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Defining occult disease in glioblastoma using spectroscopic MRI: implications for clinical target volume delineation

Jonathan B. Bell[1], Sulaiman Sheriff[2], Mohammed Z. Goryawala[2], Kaylie Cullison[1], Gregory A. Azzam[1], Jessica Meshman[1], Matthew C. Abramowitz[1], Michael E. Ivan[3], Macarena I. de la Fuente[4] and Eric A. Mellon[1*]

Abstract

Background Outcomes in glioblastoma are improved by surgical resection and adjuvant radiation (RT). In primary GBM (pGBM), large clinical target volume (CTV) margins typically cover occult invasion. In recurrent GBM (rGBM), RT often uses tiny CTV margins that likely omit occult invasion due to re-RT radiation necrosis concerns. Whole-brain spectroscopic MRI (sMRI) is an emerging technique with similar resolution to PET that may help define the CTV for rGBM.

Methods Patients with pGBM ($n=18$) and rGBM ($n=19$) underwent sMRI with RT simulation. T1-post contrast (T1PC) and T2/FLAIR MRI volumes were contoured. sMRI generated choline/N-acetylaspartate > 2x (Cho/NAA > 2x) volumes are known to correlate with high-risk invasion. Hausdorff distances were calculated to define the margin necessary to cover Cho/NAA > 2x in pGBM and rGBM. In rGBM, mock CTV expansions from T1PC volumes were created to determine non-selective CTV expansion sizes needed to cover Cho/NAA > 2x volumes.

Results For pGBM, the median T1PC, Cho/NAA > 2x, and T2/FLAIR volumes were 32.3 cc, 45.0 cc, and 74.8 cc respectively. For rGBM, the median T1PC, Cho/NAA > 2x, and T2/FLAIR volumes were 21.7 cc, 58.9 cc, and 118.3 cc, respectively. T2/FLAIR volumes increased more relative to T1PC volumes in rGBM than pGBM ($p \leq 0.001$). Meanwhile, the median Hausdorff distance between T1PC and Cho/NAA > 2x was 22.9 mm in pGBM and 25.7 mm in rGBM, suggesting that the high-risk volume does not significantly change. In rGBM, it is common to use no CTV expansion from the T1PC volume which only included 61% of high-risk Cho/NAA > 2x volume. Conversely, T1PC expansions of 10-, 15-, and 20-mm covered 87%, 94%, and 98% of Cho/NAA > 2x volume.

Conclusions sMRI Cho/NAA > 2x delineates high-risk occult disease in glioblastoma and extends beyond T1PC MRI borders. Typical large CTV expansions in pGBM mostly include Cho/NAA > 2x volumes. However, small CTV expansions commonly used in rGBM poorly cover Cho/NAA > 2x, suggesting that larger CTV expansions or Cho/NAA > 2x guidance may be of benefit.

Keywords Spectroscopic MRI, Glioblastoma

*Correspondence:
Eric A. Mellon
eric.mellon@med.miami.edu
[1]Department of Radiation Oncology, Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, 1475 NW 12th Ave, Miami, FL 33136, USA
[2]Department of Radiology, Miller School of Medicine, University of Miami, Miami, FL, USA
[3]Department of Neurological Surgery, Miller School of Medicine, University of Miami, Miami, FL, USA
[4]Department of Neurology and Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL, USA

Background

Glioblastoma (GBM) is a deadly brain cancer treated with surgical resection or biopsy followed by adjuvant radiation therapy (RT) and chemotherapy. Following surgery for either newly-diagnosed (primary) GBM (pGBM) or recurrent GBM (rGBM), post-operative MRI is used to delineate RT volumes. As GBM is a highly invasive malignancy, RT margins are designed to cover occult disease in the brain.

