Neuro-Oncology Practice
9(5), 380–389, 2022 | https://doi.org/10.1093/nop/npac044 | Advance Access date 26 May 2022

Incidence and extent of disease progression on MRI between surgery and initiation of radiotherapy in glioblastoma patients

Ryan D. Kraus,[†] Christopher R. Weil,[†] Fan-Chi Frances Su, Donald M. Cannon, Lindsay M. Burt, and Joe S. Mendez

Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA (R.D.K., C.R.W., F.F.S., D.M.C., L.M.B.); Department of Neurosurgery, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA (J.S.M.)

Corresponding Author: Joe S. Mendez, MD, Department of Neurosurgery, Huntsman Cancer Institute at the University of Utah, 2000 Circle of Hope, Suite 2100, Salt Lake City, UT 84112, USA (Joe.Mendez@hci.utah.edu).

[†]These authors contributed equally to this paper and are listed as co-first authors.

Abstract

Background. A post-operative MRI ($MRI_{post\text{-}op}$) performed within 72 h is routinely used for radiation treatment planning in glioblastoma (GBM) patients, with radiotherapy starting about 4–6 weeks after surgery. Some patients undergo an additional pre-radiotherapy MRI ($MRI_{pre\text{-}RT}$) about 2–6 weeks after surgery. We sought to analyze the incidence of rapid early progression (REP) between surgery and initiation of radiotherapy seen on $MRI_{pre\text{-}RT}$ and the impact on radiation target volumes.

Methods. Patients with GBM diagnosed between 2018 and 2020 who had an $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ were retrospectively identified. Criteria for REP was based on Modified RANO criteria. Radiation target volumes were created and compared using the $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$.

Results. Fifty patients met inclusion criteria. The median time between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ was 26 days. Indications for $MRI_{pre\text{-}RT}$ included clinical trial enrollment in 41/50 (82%), new symptoms in 5/50 (10%), and unspecified in 4/50 (8%). REP was identified in 35/50 (70%) of patients; 9/35 (26%) had disease progression outside of the $MRI_{post\text{-}op}$-based high dose treatment volumes. Treatment planning with $MRI_{post\text{-}op}$ yielded a median undertreatment of 27.1% of enhancing disease and 11.2% of surrounding subclinical disease seen on $MRI_{pre\text{-}RT}$. Patients without REP had a 38% median volume reduction of uninvolved brain if target volumes were planned with $MRI_{pre\text{-}RT}$.

Conclusion. Given the incidence of REP and its impact on treatment volumes, we recommend using $MRI_{pre\text{-}RT}$ for radiation treatment planning to improve coverage of gross and subclinical disease, allow for early identification of REP, and decrease radiation treatment volumes in patients without REP.

Keywords

glioblastoma | rapid early progression | radiation therapy | treatment planning

Glioblastomas (GBMs) are the most common primary malignant brain tumor in the United States, with an estimated incidence of 12,970 cases in 2021.[1] Unfortunately, the prognosis is dismal, with high rates of local recurrence despite aggressive therapy.[1,2] The current standard of care for GBM treatment involves maximal safe resection followed by radiotherapy with concurrent and adjuvant temozolomide (TMZ).[3] Radiotherapy is generally initiated 4–6 weeks following surgery.

In the United States, radiotherapy commonly employs two stages per Radiation Therapy Oncology Group (RTOG) guidelines.[4] The first phase of treatment targets the gross tumor volume 1 (GTV_1) which includes the resection cavity, gross residual enhancing disease identified on the immediate post-operative T1 post-gadolinium MRI ($MRI_{post\text{-}op}$), and abnormal signal hyperintensity and edema seen on T_2/FLAIR sequences. Clinical target volume 1 (CTV_1), which represents areas of possible microscopic spread, is created by performing a 2 cm isometric expansion of the GTV_1 volume trimmed to anatomic boundaries. CTV_1 is then treated to 46 Gray (Gy) in 23 fractions. The second phase of treatment involves a gross tumor volume 2 (GTV_2), comprised of the resection cavity and any gross residual enhancing disease, which is expanded by 2 cm and trimmed to anatomic boundaries to create clinical target volume 2 (CTV_2). This smaller volume is treated with an additional 14 Gy in 7 fractions to ensure the gross disease encompassed by CTV_2 receives a cumulative dose of 60 Gy.

Radiotherapy is generally planned using the $MRI_{post\text{-}op}$ even though radiotherapy typically starts 4–6 weeks after surgery.[5,6] Multiple studies have shown that over half of patients have tumor regrowth between surgery and initiation of radiotherapy, referred to in the literature as rapid early progression (REP).[7–10] Till date, there is minimal data evaluating the REP that falls outside of the high dose CTV_2 volume based on $MRI_{post\text{-}op}$. Given this uncertainty, this study aims to quantify the incidence and extent of REP and the potential impact it has on radiotherapy treatment volumes.

Materials and Methods

With institutional review board approval, we conducted a retrospective review of patients diagnosed with WHO grade IV isocitrate dehydrogenase (IDH)-wildtype GBM between 2018 and 2020. Patients were identified within our institutional oncology database and patient clinical and treatment details were extracted from the electronic medical record.

Patients were included if they had both an $MRI_{post\text{-}op}$ and an $MRI_{pre\text{-}RT}$ available for assessment of REP. MR sequences included sagittal T_1-weighted spin-echo, axial diffusion-weighted image (DWI) echo-planar imaging, axial T_2/FLAIR, and multiplanar gadolinium contrast-enhanced T_1-weighted sequences. For each patient, $MRI_{post\text{-}op}$ was performed within 72 h of surgical resection and $MRI_{pre\text{-}RT}$ was performed at least 10 days after $MRI_{post\text{-}op}$. Imaging was independently reviewed by a neuroradiologist and two radiation oncologists to ensure that there was agreement regarding the presence and extent of REP. Patients were considered to have REP based on a modified response assessment in neuro-oncology (m-RANO) criteria for GBM patients if there was (1) ≥25% increase in the sum of products of perpendicular diameters, (2) ≥40% increase in the total volume of enhancing disease, or (3) new measurable disease >10 mm × 10 mm including new satellite lesions or distant disease.[11]

For patients with REP, $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ were fused to the patient's CT simulation scan in Eclipse treatment planning software (version 15.5, Varian Medical Systems, Palo Alto, CA).

