drafted and submitted this paper.

Martin Ebert provided the original data and outlined the research question. He reviewed the final paper and provided comments prior to submission.

Roslyn Francis provided the original data. She was the original principal investigator on the 'Determining prognosis and treatment response: novel imaging modalities for glioblastoma" trial. She reviewed the final paper and provided comments prior to submission.

Peter Ferjančič carried out research on the same datasets and provided his data as a starting point for this research. He reviewed the final paper and provided comments prior to submission.

Sweet Ping Ng reviewed radiation therapy planning volumes and provided advice on the methodology. She reviewed the final paper and provided comments prior to submission.

Eng-Siew Koh reviewed radiation therapy planning volumes and provided advice on the methodology. She reviewed the final paper and provided comments prior to submission.

Moshi Geso provided advice on the methodology. He reviewed the final paper and provided comments prior to submission.

Jennifer Kelly reviewed the final paper and provided comments prior to submission.

Nick Hardcastle provided continuous input into the methodology and analyses used in this study. He enabled some of the planning techniques used. He reviewed the final paper and provided comments prior to submission.

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.

Acknowledgements

Seonad Madden for all the proofreading and advice around syntax.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, athttps://doi.org/10.1016/j.phro.2024.100536.

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