For pGBM, the Radiation Therapy Oncology Group (RTOG)/NRG Oncology recommends a sequential boost approach which incorporates two dose levels based on T1-post contrast (T1PC) and T2/FLAIR MRI [1]. In the first phase, an initial clinical target volume 1 (CTV1) is generated from the T2/FLAIR, gross tumour volume 1 (GTV1), expanded by 2 cm. A boost CTV2 is generated from the resection cavity and any T1PC-enhancing residual disease (GTV2), also expanded by 2 cm. For rGBM, there is no consensus on the appropriate RT volumes. In the landmark phase II study of re-irradiation for rGBM, NRG Oncology/RTOG 1205, radiation was delivered to the recurrent disease without CTV margin in most patients [2]. This was done to limit the amount of normal brain receiving re-irradiation, thus reducing the risk of radiation necrosis. NRG Oncology/RTOG 1205 showed a borderline ($p = 0.05$) progression free survival benefit at six months, suggesting that RT can improve outcomes in rGBM, while there could be room for further improvement. We hypothesize that the lack of a CTV margin misses invasive disease.

Spectroscopic MRI (sMRI) is a whole-brain magnetic resonance spectroscopic imaging technique used to detect native metabolites in normal brain and gliomas [3]. Choline is a marker of cell membrane proliferation and is increased in tumour cells. N-acetylaspartate (NAA) is a maker of neuronal density and is decreased in GBM and other gliomas [3]. The ratio of choline/NAA is normalized to the normal appearing contralateral white matter, and a higher ratio correlates with higher tumour cell density [4]. Areas with elevated choline/NAA > 2x are highly predictive of the presence of microscopic disease in primary GBM and recurrence patterns, and stereotactic biopsies have validated the use of this imaging biomarker [5, 6]. In a multi-institutional prospective study, dose-escalation to residual T1PC-enhancing and choline/NAA > 2x volumes in pGBM was safe and yielded favourable overall and progression-free survival [7].

We previously demonstrated that choline/NAA > 2x volumes identified significant infiltrative disease in rGBM not detected by other MRI techniques [8]. In this study, we sought to compare T1PC and T2/FLAIR MRI with choline/NAA > 2x maps in pGBM and rGBM to demonstrate how choline/NAA > 2x volumes might be useful for target delineation and suggest non-selective CTV margins for rGBM for centers without the sMRI technique.

Methods

Patient selection and characteristics

We analysed MRIs from 18 pGBM and 19 rGBM patients at the time of RT planning. Infratentorial tumours and tumours near the base of skull were excluded as the quality of the spectroscopic MRI is poor in these regions of the brain. Patients were prospectively consented by a non-therapeutic institutional review board approved protocol. Patients were diagnosed based on the 2021 World Health Organization (WHO) classification system for GBM [9].

Image acquisition and contouring

Conventional MRI and whole-brain sMRI were acquired using a 3T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) as previously described [7]. Metabolite maps were generated with a voxel size of 4.4 mm × 4.4 mm × 5.6 mm. Choline/NAA ratio maps were generated and normalized to contralateral normal-appearing white matter in the MIDAS software suite [10]. The Cho/NAA maps were exported in DICOM format to MIM (MIM Software Inc; Beachwood, OH) and overlaid upon conventional MRI for analysis. Regions with Cho/NAA > 2x (Cho/NAA ratio at least twice the mean of the Cho/NAA ratio in contralateral normal-appearing white matter) were delineated in MIM using the threshold tool and individually reviewed for spectral quality. Contrast-enhancing volumes were contoured using post-contrast T1-weighted (T1PC) imaging. Resection cavities were included in T1PC volumes. FLAIR volumes were contoured using T2/FLAIR imaging. Sequential CTV expansions of 0, 3, 5, 10, 15, and 20 mm were performed in MIM and cropped to respect natural barriers of spread. Hausdorff distances were calculated in MIM.

Statistics

Unpaired two-sample t-tests were performed to evaluate volumetric differences between two groups (primary and recurrent GBM). Repeated measures ANOVA were performed to evaluate volumetric differences between three groups. A p-value ≤ 0.05 was deemed statistically significant. All statistics were performed in GraphPad Prism version 9.3.1 for PC (San Diego, CA).