GTV_1 volumes were created based on the $MRI_{post\text{-}op}$ ($GTV_{1\_post\text{-}op}$) and $MRI_{pre\text{-}RT}$ ($GTV_{1\_pre\text{-}RT}$). Each GTV volume included contrast-enhancing disease on a T_1-weighted sequence, the resection cavity, and peritumoral edema identified on a T_2/FLAIR sequence. Two centimeter anatomically constrained expansions were performed on the GTV_1 volumes to create the CTV_1 volumes $CTV_{1\_post\text{-}op}$ and $CTV_{1\_pre\text{-}RT}$, representing the volume that is treated to 46 Gy. GTV_2 volumes were created based on the $MRI_{post\text{-}op}$ ($GTV_{2\_post\text{-}op}$) and $MRI_{pre\text{-}RT}$ ($GTV_{2\_pre\text{-}RT}$). Each GTV volume included contrast-enhancing disease on a T_1-weighted sequence and the resection cavity. Two centimeter anatomically constrained expansions were similarly performed on the GTV_2 volumes to create the CTV_2 volumes $CTV_{2\_post\text{-}op}$ and $CTV_{2\_pre\text{-}RT}$, representing the volume that is treated to a full 60 Gy dose.[5] Example volumes are shown in Figure 1. All treatment volumes were reviewed by a second unblinded radiation oncologist to confirm they were designed in accordance with RTOG guidelines. In an effort to assess for bias in target volume design, a third radiation oncologist, who was blinded to patient identifiers and whether the MRI was performed post-op or pre-RT, independently created an additional set of post-op and pre-RT GTV_1 and GTV_2 volumes for 20 randomly selected patients within the study cohort. These second set of GTV volumes ($GTV_{comparison}$) were then compared to the initial GTV volumes ($GTV_{initial}$) analyzed in this study to assess for concordance ($GTV_{initial}$/$GTV_{comparison}$).

All patients in this cohort were treated using $MRI_{pre\text{-}RT}$-based volumes; volumes based on the $MRI_{post\text{-}op}$ were generated for comparison only as $MRI_{post\text{-}op}$-based volumes represent the standard of care at most treatment centers. CTV volumes were analyzed to identify areas of overtreatment and areas of undertreatment. The volume of overtreated brain tissue was defined as the $CTV_{post\text{-}op}$ volumes that extended outside $CTV_{pre\text{-}RT}$, which would have received radiation if the treatment plan were based on the standard of care $MRI_{post\text{-}op}$ but not if the plan were based on $MRI_{pre\text{-}RT}$. The volume of undertreated gross and subclinical disease was defined as the areas of $CTV_{pre\text{-}RT}$ that did not overlap with $CTV_{post\text{-}op}$ and would have received radiation if the treatment plan was based on $MRI_{pre\text{-}RT}$ but not if the treatment plan was based on the current standard $MRI_{post\text{-}op}$ as shown in Figure 2. The $GTV_{post\text{-}op}$ and $GTV_{pre\text{-}RT}$ volumes were similarly compared.

Length of follow-up and time to initiation of adjuvant therapy were defined as the time from surgery until the respective event occurred. Time to progression and survival time were defined as the time from surgery until patient had disease progression[11] or death, respectively, or censored at last follow-up. Two-sided *t*-tests, χ^2 and Fisher exact tests were performed to compare baseline patient cohort characteristics between patients with and without disease progression. Overall survival (OS) and progression free survival (PFS) was calculated using Kaplan–Meier method with log rank analysis. Factors associated with progression were analyzed with univariable and multivariable regression. Statistical analysis was performed in STATA/IC-14.

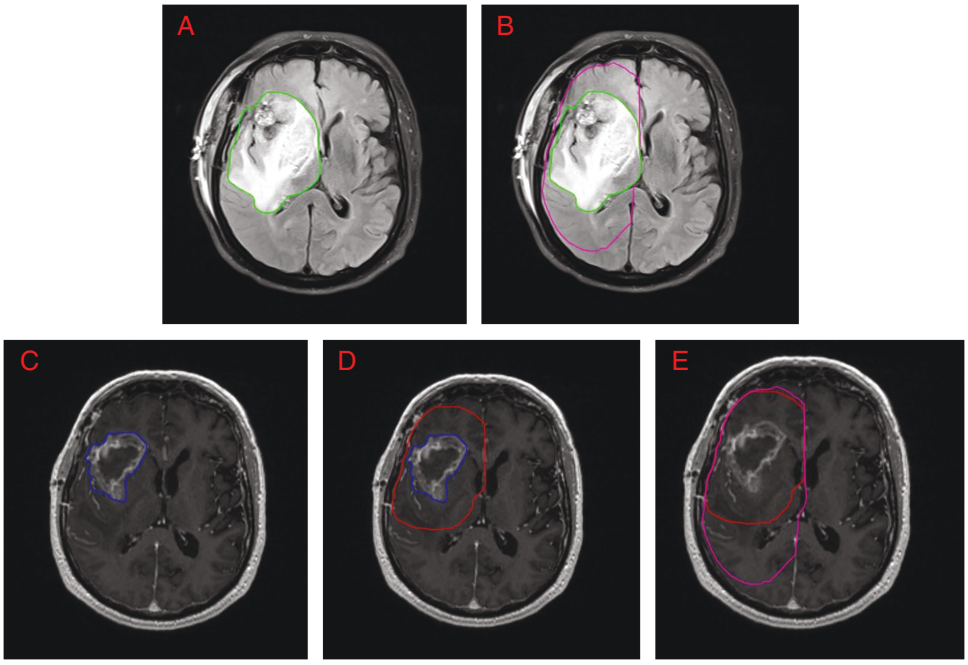

Fig. 1 Radiation Therapy Oncology Group (RTOG) contouring volumes. (A) GTV_1 in green encompassing the resection cavity, gross residual enhancing disease, and edema. (B) CTV_1 in pink created by performing a 2 cm geometric expansion on GTV_1 (green) which is trimmed to respect anatomic boundaries. This volume is treated to 46 Gy. (C) GTV_2 in blue encompassing the resection cavity and gross residual enhancing disease. (D) CTV_2 in red created by performing a 2 cm geometric expansion on GTV_2 (blue) which is trimmed to respect anatomic boundaries. This volume is treated with an additional 14 Gy and receives a cumulative dose of 60 Gy. (E) CTV_1 in pink which is treated to 46 Gy and CTV_2 in red which is treated with an additional 14 Gy for a cumulative dose of 60 Gy.

