White-Matter Informed Tumour Spread Mapping and Diffusion/Perfusion MRI for Personalized GBM Targeting

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MOTIVATION

Radiotherapy of glioblastoma (GBM), the most aggressive type of brain tumour, currently does NOT utilize personalized radiation treatment margins.

Radiotherapy (RT) planning begins with a simple outlining of the Gross Tumour Volume (GTV), with a 15-20 mm fixed spatial margin (Clinical Target Volume-CTV), and an additional 5 mm margin (Planning Target Volume-PTV), see Fig.1.

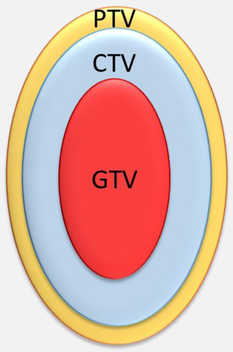


Figure 1. Standard RT volumes

However, studies have shown integrating data from multiple advanced Magnetic Resonance Imaging (MRI) techniques can enhance the detection of glioblastoma[1-3].

Kim et al[4] demonstrated the unique Biological Target Volume (BTV) subregions identified by combining high b-value diffusion MRI with relative Cerebral Blood Volume (rCBV) maps. Grade IV glioma cells have also been shown to infiltrate healthy tissue through white matter (WM) tracts[5].

In our previous work[6], we have introduced a new metric, i.e. the Tumour Spread (TS) map, which was developed using Diffusion Tensor Imaging (DTI), to predict the pattern of tumour growth via WM tracts. We used this map to personalize the clinical target volume to better contour regions at high risk of spread and recurrence.

The TS map was calculated for every voxel in the brain using in-house MATLAB code, based on the ratio of the number of WM fiber tracts within that voxel extending to the GTV tumor surface (N) and the square of the lengths of those fibers (L), i.e. $TS \propto \frac{N}{L^2}$

The resulting TS map was then thresholded to define the personalized CTV (i.e. $pCTV_G$), which was unique to each patient's brain anatomy, see Fig. 2.

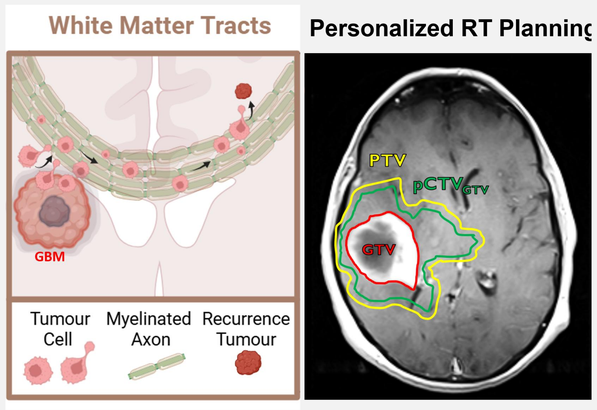


Figure 2. Illustration of (a) GBM cells invading fiber bundles, (b) personalized radiotherapy target volumes from GTV.

This study aims to build on our earlier work[6] with the TS map to further personalize treatment volumes by using the BTV instead of the GTV by:

- Developing a pipeline to contour the BTV using Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) maps from a single-shell DTI scan, along with the relative Blood Volume (rBV) map from DSC imaging.
- Calculating the TS map using both GTV and BTV, respectively.
- Comparing the three RT treatment planning approaches:
  1- Traditional CTV based on GTV,
  2- Personalized CTV based on GTV (i.e. $pCTV_G$),
  3- Personalized CTV based on BTV (i.e. $pCTV_B$).

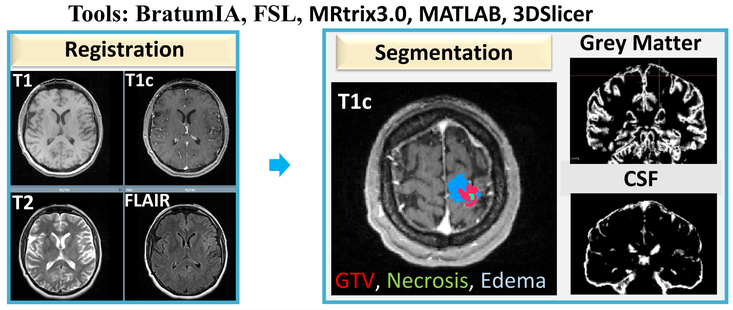
METHODS AND MATERIALS

The data comprised MRI scans from the UPENN-GBM dataset, sourced via The Cancer Imaging Archive (TCIA). Ten glioblastoma patients (3 female, 7 male), all over 40 years of age, who had undergone surgery, radiotherapy, and chemotherapy, were selected for the study. MRI Imaging included: a pre-operative and follow-up (FU) within 3-6 months, DTI scan (b = 0, b = 1000 s/mm²; 30 directions; 128×128 matrix; 40 slices; voxel size 1.7×1.7×3.0 mm³), post-contrast T1-weighted image (182×218 matrix; 182 slices; voxel size 1.0×1.0×1.0 mm³), and a DSC perfusion image (128×128 matrix; 20 slices; voxel size 1.7×1.7×3.0mm³).