Results

Patient baseline demographics

Median ages for pGBM and rGBM were 63 and 53 years old, respectively (Table 1). All tumours were IDH-wild-type. MGMT was hypermethylated in 17% of pGBM and 26% of rGBM patients. Patients underwent different extents of resection for pGBM and re-resection for

Table 1 Patient characteristics

Characteristic	Primary GBM	Recurrent GBM
Patients, n	18	19
Median age, years	63	53
Gender, n (%)		
Male	13 (72)	10 (53)
Female	5 (28)	9 (47)
MGMT status, n (%)		
Not hypermethylated	9 (50)	11 (58)
Hypermethylated	3 (17)	5 (26)
Unknown	6 (33)	3 (16)
Resection/Re-Resection, n (%)		
Gross total resection	5 (28)	2 (11)
Subtotal resection	8 (44)	6 (32)
Biopsy	5 (28)	1 (5)
None	0 (0)	10 (53)
ECOG performance status, n (%)		
0	9 (50)	4 (21)
1	7 (39)	10 (53)
2	1 (6)	2 (11)
3	1 (6)	3 (16)

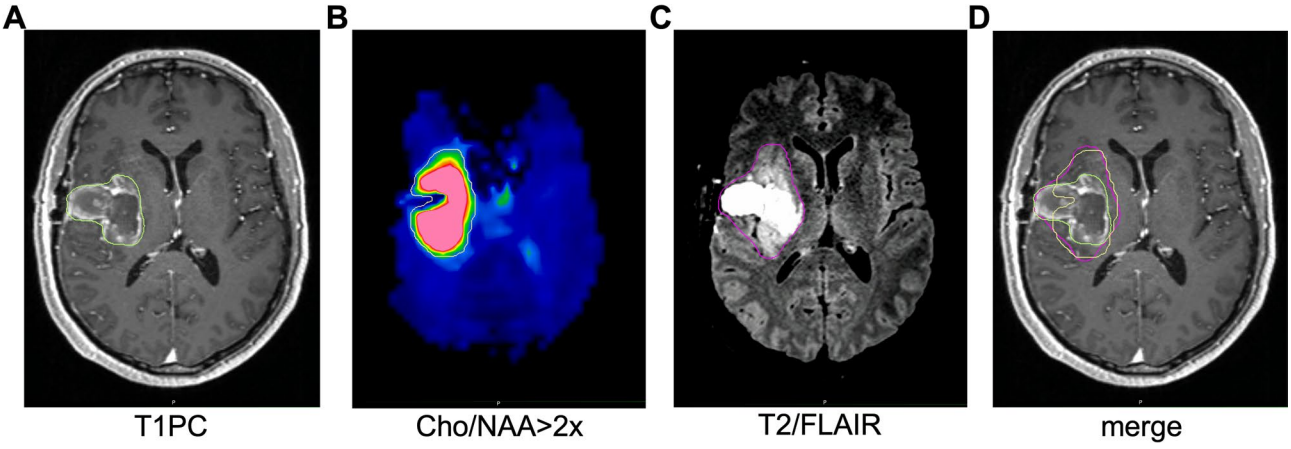

Fig. 1 Example contours from a patient with primary GBM. **A-D.** Example contours for a patient with pGBM show T1PC, Cho/NAA > 2x, and T2/FLAIR volumes. Merge image shows extension of Cho/NAA > 2x outside of the T1PC-defined volume but mostly within the T2/FLAIR volume

rGBM. Greater than half of patients with rGBM (53%) did not undergo re-biopsy or re-resection. Performance status varied between patients with worse performance status among rGBM patients.

Spectroscopic MRI contours

T1PC, Cho/NAA > 2x, and T2/FLAIR volumes in pGBM and rGBM were contoured. Example contours from a patient with pGBM show the Cho/NAA > 2x volume extends beyond the T1PC volume and are slightly smaller than the T2/FLAIR volume (Fig. 1). Example contours from a patient with rGBM shows the Cho/NAA > 2x extends beyond the T1PC volume but is substantially smaller than the T2/FLAIR volume (Fig. 2).