Results

We identified 123 patients who were diagnosed with IDH-wildtype GBMs between 2018 and 2020. Of the 123 patients 67 were excluded due to not have a $MRI_{pre\text{-}RT}$, 5 were excluded due to not having a $MRI_{post\text{-}op}$ within 72 h of surgery, and 1 patient was excluded due to a post-operative abscess which made an assessment of disease progression infeasible. The remaining 50 patients had an $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ available for assessment. $MRI_{pre\text{-}RT}$ was performed at a median of 26 days (range 11–46) after $MRI_{post\text{-}op}$. Radiation was started at a median of 11 days (range 2–39) following $MRI_{pre\text{-}RT}$. The majority of patients received concurrent TMZ (94%) and completed their radiation course (94%) while just under half (42%) of patients received adjuvant TMZ. Patient characteristics are illustrated in Table 1.

Of the 50 patients available for assessment, 35 (70%) had REP. Nine (26%) of the patients who had REP had new gross disease which extended beyond the $CTV_{2\_post\text{-}op}$ high dose radiotherapy field and 2 (6%) had REP that extended beyond the larger $CTV_{1\_post\text{-}op}$ radiotherapy field. In patients who had REP extending beyond the $CTV_{2\_post\text{-}op}$ volume, a median CTV expansion of 2.9 cm (2.4–5.8) would have been required to encompass all enhancing progressive disease. REP most commonly occurred locally within the resection cavity (60%) followed by a new satellite lesion or distant site of disease outside of the resection cavity (40%).

Changes in GTV and CTV volumes as well as the volume of overtreated normal brain and undertreated disease are shown in Table 2 with individual patient data given in Figure 3. When assessing the $GTV_{comparison}$ and $GTV_{initial}$ volumes for concordance we found a median difference of 1.1% (range –1.8% to 2.4%) indicating that observer bias and operator variation was likely limited. The majority of patients (64%) had a decrease in the GTV_1 volume between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$. The median change in $GTV_{1\_post\text{-}op}$ to $GTV_{1\_pre\text{-}RT}$ volume was –10.6 cc (range –161 to 86) which corresponded to a median change in $CTV_{1\_post\text{-}op}$ to $CTV_{1\_pre\text{-}RT}$ volume of –9.9 cc (–407 to 205). The decrease in GTV_1 and CTV_1 volumes were largely due to decrease in FLAIR signal secondary to improvement in vasogenic edema following resection of tumor and/or improvement in post-operative edema over time. Treating using the $CTV_{1\_pre\text{-}RT}$, which accounted for the decrease in vasogenic edema, allowed for a median of 21.8 cc (0–406) of normal brain tissue to be spared from inclusion in the 46 Gy treatment volume, equivalent to a 9.6% volume reduction.

Conversely, in the interval between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ the majority of patients (66%) had an increase in the GTV_2 volume. It is worth noting that although 70% of patients had REP only 66% had an increase in their GTV_2 volume. This is due to resection cavity collapse which, in some patients, compensates for the increased enhancing disease. The median change in $GTV_{2\_post\text{-}op}$ to $GTV_{2\_pre\text{-}RT}$ volume was 5.9 cc (–32 to 133) which corresponded to a

