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ORIGINAL ARTICLE

The Effect of Surgical Resection Extent on Boost Volume Changes During Radiotherapy for Glioblastoma

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OBJECTIVE

This study aimed to investigate the boost volume changes on adaptive magnetic resonance imaging (MRI) performed before the second phase of the radiotherapy (RT) for glioblastoma (GBM) and to examine whether the extent of surgery affected the boost volume changes.

METHODS

Among 50 GBM patients included in this study, 30 had Gross total resection (GTR), 14 had STR (subtotal resection), and sixpatients had biopsy.Treatments were planned in twophases according to the RTOG recommendations. Computed tomography (CT) for treatment planning and MRI for target volume determination were performed twice, before treatment and around the 20th fraction. Boost volumes were delineated on both images to compare volume changes.Wilcoxon two-related t-test was used to evaluate the boost volume changes. Growth and shrinkage trends were analyzed according to the type of resection.

RESULTS

The change between the determined boost volumes on two scans wasfound to be statistically significant. Twenty-four of 30 patients (80%) who underwent GTR had a reduced GTV, and threehad enlargement. Among patients who had an STR, GTV volume decreased in sevenof 14 patients (50%) and enlarged in 6 (43%).GTV shrank in twoof sixpatients (33%) with biopsy and enlarged in four.

CONCLUSION

This study demonstrated that there were considerable radiological changes occurring during RT for GBM patients. The boost volume variations occurring during RT require repeat CT/MRI for the second phase of RT. The extent of surgery can be considered while generating CTV and PTV margins.

Keywords: Adaptive radiotherapy; extent of surgical resection; GBM.

INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Multidisciplinary treatment approach for GBM requires surgery followed by adjuvant radiotherapy (RT) and temozolomide. Despite all efforts with multimodality treatments, the median survival time of GBM patients remains between 14 and 16 months.[1]

Maximum safe resection is an important component of the treatment and the extent of resection positively affects the results of the treatment.[2] The most common site of recurrence is the initial contrast-enhancing area in magnetic resonance imaging (MRI).[3,4]

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Therefore, accurate delineation of the tumor bed is very important for adjuvant RT treatment planning. RTOG 0825 recommended the use of computed tomography (CT) simulation with pre-and post-operative MR scans for target volume delineation.[5] The post-operative MR scans are used for contouring and adaptive MRIis not common during the course of RT.

According to a multicentric study that examined the changes in boost volume with a mid-treatment MRI in GBM patients, when compared to a pretreatment MRI scan, there was 80% variation in the gross tumor volume (GTV).[6] Another study reported that routinely monitoring changes in tumor volume during the first 3 weeks of RTwereessential for the entire boost volume to receive the scheduled dose.[7] The previous studies have shown that in GBM patients who underwent gross total resection (GTR), the target volume changes continue during the entire RT course, secondary to surgical defect alterations.[6,8] In another study, which included 19 patients who underwent GTR, the GTV volume was found to decrease in all patients at the time of first RT simulation and MRI before the boost treatment, when compared to early post-operative MR scans.[8]

In our recent publication, we showed an adaptive treatment plan based on target volumes defined using pre-boost MR scans that could provide better normal tissue sparing or avoidance of undercoverage given the volume changes occurring during RT, especially when limited-fields were used.[9]

The aim of the present study is to investigate the changes in the boost volume during the course of RT by comparing initial and boost simulation MR scans in a larger number of patients to determine whether the extent of surgical resection had any effect on these changes.

MATERIALS AND METHODS

Fifty GBM patients treated in our clinic between January 2019 and April 2021 were included in the study. GTR was performed in 30 of 50 patients and 14 patients underwent STR and biopsy was performed in six patients.

Thermoplastic head masks were used to immobilize all patients. Pre-operative MRI was used to determine the initial shape, size, and location of the tumor. The first simulation (CT_initial and MR_initial) was performed a few days before the start of treatment and the second simulation (CT_boost, MR_boost) was done before the boost phase. Simulation CT images 2–3 mm with slice thickness were obtained for treatment planning and same day MR T1 pre-and post-gadolinium and T2 fluid-attenuated inversion recovery (flair) sequences were anatomically registered with planning CT scan using Eclipse treatment planning system (Version 13.6, Varian Medical Systems, Palo Alto, CA).

According to our clinical protocol, during the first phase of target delineation, GTV_1 (surgical cavity including suspicious involvement and edema) was determined throughT2-weighted MR_initial sequences, and it was expanded by 0.5–1cm to create clinical target volume (CTV_1) and by 1–2 mm to determine planning target volume (PTV_1). For statistical comparison $GTV_{2\text{-initial}}$, volume was determined on the MR_initial T1 contrast images to include the contrast-enhancing area and surgical cavity and was extended by 0.5–1 cm margin to create $CTV_{2\text{-initial}}$ and 1–2 mm margin to generate $PTV_{2\text{-initial}}$ volumes. CT_boost and MR_boost images were obtained for adaptive planning for the second phase of the treatment at around 21±1st fraction. MR_boost T1 contrast images were used to define GTV_{2_boost}. CTV_{2_boost} volumes were created on CT_boost by adding a margin of 0.5–1cm to the GTV_{2_boost} and PTV_{2_boost} volume was generated by adding a margin of 1-2 mm to CTV_{2_boost}. CTV was modified to respect the anatomical boundaries. By examining the differences between the volumes measured in the initial and boost simulations, the change in the growth and shrinkage tendency according to the extent of surgery was investigated. We investigated whether GTR, STR, or biopsy performed before RT was determinative about the direction of the volume changes. Target volume changes between initial and boost CT/MR simulations were evaluated. All variables were compared using a two-related-sample test Wilcoxon for volume differences for GTV, CTV, and PTV average±standard deviation, median (max-min) values. GTV volume changes of less than 5% were accepted as stable.