Spectroscopic MRI volumetric analysis

Comparison of volumes in pGBM and rGBM show that T1PC volumes are smaller than Cho/NAA > 2x volumes which are smaller than T2/FLAIR volumes (Fig. 3A-B). As compared to pGBM, T2/FLAIR volumes were generally larger in rGBM and the ratio of T1PC to T2/FLAIR was smaller in recurrent GBM (Fig. 3C). Specifically, median FLAIR volumes were approximately 2x greater than T1PC volumes in pGBM (ratio T1PC/FLAIR = 0.48), while FLAIR volumes were approximately 5x greater than T1PC volumes in rGBM (ratio T1PC/FLAIR = 0.19) ($p < 0.01$).

The Hausdorff distances between the T1PC disease and the Cho/NAA > 2x volumes were calculated for pGBM and rGBM (Fig. 4A-C). The median Hausdorff distance

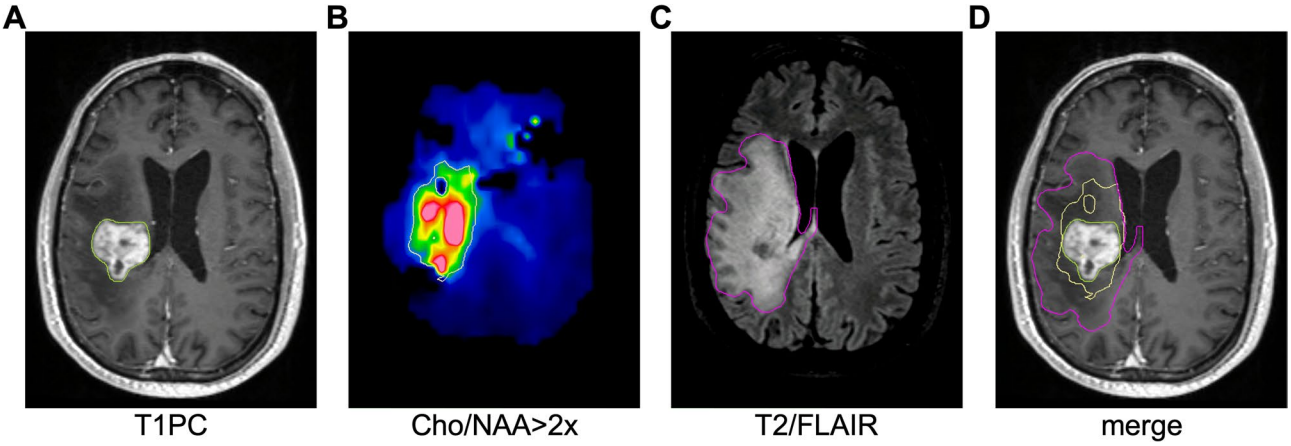

Fig. 2 Example contours from a patient with recurrent GBM. **A-D.** Example contours for a patient with rGBM show T1PC, Cho/NAA > 2x, and T2/FLAIR volumes. Merge image shows extension of Cho/NAA > 2x outside of the T1PC-defined volume but within the T2/FLAIR volume