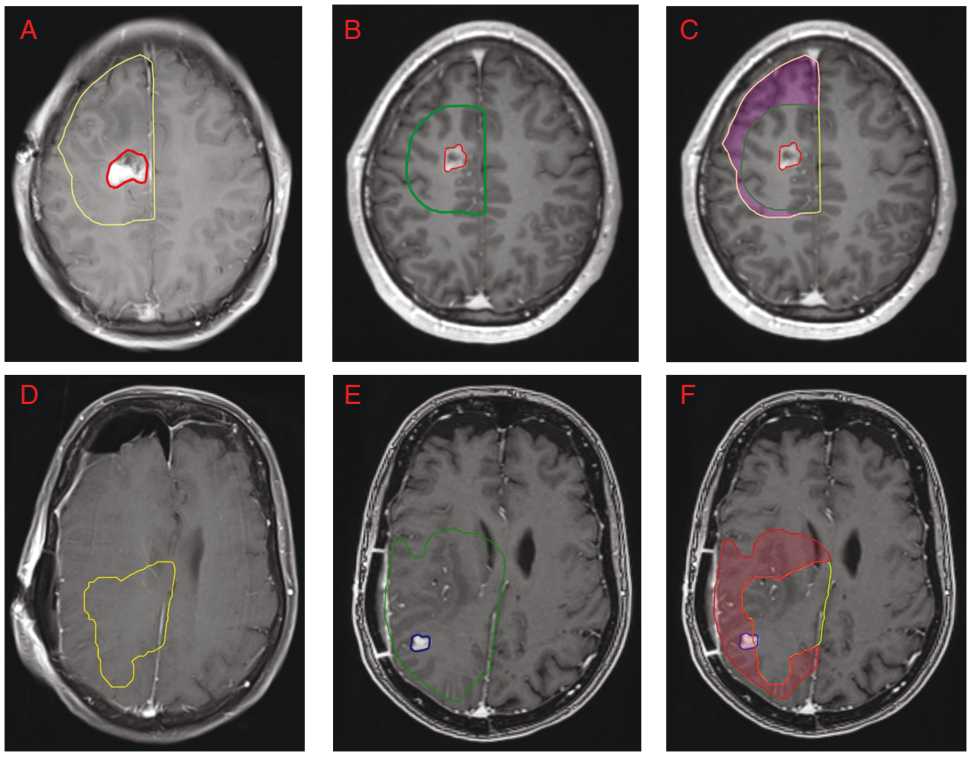

Fig. 2 MRI T_1 postgadolinium sequences shown as used in radiation treatment volume design to identify the overtreated and undertreated volumes. (A) $GTV_{2\_post\text{-}op}$ (red) and $CTV_{2\_post\text{-}op}$ (yellow) created using $MRI_{post\text{-}op}$. (B) $GTV_{2\_pre\text{-}RT}$ (red) and $CTV_{2\_pre\text{-}RT}$ (green) created using $MRI_{pre\text{-}RT}$. (C) $CTV_{2\_post\text{-}op}$ (yellow) overlayed on $CTV_{2\_pre\text{-}RT}$ (green), area of overtreatment (where $CTV_{2\_post\text{-}op}$ does not overlap with $CTV_{2\_pre\text{-}RT}$) outlined and shaded in pink. (D) $CTV_{2\_post\text{-}op}$ (yellow) created using $MRI_{post\text{-}op}$. E. $GTV_{2\_pre\text{-}RT}$ (blue) and $CTV_{2\_pre\text{-}RT}$ (green) created using $MRI_{pre\text{-}RT}$. F. $CTV_{2\_post\text{-}op}$ (yellow) overlayed on $CTV_{2\_pre\text{-}RT}$ (green), area of undertreatment (where $CTV_{2\_pre\text{-}RT}$ does not overlap with $CTV_{2\_post\text{-}op}$) outlined and shaded in red.

median change in $CTV_{2\_post\text{-}op}$ to $CTV_{2\_pre\text{-}RT}$ volume of 16.6 cc (–89 to 148). The median increase in GTV_2 and CTV_2 volumes were largely due to disease progression. Had the $MRI_{post\text{-}op}$ been used for treatment planning this would have led to a median of 27.1% of the $GTV_{2\_pre\text{-}RT}$ volume and 11.2% of the $CTV_{2\_pre\text{-}RT}$ volume being undertreated.

With a median follow-up of 14.0 months, 15/50 (30%) patients remained alive. The median OS (mOS) was 14.2 months and the median PFS (mPFS) was 5.1 months. Patients with REP had worse mOS compared to patients without REP (11.1 vs 21.6 months, $P = .0024$). There was not a statistically significant difference in mOS between patients with REP extending outside of $CTV_{2\_post\text{-}op}$ versus patients with REP encompassed by $CTV_{2\_post\text{-}op}$ (5.6 vs 11.6 months, $P = .08$). Patients with REP had a significantly worse mPFS compared to patients without REP (4.1 vs 7.3 months, $P = .041$). OS and PFS are shown in Figure 4.

Discussion

The data on the incidence of REP in patients with GBM is largely based on small retrospective studies, with rates varying between 20% and 72%,[7–10,12,13] with rates higher than 50% being most common. The range of REP incidence could be attributed to differences in diagnostic criteria and imaging modalities used. The 70% incidence of REP identified in this study is consistent with the range of REP previously reported. The high incidence of REP fits with our understanding of the biology of GBMs with prior studies reporting a median volumetric doubling time of 21–30 days.[14,15]

REP most frequently occurred locally within the resection cavity (60%) followed by a new focus of disease outside of the resection cavity (40%), similar to prior reports.[8] We found that REP is associated with a shorter mPFS (4.1 vs 7.3 months) and mOS (11.1 vs 21.6 months) as has been previously reported.[7–10,12,13] This significant difference in mOS occurred despite the $MRI_{pre\text{-}RT}$ being utilized for treatment planning in this patient cohort. This supports the notion that using a $MRI_{pre\text{-}RT}$ does not fully compensate for the negative prognostic significance of REP. As all patients in this study were treated using a $MRI_{pre\text{-}RT}$ we are unable to quantify the therapeutic benefit of using a $MRI_{pre\text{-}RT}$ for radiation treatment planning. However, we theorize that if patients with REP are not identified due to omission of a $MRI_{pre\text{-}RT}$, and then are treated with a radiation plan that does not account for occult progression, they may be at risk of having worse outcomes than what was identified in this patient cohort. This undertreatment of gross disease, which could be prevented with a preradiotherapy MRI,

Table 1 Patient Characteristics for All Patients, REP vs no REP, and REP Within the $MRI_{post\text{-}op}$ High Dose CTV_2 Volume vs REP that Would not have been Encapsulated Within the $MRI_{post\text{-}op}$ High Dose CTV Volume.