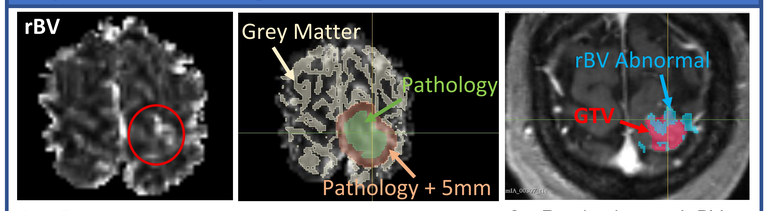
Pipeline - MRI to BTV to pCTV

Step 1. Registration and Tissue Segmentation

Tools: BratumIA, FSL, MRtrix3.0, MATLAB, 3DSlicer



Step 2. BTV – rBV Segmentation



2a. rBV map showing abnormal regions (circled)

2b. Find mean rBV in normal Grey Matter (Excluded pathology + 5mm)

2c. Retain abnormal rBV regions (> mean + SD) within the GTV + 5 mm margin.

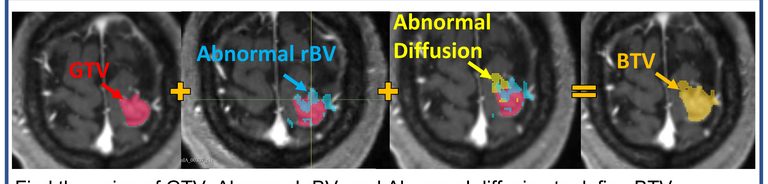
Step 3. BTV – Diffusion Segmentation

3a. Find abnormal FA using the threshold of: >0.21 within Pathology[7]

3b. Find abnormal ADC using the threshold of: $< 1.08 \times 10^{-3}$ mm²/s within Pathology[8]

3c. Find intersection of High FA and Low ADC to target highly abnormal diffusion regions

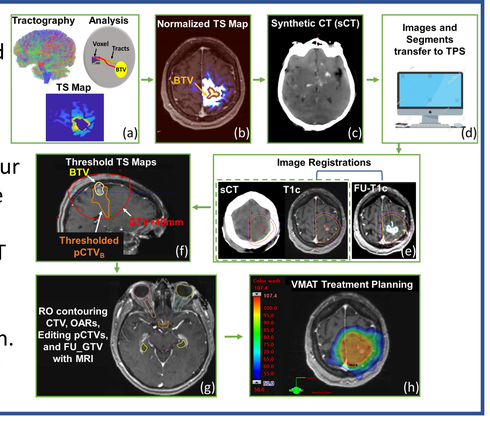
Step 4. BTV – Union



Find the union of GTV, Abnormal rBV, and Abnormal diffusion to define BTV.

Step 5. Tumour Spread Map Quantification and Treatment Plans

MRtrix 3.0 was used to preprocess the DTI data and perform probabilistic tractography seeding from the BTV. TS index per voxel was then calculated using our in-house MATLAB code. The resulting TS map was imported into the Eclipse RT treatment planning system, thresholded, and used to generate the treatment plan. The workflow was repeated for the GTV.



RESULTS

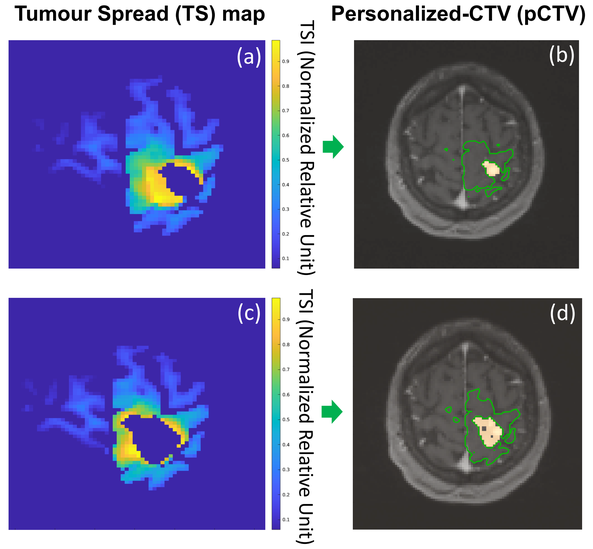


Figure 3. Tumor spread map (TS) of a representative patient on an axial slice: (a) TS map based on GTV, where yellow voxels represent higher probability, and dark blue regions represent lower probability of tumor spread, (b) pCTV after thresholding; (c) TS map based on BTV, and (d) corresponding pCTV after thresholding.