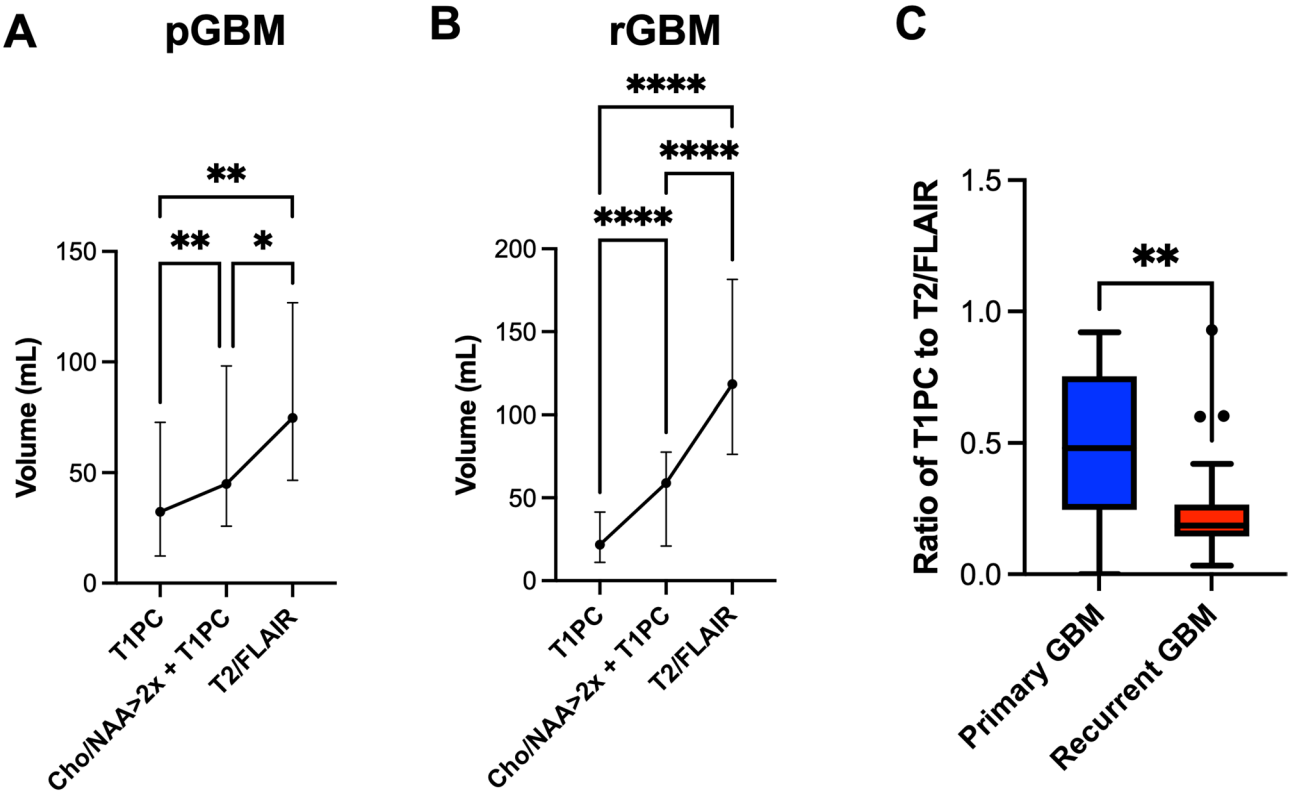

Fig. 3 Comparison of conventional and spectroscopic MRI volumes. **(A)** Comparison of the T1PC, Cho/NAA > 2x, and T2/FLAIR volumes from 18 patients with pGBM. Repeated measures one-way ANOVA with multiple comparisons shows sequentially larger volumes from T1PC to Cho/NAA > 2x to T2/FLAIR. Error bars represent interquartile range. **(B)** Comparison of the T1PC, Cho/NAA > 2x, and T2/FLAIR volumes from 19 patients with rGBM. Repeated measures one-way ANOVA with multiple comparisons shows sequentially larger volumes from T1PC to Cho/NAA > 2x to T2/FLAIR. Error bars represent interquartile range. **(C)** Ratio of T1PC to T2/FLAIR volumes of 18 patients with pGBM and 19 patients with rGBM shown using Tukey's boxplots. Unpaired two-tailed t-test shows significant difference between ratios in pGBM and rGBM. *$p \le 0.05$, **$p \le 0.01$, ***$p \le 0.001$, and ****$p \le 0.0001$

between the T1PC and the Cho/NAA > 2x volume was 22.9 mm in pGBM and 25.7 mm in rGBM, although this difference was not statistically significant (Fig. 4D). For patients with rGBM, simulated CTV expansions ranging from 0 to 20 mm were contoured (Fig. 5A). These simulated CTVs were then compared to the high-risk disease volume (i.e., T1PC plus Cho/NAA > 2x volume) and the percentage of coverage was calculated (Fig. 5B). A 0 mm CTV expansion covered 61% of total disease (enhancing and occult), 3 mm covered 69%, 5 mm covered 73%, 10 mm covered 87%, 15 mm covered 94%, and 20 mm covered 98%.