	All patients	No REP	REP	*P*-value	REP within $MRI_{post\text{-}op}$ high dose CTV	REP outside $MRI_{post\text{-}op}$ high dose CTV	*P*-value
	(*n* = 50)	(*n* = 15)	(*n* = 35)		(*n* = 26)	(*n* = 9)	
	n (%)	*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Sex				.70			.94
Male	32 (64)	9 (60)	23 (66)		17 (65)	6 (67)	
Female	18 (36)	6 (40)	12 (34)		9 (35)	3 (33)	
Age at diagnosis				.06			.85
<50	10 (20)	4 (27)	6 (17)		5 (19)	1 (11)	
50–69	26 (52)	4 (27)	22 (63)		16 (62)	6 (67)	
70+	14 (28)	7 (56)	7 (20)		5 (19)	2 (22)	
Vital status				.05			.08
Alive	15 (30)	7 (47)	7 (20)		7 (27)	0 (0)	
Dead	35 (70)	8 (53)	28 (80)		19 (63)	9 (100)	
Time to death				<.01			.08
Median (months)	14.2	21.6	11.1		11.6	5.6	
Surgery				<.01			.33
GTR	18 (36)	10 (67)	8 (23)		7 (27)	1 (11)	
STR or biopsy	32 (64)	5 (33)	27 (77)		19 (63)	8 (89)	
MGMT status				.67			.17
Methylated	16 (32)	4 (27)	12 (34)		11 (42)	1 (11)	
Unmethylated	33 (66)	11 (63)	22 (63)		14 (54)	8 (89)	
Indeterminate	1 (2)	0 (0)	1 (3)		1 (4)	0 (0)	
EGFR status				.24			.45
Amplified	19 (38)	6 (40)	13 (37)		9 (35)	4 (44)	
Non-amplified	31 (62)	9 (60)	22 (63)		17 (65)	5 (56)	
Concurrent TMZ				.90			.01
Yes	47 (94)	14 (93)	33 (94)		26 (100)	7 (78)	
No	3 (6)	1 (7)	2 (6)		0 (0)	2 (22)	
Adjuvant TMZ				.42			.93
Yes	21 (42)	5 (33)	16 (46)		12 (46)	4 (44)	
No	29 (58)	10 (67)	19 (54)		14 (54)	5 (56)	
On clinical trial				<.01			.38
Yes	25 (50)	13 (87)	12 (34)		10 (38)	2 (22)	
No	25 (50)	2 (13)	23 (66)		16 (62)	7 (78)	
Time, surgery to RT start				.21			.57
<6 weeks	39 (78)	14 (93)	25 (71)		18 (69)	7 (78)	
6–8 weeks	8 (16)	1 (7)	7 (20)		5 (19)	2 (22)	
>8 weeks	3 (6)	0 (0)	3 (9)		3 (12)	0 (0)	
Completed RT course				.24			.09
Yes	47 (94)	15 (100)	32 (91)		25 (96)	77 (78)	
No	3 (6)	0 (0)	3 (9)		1 (4)	2 (22)	
Time, $MRI_{post\text{-}op}$ to $MRI_{pre\text{-}RT}$				.26			.19
10–14 days	6 (12)	0 (0)	6 (17)		6 (23)	0 (0)	
15–21 days	11 (22)	4 (27)	7 (20)		4 (16)	3 (33)	
22–28 days	17 (34)	7 (53)	10 (29)		6 (23)	4 (45)	
>28 days	16 (32)	4 (40)	12 (34)		10 (38)	2 (22)	
Reason for $MRI_{pre\text{-}RT}$				.32			.99
Trial enrollment	41 (82)	14 (93)	27 (78)		20 (76)	7 (78)	
New symptoms	5 (10)	1 (7)	4 (11)		3 (12)	1 (11)	
Unknown	4 (8)	0 (0)	4 (11)		3 (12)	1 (11)	

Abbreviations: GTR, gross total resection; STR, subtotal resection; MGMT, O^6-methylguanine-DNA-methyltransferase; EGFR, epidermal growth factor receptor; TMZ; temozolomide; RT, radiation; MRI, magnetic resonance imaging; $MRI_{post\text{-}op}$, post-operative MRI; $MRI_{pre\text{-}RT}$, delayed MRI for radiation treatment planning; REP, rapid early progression; CTV, clinical target volume.

Table 2 Changes in GTV_1, CTV_1, GTV_2 and CTV_2 Treatment Volumes Between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$. The Undercovered Volume is Defined as the Respective Volume of $GTV_{pre\text{-}RT}$ or $CTV_{pre\text{-}RT}$ that Extended Outside of the $GTV_{post\text{-}op}$ or $CTV_{post\text{-}op}$, Respectively, that Represents Disease on $MRI_{pre\text{-}RT}$ that Would not have been Treated if the Treatment Plan was Based on $MRI_{post\text{-}op}$. The Overtreated Volume was Defined as the Volume of $GTV_{post\text{-}op}$ or $CTV_{post\text{-}op}$ that Extended Outside $GTV_{pre\text{-}RT}$ or $CTV_{pre\text{-}RT}$, Respectively, which Represents Uninvolved Brain on $MRI_{pre\text{-}RT}$ that Would Have Received Radiation if the Treatment Plan were Based on the Standard of Care $MRI_{post\text{-}op}$.

	Median volume, cc (range)			
	GTV_1	CTV_1	GTV_2	CTV_2
$MRI_{post\text{-}op}$	108 (12.2–264)	373 (79.3–734)	25.6 (1–112)	221 (60–409)
$MRI_{pre\text{-}RT}$	69.2 (10.5–267)	310 (71.5–726)	36.4 (4.4–206)	221 (64–522)
Delta ($MRI_{pre\text{-}RT}$ –$MRI_{post\text{-}op}$)				
Net	–10.6 (–161 to 86)	–9.9 (–407 to 205)	5.9 (–32 to 133)	16.6 (–89 to 148)
Undercovered	5.2 (0–113)	5.5 (0–220)	7.1 (0.3–136)	21.1 (0.1–146)
Undercovered/Total volume (%)	8.1 (0–69)	1.8 (0–39)	27.1 (0.5–73)	11.2 (0.04–50)
Overcovered	17.5 (0.1–167)	21.8 (0–406)	1.8 (0–42)	3 (0–88)
Overcovered/Total volume (%)	26.2 (0.8–1001)	9.6 (0–384.6)	3.8 (0–57)	1.5 (0–28)

Abbreviations: $MRI_{post\text{-}op}$, post-operative MRI; $MRI_{pre\text{-}RT}$, delayed MRI for radiation treatment planning; GTV_1, gross tumor volume 1 (encompassing enhancing disease, surgical resection cavity and edema); CTV_1, clinical target volume 1 (GTV_1 with a 2 cm isometric but anatomic boundary-confined expansion, representing the 46 Gy target volume); GTV_2, gross tumor volume 2 (encompassing enhancing disease and surgical resection cavity); CTV_2, clinical target volume 2 (GTV_2 with a 2 cm isometric but anatomic boundary-confined expansion, representing the 60 Gy target volume).

may contribute to the high rate of central failures that have been reported after chemoradiation.[2] This is supported by the finding that with follow-up 74% of patients with REP will recur at the site of REP.[12] The worse outcomes seen with REP could be due to more aggressive disease biology and patients with REP may represent a population that could benefit from treatment intensification.