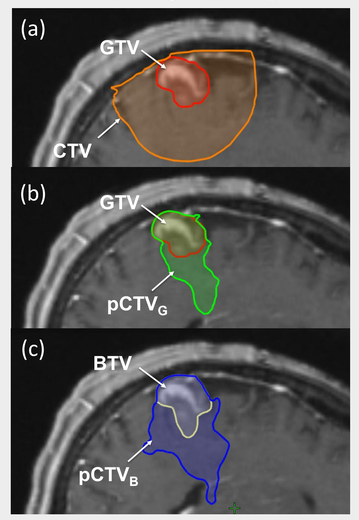


Figure 4. CTV vs. personalized CTV (pCTV): (a) the original CTV (20 mm from GTV) margin, (b) $pCTV_G$ showing the most probable tumour spread pathway based on the GTV, (c), $pCTV_B$ showing the most probable tumour spread pathway using the BTV.

Validation: Follow-Up Recurrence

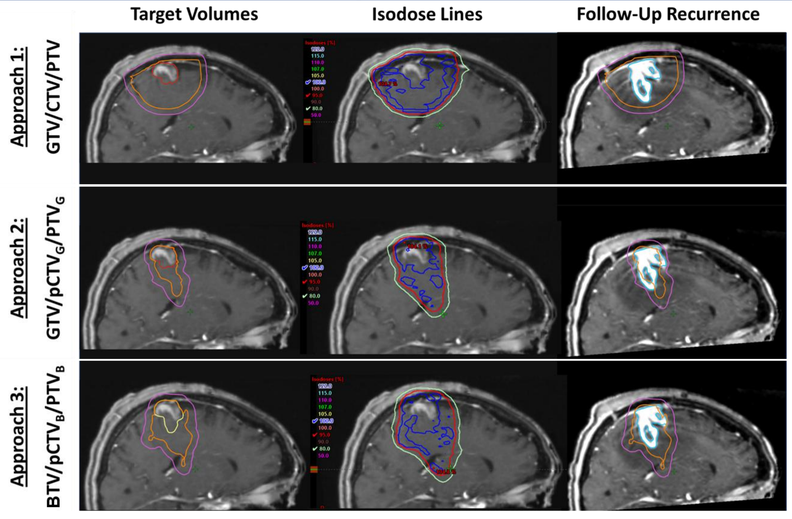


Figure 5. Comparison of target volumes, treatment plans, and follow-up recurrence coverage for three radiotherapy planning approaches in a representative subject. Each row displays the corresponding target volumes (left), the 80%, 95%, and 100% prescription isodose lines (center), and the recurrence overlay from follow-up imaging (right). Both personalized approaches demonstrate reduced target volumes while maintaining recurrence coverage.

Both $pCTV_G$ and $pCTV_B$ were consistently smaller than the standard CTV, reducing irradiated volume while preserving tumor coverage. The $pCTV_G$ and $pCTV_B$ spared **59%** and **49%** of the standard CTV margin volume, respectively. All plans met clinical conformality thresholds, and mean doses to organs at risk (OARs) were lower with both personalized strategies. At follow-up, the volume of recurrent tumor included in the standard PTV was **98%**, **95%** for PTV_G, and **97%** for PTV_B. Dose coverage of ≥80% was achieved in 99% of the recurrence volume with standard PTV, and in 98% with both PTV_G and PTV_B.

CONCLUSIONS

- This pilot study demonstrates the potential use of a BTV instead of a standard GTV to better target the core tumour as identified with advanced MRI, and a pCTV instead of a standard CTV to identify the probable paths of microscopic tumour spread.
  - In this work we utilized the perfusion and diffusion maps available in the TCIA dataset to identify the BTV, however this could easily be extended to include whole brain MRSI, CEST and other biological maps.
  - Based on this pilot study on ten subjects, and comparison of our proposed target volumes to the follow-up images, our technique showed promise in identifying regions at high risk of recurrence while sparing healthy tissue from unnecessary radiation.
  - This represents a significant advance from the standard GTV/CTV approach to a method that takes full advantage of the advanced biological information and white matter spread pathways available from advanced MRI.

REFERENCES

[1] Ryan JY et al. (2022); [2] Aldawsari et al. (2023); [3] Breen WG et al. (2024); [4] Kim MM et al. (2019); [5] Scherer H et al. (1940); [6] Abbasian et al. (2025); [7] Huber et al. (2017); [8] Maier et al. (2010)