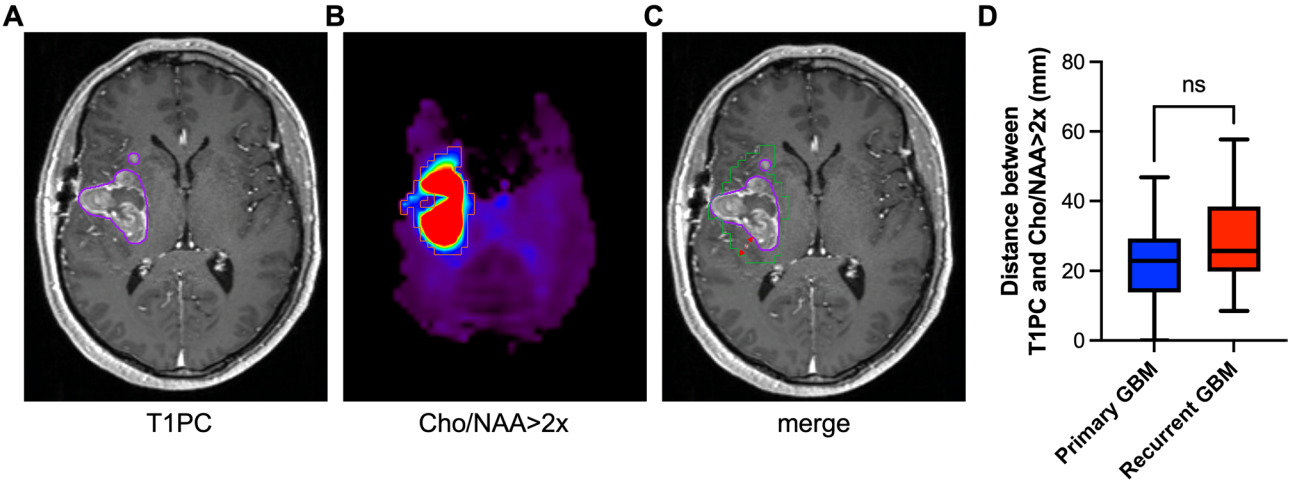

Fig. 4 Occult GBM invasion detected on spectroscopic MRI. **A-C.** Example contours for a patient with primary GBM shows T1PC and Cho/NAA > 2x volumes. Merge image shows extension of Cho/NAA > 2x outside of the T1PC-defined volume. Red line shows distance between T1PC and Cho/NAA > 2x volumes. **D.** Hausdorff distances between T1PC and Cho/NAA > 2x volumes for 18 patients with primary GBM and 19 patients with recurrent GBM shown using Tukey's boxplots. Unpaired two-tailed t-test shows non-significant difference between distances in primary and recurrent GBM