Between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ the median change in absolute GTV_2 volume was 5.9 cc and the median relative tumor growth was 27.1%, consistent with a previously reported study of 12 patients with high-grade gliomas.[16] The changes in GTV_2 volume in this study were due to tumor growth and collapse of the resection cavity. We identified a number of CTV_1 and CTV_2 volumetric changes due to REP. In general, CTV_1 tended to be smaller and CTV_2 tended to be larger when using a $MRI_{pre\text{-}RT}$ for radiation treatment planning. This ultimately resulted in improved sparing of normal brain tissue from inclusion in the CTV_1 46 Gy treatment volume, particularly among patients without REP, and improved coverage of gross disease within the CTV_2 60 Gy treatment volume in patients with REP.

In regard to changes in CTV_1, 58% (29/50) of patients had a smaller $CTV_{1\_pre\text{-}RT}$ than $CTV_{1\_post\text{-}op}$ volume and would have been overtreated when a $MRI_{post\text{-}op}$ was used for treatment planning. This decrease in CTV_1 was most pronounced among patients without REP. In these patients, using a $MRI_{pre\text{-}RT}$ enabled a median 38% volume reduction of CTV_1 due to resolved post-op peritumoral edema sparing a median of 117 cc of normal brain tissue from inclusion in the 46 Gy CTV_1 volume. These findings provide evidence that patients without REP benefit from a $MRI_{pre\text{-}RT}$ as a way to reduce the toxicity of treatment by allowing for smaller treatment volumes. Historically, high-grade gliomas were treated with surgery followed by whole brain radiotherapy to a dose of 60 Gy.[17] Over time, advancements in imaging and mechanisms of radiotherapy treatment delivery have allowed for treatment with smaller volumes. Utilizing a $MRI_{pre\text{-}RT}$ for radiation treatment planning may be the next logical step in further reducing radiation treatment volumes. This may decrease the toxicity of radiotherapy, as side effects from radiotherapy are in part a function of the dose and volume of tissue treated. Using a $MRI_{pre\text{-}RT}$ may also assist in the goal of many recent clinical trials which have tried to find a balance between escalating the dose of radiotherapy delivered while respecting the radiation dose tolerance of nearby organs at risk through the use of smaller treatment margins.[18] This balance could be achieved through the utilization of a $MRI_{pre\text{-}RT}$, enabling increased sparing of normal brain tissue, with the potential for delivery of dose-escalated radiation.

Additionally, the smaller CTV_1 treatment volumes achieved when using a $MRI_{pre\text{-}RT}$ may provide a benefit when patients have disease recurrence. Patients with recurrent GBM are often treated with reirradiation. The dose of reirradiation that can be offered is often limited by the initial radiation dose delivered to nearby organs at risk such as the brainstem or optic structures. The reduction in CTV_1 treatment volumes achieved by using a $MRI_{pre\text{-}RT}$ to plan a patient's initial radiotherapy course may lead to greater sparing of organs at risk making delivery of higher doses of radiation in a second course of radiotherapy more feasible.

While a $MRI_{pre\text{-}RT}$ allowed for sparing of normal brain tissue from the CTV_1 46 Gy treatment volumes it also plays an important role in ensuring appropriate coverage of gross disease. As previously mentioned, given the high incidence of REP, the CTV_2 volumes tended to be larger when a $MRI_{pre\text{-}RT}$ was used for treatment planning. Since it can be difficult to conceptually analyze the significance of these CTV_2 volumetric changes, it may be beneficial to