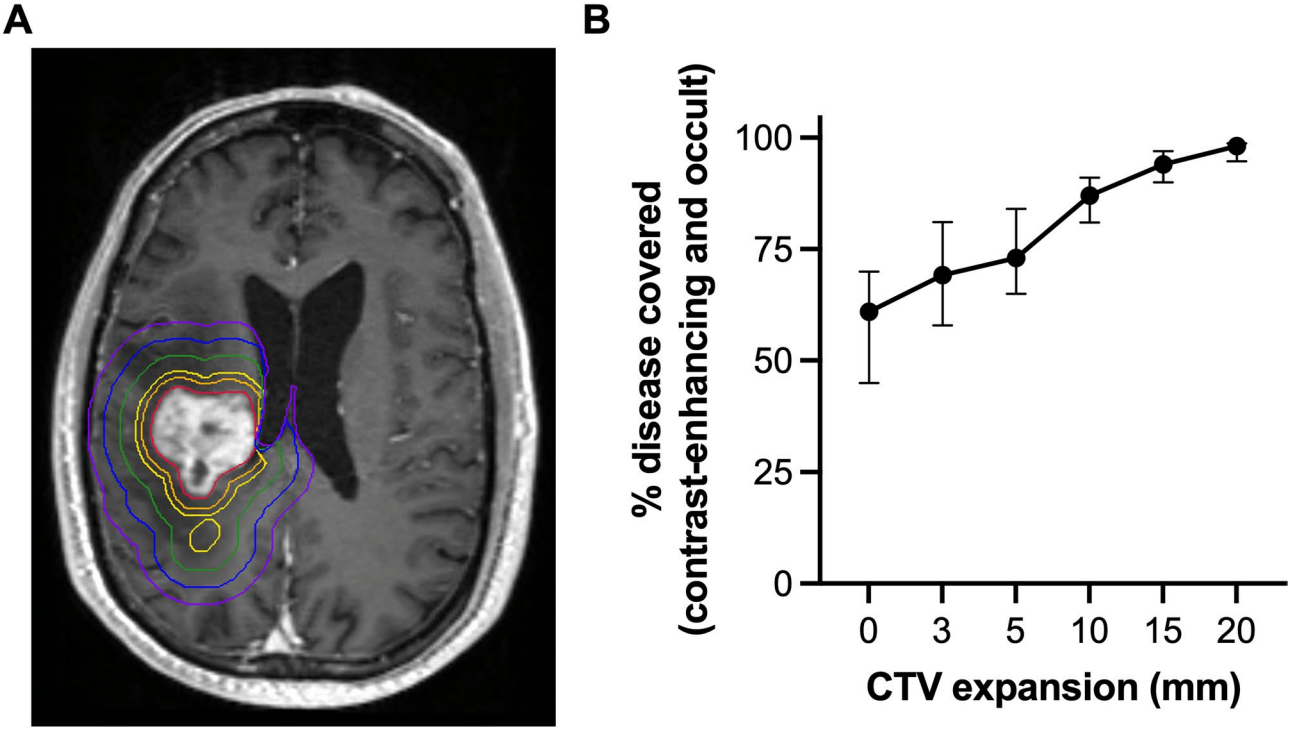

Fig. 5 Simulated CTV expansions to cover occult disease in recurrent GBM. **(A)** Example CTV expansions cropped to anatomical boundaries of spread. **(B)** Sequential CTV expansions show increasing coverage of both contrast-enhancing disease and spectroscopic MRI-defined occult disease

Discussion

In this prospective study, we used whole brain sMRI to generate Cho/NAA > 2x maps in 18 patients with pGBM and 19 patients with rGBM. While it is known that sMRI demonstrates elevated Cho/NAA extending from the tumour in rGBM, the implications for radiation therapy margins have not previously been described [4, 5, 11, 12]. The Hausdorff distances between the T1PC and the Cho/NAA > 2x volumes suggest that occult disease extends several centimetres beyond contrast-enhancing disease in both pGBM and rGBM. Although some have suggested shrinking margins for GBM, this study demonstrates that conventional 2 cm margins for pGBM provide good coverage of occult high-risk disease defined by sMRI, while such margins are essentially ignored in rGBM and could result in excess treatment failures [13–15].

There is a common concern among radiation oncologists that volume expansion in rGBM will lead to unacceptable toxicities. A 2008 analysis (pre-bevacizumab) identified that the volume of brain re-irradiated in prior rGBM studies inversely correlated with dose (i.e., higher doses were given to smaller volumes) [16]. Volumes are based on investigator choice in the designs of those studies because it is well known based on radiosurgery re-irradiation studies that increasing treatment volumes lead to increasing toxicity for the same treatment doses [17]. A large modern series of re-irradiation treated without expansions led to NRG Oncology/RTOG 1205 which tested whether bevacizumab with or with re-irradiation improves outcomes in rGBM [2, 18]. Re-irradiation was safe, well tolerated, and led to an approximately 3-month improvement in progression-free survival. However, overall survival was not improved with re-irradiation. Novel radiation approaches may improve outcomes in rGBM, and re-irradiation appears safe with carefully defined treatment volumes.

CTVs in rGBM are typically minimized to avoid reirradiation of large areas of brain, due to the fear of toxicity (i.e., radiation necrosis). In RTOG 1205, no CTV margin was mandated nor added for most patients. However, toxicity remains low, even in the re-irradiated brain, suggesting the potential for larger margins to treat invasive disease likely missed by small RT volumes [2]. In a multi-institutional study of sMRI-guided radiation in GBM, larger radiation volumes did not result in unacceptable toxicities or higher rates of radiation necrosis than expected, and most high-grade toxicities were attributed to temozolomide rather than radiation [7]. Models suggest that tumours invade, often non-uniformly, well into normal-appearing brain [19]. Larger T2/FLAIR volumes following radiation, possibly indicating untreated microscopic disease, are associated with poorer outcomes in GBM [20]. In a recent analysis of 129 patients with rGBM treated with re-irradiation, T2/FLAIR abnormalities were typically not included, and marginal recurrences were more common in patients treated with bevacizumab, suggesting that larger treatment volumes may be needed to encompass microscopic disease particularly in patients receiving anti-VEGF therapies [21, 22].

sMRI has the potential to improve radiation targeting in both pGBM and rGBM. In our recent prospective study of 14 patients with rGBM, radiation treatment targeting sMRI-defined occult disease was well tolerated and led to no grade 3 or higher toxicities [8]. This study was the first to demonstrate the feasibility of sMRI for radiation target delineation in rGBM. Outcomes were promising with a median progression-free and overall survival of 6.5 and 7.1 months, respectively. Several patients failed within the sMRI-defined volume but outside the T1PC-defined recurrence suggesting that sMRI may identify occult high-risk disease. The recently published randomized trial, SPECTRO GLIO, utilized magnetic resonance spectroscopic imaging (MRSI) to define radiation boost volumes in pGBM. Although the experimental treatment was well tolerated, it did not result in an improvement in overall survival [23]. This may be due, in part, to the small radiation volumes used and the less advanced sequence used in MRSI as compared to sMRI [24].

Beyond sMRI, other advanced imaging techniques may provide insight into microscopic tumour invasion in GBM. Positron emission tomography (PET) using 18-F-fluroethyltryosine (FET) and other radiotracers can be used to delineate non-enhancing tumour [25]. As such, FET PET has been incorporated as an optional imaging modality in the European Society for Radiotherapy (ESTRO)-European Association of Neuro-Oncology (EANO) guidelines for radiation target delineation in GBM [26–28]. There are also opportunities to use MRI-defined radiomics to guide radiation therapy volumes in GBM [29, 30]. Larger prospective trials are needed to determine how these imaging modalities fit into the landscape of GBM radiation planning.

Our study provides more evidence that radiation volumes in pGBM and rGBM should be expanded beyond what is visible on standard MRI sequences to adequately cover microscopic invasive disease. However, there are limitations to our study including the single institution nature, relatively small size of the study, and the lack of randomization. Cho/NAA > 2x volumes did not extend significantly beyond T1PC volumes in all patients, suggesting that some patients may not benefit from volume expansions. Larger studies may identify specific cohorts that would specifically benefit from sMRI for radiation planning. Furthermore, sMRI may not be financially or logistically feasible at all institutions. Future directions at our institution include the ongoing prospective clinical trial in rGBM using sMRI-defined maps for volume expansions and dose escalation to explore whether larger CTV margins might improve patient outcomes (NCT05284643).

Conclusions

In this study we examine whole-brain sMRI-derived Cho/NAA > 2x contours for radiation planning in pGBM and rGBM. While it is known that Cho/NAA > 2x volumes reflective of high-risk invasion extend beyond T1PC MRI, in pGBM such volumes are mostly covered by conventional large CTV expansions. Conversely, in rGBM such volumes are poorly covered by the no or limited CTV expansions used in many modern series and trials. Centers without sMRI or other advanced imaging could consider 1.5–2 cm non-selective CTV margins for re-irradiation of rGBM to achieve 94–98% coverage. Future

trials will examine whether larger volume re-irradiation guided by sMRI may improve patient outcomes in rGBM.

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Author contributions
All authors contributed to the study conception and design. Data collection and analysis were performed by Jonathan B. Bell, Sulaiman Sheriff, Mohammed Z. Goryawala, Kaylie Cullison and Eric A. Mellon. Gregory A. Azzam, Jessica Meshman, Matthew C. Abramowitz, Michael E. Ivan, Macarena I. de la Fuente, and Eric A. Mellon provided patient data. Jonathan B.) Bell wrote the first draft of the manuscript, and all authors commented on subsequent drafts of the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the University of Miami Institutional Review Board (IRB) (IRB #20190678). All patients provided written informed consent prior to enrolment in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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