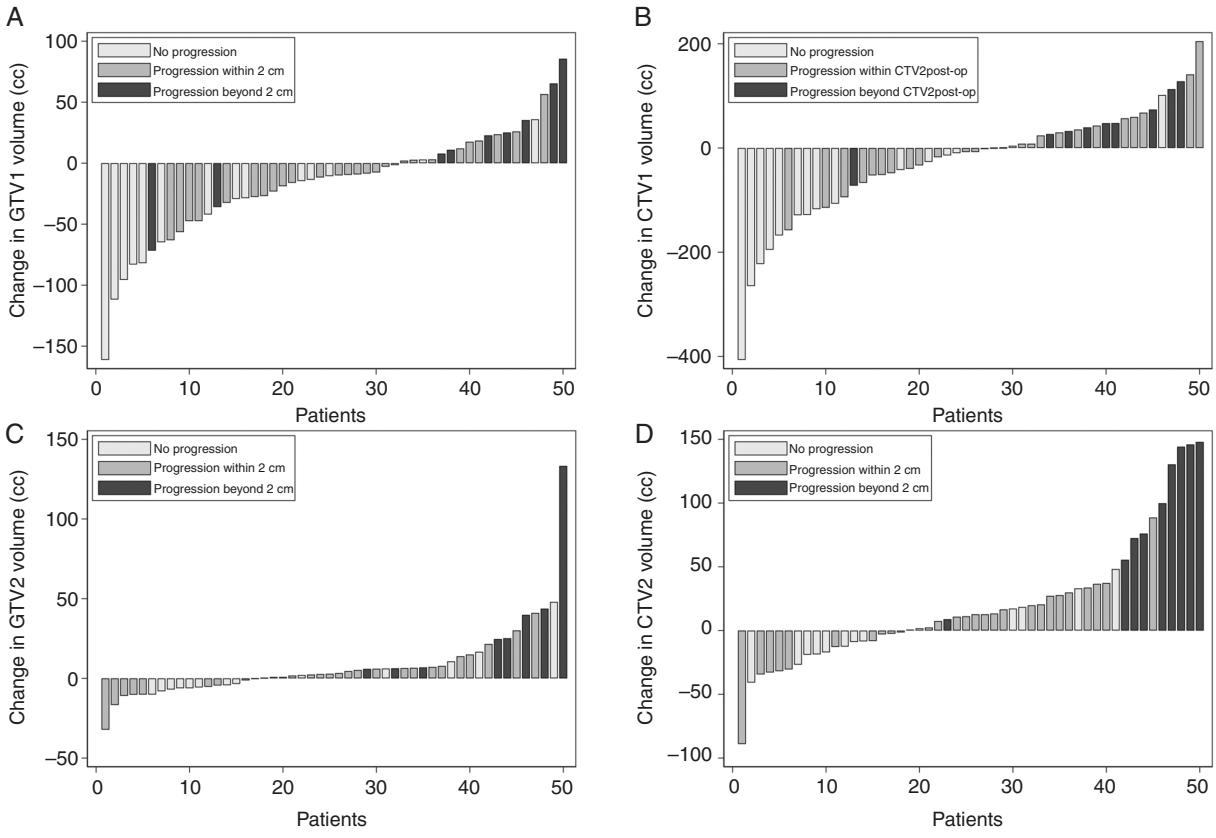

Fig. 3 Change in treatment volumes (cc) sorted by progression status. (A) Change in GTV_1 volume (cc) between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ for patients with no REP, patients with REP that did not extend outside of $CTV_{2\_post\text{-}op}$ and patients with REP that extended outside of $CTV_{2\_post\text{-}op}$. (B) Change in CTV_1 volume (cc) between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ for patients with no REP, patients with REP that did not extend outside of $CTV_{2\_post\text{-}op}$, and patients with REP that extended outside of $CTV_{2\_post\text{-}op}$. (C) Change in GTV_2 volume (cc) between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ for patients with no REP, patients with REP that did not extend outside of $CTV_{2\_post\text{-}op}$, and patients with REP that extended outside of $CTV_{2\_post\text{-}op}$. (D) Change in CTV_2 volume (cc) between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ for patients with no REP, patients with REP that did not extend outside of $CTV_{2\_post\text{-}op}$, and patients with REP that extended outside of $CTV_{2\_post\text{-}op}$.

use 30 cc as a reference, as this is approximately equivalent to the 25.6 cc median volume of the post-op resection cavity and residual enhancing disease ($GTV_{2\_post\text{-}op}$). With this reference in mind, 43% (15/35) of patients with REP would have had ≥30 cc (range 30–146.1) of their $CTV_{2\_pre\text{-}RT}$ volume extending outside of their $CTV_{2\_post\text{-}op}$ and not included in the high dose treatment volume if an $MRI_{post\text{-}op}$ were used for planning volumes. This represents significant undertreatment of subclinical disease, larger than the approximate volume of the original tumor itself.

Even more concerning is that 18% (9/50) of patients were found to have gross disease extending outside of $CTV_{2\_post\text{-}op}$ due to the extent of REP. If the standard $MRI_{post\text{-}op}$ had been used for radiation treatment planning, this would have led to gross disease extending outside of the 60 Gy treatment volume. Although this area of progression could still be captured within the 46 Gy volume, this would still represent an undertreatment via an unintentional dose reduction of at least 25%. These findings could have implications for those who treat GBMs with radiation volumes per the European Organization of Research and Treatment of Cancer (EORTC) guidelines. The EORTC approach involves treating a single volume, equivalent to CTV_2 from RTOG guidelines, to approximately 60 Gy.[5] Unlike RTOG guidelines, this EORTC approach does not specifically target peritumoral edema as identified on T_2/FLAIR MRI. This difference means that patients with REP with gross disease extending outside of a 2 cm expansion on the EORTC GTV volume would have gross disease outside of all treatment volumes rather than having the possibility of still being included in the RTOG CTV_1 volume dosed at 46 Gy.

With 18% of patients on this study having REP outside of the $CTV_{2\_post\text{-}op}$, this suggests more than one in six patients are being undertreated if a $MRI_{post\text{-}op}$ is used for treatment planning; however, these rates are higher than other reports. A prospective study by Pennington et al. reported that one of twelve high grade glioma patients they assessed had REP which extended >2 cm beyond the original tumor.[16] The differences in the incidence and extent of REP between the studies may be

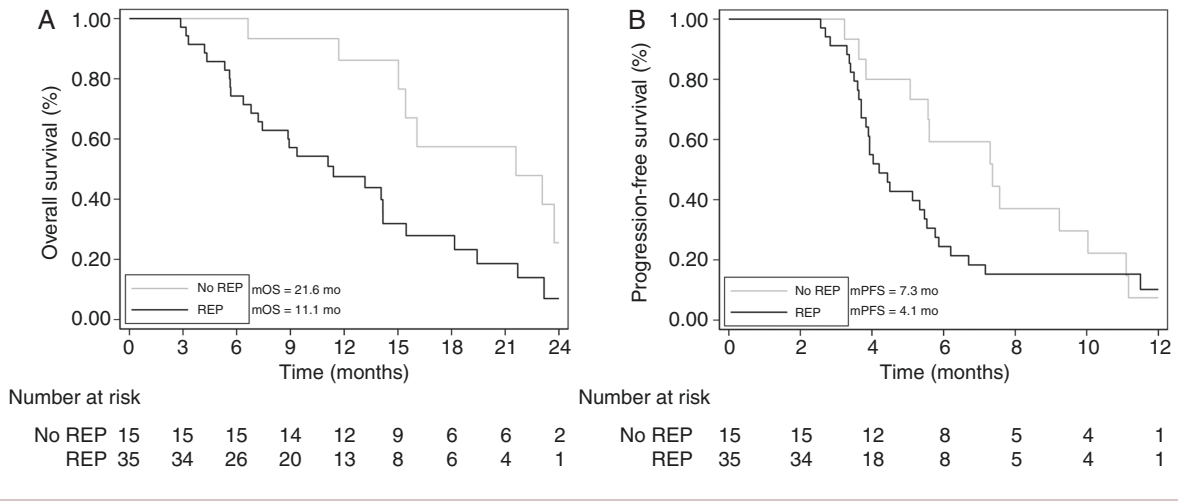

Fig. 4 Graph of OS (A) and PFS (B) by progression status in patients with REP and without REP.

due to the small sample sizes and inclusion of non-GBM high grade gliomas in Pennington et al., or differences in the proportion of patients with unfavorable molecular markers. To encompass all gross disease among all patients with REP, a CTV_2 expansion of 5.8 cm on the $GTV_{2\_post\text{-}op}$ would have been required. A routine expansion of this size would be infeasible due to toxicity, and would be unnecessary if all patients received an $MRI_{pre\text{-}RT}$ for treatment planning. These large changes in treatment volume and undertreatment of gross disease may have a significant impact on the effectiveness and toxicity of radiotherapy.

It is worth noting that some patients with REP had a smaller CTV_2 volume when a $MRI_{pre\text{-}RT}$ was used for treatment planning. Overall, 17% (6/35) of patients with REP had ≥30 cc (31.2–88.3) of their $CTV_{2\_post\text{-}op}$ volume extending outside of their $CTV_{2\_pre\text{-}RT}$ leading to a large amount of normal brain tissue falling within the high dose treatment volume unnecessarily. Additionally, patients without REP had a median of 8% volume reduction of CTV_2 when a $MRI_{pre\text{-}RT}$ was used for treatment planning. This reduction in CTV_2 among patients without REP was largely due to collapse of the resection cavity and highlights the previously mentioned benefits of a $MRI_{pre\text{-}RT}$ in sparing normal brain tissue from inclusion in radiation treatment volumes.

In addition to improving coverage of gross and subclinical disease among patients with REP and decreasing treatment toxicity through reduced treatment volumes, there are other potential benefits to performing an $MRI_{pre\text{-}RT}$ due to the early identification of REP. If REP is not identified until the post-radiotherapy MRI, it may mistakenly be believed to be a radiation treatment effect, true progression, or pseudoprogression. Recognizing REP before treatment may help differentiate pseudoprogression, which occurs in approximately one-third of patients,[19] from true progression. Uncertainty regarding pseudoprogression can have a significant impact on patient management as well as lead to delays in initiation of second-line therapy and cause undue anxiety for patients.[20] Additionally, if REP is not identified before radiotherapy it may be assumed to be progression during concurrent chemoradiation and inappropriately lead to early initiation of second-line therapy.

We did not identify any clinical factors on multivariable regression which were predictive of REP or that could be used to selectively identify patients who would most benefit from a $MRI_{pre\text{-}RT}$ due to our small sample size as shown in Supplementary Table S1. However, other studies have found the extent of surgical resection is predictive of REP with one study reporting REP occurring in 78% of patients with STR and 34% of patients with gross total resection (GTR).[8–10] There is mixed data regarding whether the time between $MRI_{post\text{-}op}$ and $MRI_{pre\text{-}RT}$ was associated with REP.[8,9,13] However, a study by Wee et al. quantified the risk of REP based on the extent of residual disease and time between surgery and initiation of radiotherapy and found that for every 1 cc increase in residual enhancing tumor there was a 3.9% increased risk of REP, with the risk of REP increasing by 8.1% for each additional day interval between surgery and radiotherapy.[13] Additionally, they reported that an interval between surgery and radiotherapy of >40 days was associated with a significantly higher risk of REP compared to patients with an interval ≤40 days (43.8% vs 16.7%). In a low resource setting, these clinical factors may help identify which patients could potentially most benefit from an $MRI_{pre\text{-}RT}$. However, in our study, if an $MRI_{pre\text{-}RT}$ had been reserved for patients with a STR or a >40 day interval between surgery and initiation of radiotherapy, 23% of patients with REP would not have been identified. Importantly, those 23% of patients would still not have been identified if development of new symptoms had been used as an indication for an additional $MRI_{pre\text{-}RT}$. Only 11% (4/35) of patients with REP in our study were symptomatic; thus few of the 35 patients with REP would have received an $MRI_{pre\text{-}RT}$ if they had not been enrolled in a clinical trial. It is for these reasons that we recommend $MRI_{pre\text{-}RT}$ be performed for radiation treatment planning in all patients.

Limitations

There are several limitations to this study including its retrospective design and small population size. REP is an evolving term which has not yet been standardly defined but has been used in a way that is consistent with previously published reports. There are data suggesting T_1 enhancement on MRI may not adequately represent the volume of residual disease compared to MR spectroscopy.[21] Advanced imaging such as MR spectroscopy or perfusion scans were not routinely utilized in this study and pathologic confirmation of residual disease was not performed. In regard to the creation of treatment volumes, post-operative changes can make identification of residual disease difficult and variable use of steroids can also contribute to changes seen on MRI.[22] There remains a risk for observer bias despite our attempts to control for this by having all treatment volumes reviewed by two unblinded radiation oncologists and one blinded radiation oncologist to ensure that they were created strictly according to RTOG guidelines.

Conclusion

More than two-third of patients with GBM in our study had REP, and nearly all were asymptomatic, suggesting that REP is being underdetected prior to initiation of adjuvant therapy. Utilization of an $MRI_{pre\text{-}RT}$ leads to increased identification of REP, improved coverage of gross disease, and smaller treatment volumes for patients without REP. For these reasons, physicians should have a low threshold for ordering a $MRI_{pre\text{-}RT}$ for radiotherapy treatment planning. Additional studies are warranted using larger patient populations to confirm these findings and determine whether $MRI_{pre\text{-}RT}$-based radiotherapy treatment plans have an impact on treatment outcomes. To accomplish this, we plan to look at whether using a $MRI_{pre\text{-}RT}$ for radiation treatment planning impacts patterns of failure or the rate at which radiologists express concern for pseudoprogression on the first post-radiation MRI.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

Acknowledgments

We would like to thank Angela Lam for her expertise and assistance with data acquisition for this manuscript.

Funding

National Institutes of Health (P30CA042014).

Conflict of interest statement. The authors have no conflicts of interest to declare.

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