RESULTS

The mean time between two MR simulations for 50 patients was 30.6 days, and the median was 29 (18–45) days. Thirty-three patients were found to have GTV shrinkage, while 13 had volume enlargement and fourwere found to be stable when volumes delineated on initial and boost MR scans were compared.

There was a statistically significant difference between boost GTV, CTV, and PTV volumes defined on initial and boost CT/MR simulation images. P values for average volume difference for GTV, CTV, and PTV were 0.036, 0.013, and 0.006, respectively. Table 1 shows the mean±standard deviation and me-

Table 1 Mean±standard deviation and median (minimum-maximum) volume changes between two simulation MR images for all patients

All patients n=50	Initial simulation volumes (cc) mean±SD median (min-max)	Boost simulation volumes (cc) mean±SD median (min-max)	Differences ΔTV (cc) mean±SD median (min-max)	Differences ΔTV (%) mean±SD median (min-max)	p
GTV	40.6±25.6 34.4 ([4.2]–[111.1])	41.3±31.4 32.8 ([1.8]–[151.3])	0.72±21.8 -3.7 ([-28.3]–[78.5])	5.68±73.6 (-16.75) ([-60]–[295.1])	0.036
CTV	115.7±48.8 109.1([36.3]–[278.5])	111.4±52.23 106.6 (32.6–287.4)	-4.31±35.8 -11.7 (-78.1–123)	0.62±43.7 -11.0 (-38.8–209.2)	0.013
PTV	145.8±57.3 132.9 ([48]–[327.5])	139.0±61.5 134.0 ([43.4]–[338.3])	-6.83±40.27 (-16.15) [(-84.9)–(140.7)]	(–1.68)±37.1 (-11.35) [(-35.9–175.9)]	0.006

For ΔTV, (–) values show decreasing volumes, (+) values show increasing volumes. MR: Magnetic resonance; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume

dian (minimum-maximum) results for the initial and boost simulation volumes together with the change in volumetric and proportional between the two simulations for all patients.

GTV was found to shrink in 24 (80%) of 30 patients who underwent GTR, and the median volume change was (min-max) 30.53% (5.5–60%) when boost volume was compared to the initial GTV. Three of 30 patients who underwent GTR had enlarged GTV with a median (min-max) change of 15.8% (5.59–295.1%). Three patients had stable volumes.

Figure 1 shows the graph of GTV, CTV, and PTV volume differences in 30 patients who underwent GTR. Minus (–) volume change is seen in patients with a decrease in the direction of change, and (+) volume change is observed in patients with growth.

It was found that the changes in GTV, CTV, and PTV were significant for all 30 patients who underwent GTR, with p<0.01, 0.01, and 0.01, respectively. Table 2 shows the volume changes and p values for patients who underwent GTR.

Patients who underwent GTR were evaluated in two separate groups according to growth and shrinking target volume patterns; GTV, CTV, and PTV volume changes were not significant for four patients whose volumes tended to increase (p=0.068). The changes in GTV, CTV, and PTV volumes were found to be statistically significant (p<0.001) for 26 patients whose volumes tended to decrease.

It was found that in seven of 14 patients (50%) who underwent STR, the GTV was reduced, and the median shrinkage rate was (min-max) 23.69% (10.81–31.92%) compared to the initial GTV volume. In six of 14 patients (42.8%) who underwent STR, GTV was found to have enlarged, and the median growth rate was (min-max) 48.62% (6.08–185.92%) compared to the initial GTV. One patient had stable volume. Figure 2 shows the graph of the differences in GTV, CTV, and PTV volumes for 14 patients who underwent STR.

Table 2 Volume changes and p values for patients who underwent GTR

Volume changes	GTR median (min-max) p			
Cc	Growth (n=4)	p	Shrinking (n=26)	p
ΔGTV	2.38 (6.5–60.2)	0.068	-7.9 ([-0.1]–[-28.3])	**<0.001**
ΔCTV	34.8 (6.5–68.7)	0.068	-19.6 ([-2.4]–[-78.1])	**<0.001**
ΔPTV	39.4 (4.1–71.1)	0.068	-22.1 ([-4.4]–[-84.9])	**<0.001**

For ΔTV, (–) values show decreasing volumes, (+) values show increasing volumes. GTR: Gross total resection; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume

The change in GTV, CTV, and PTV between the two simulations was not statistically significant for all 14 patients who underwent STR; p values were found to be 0.975, 0.397, and 0.552, respectively.

Table 3 shows the volume changes and p values for patients who underwent STR.

When the whole group was evaluated in patients who underwent STR, p value was not found to be statistically significant since the volume increased and

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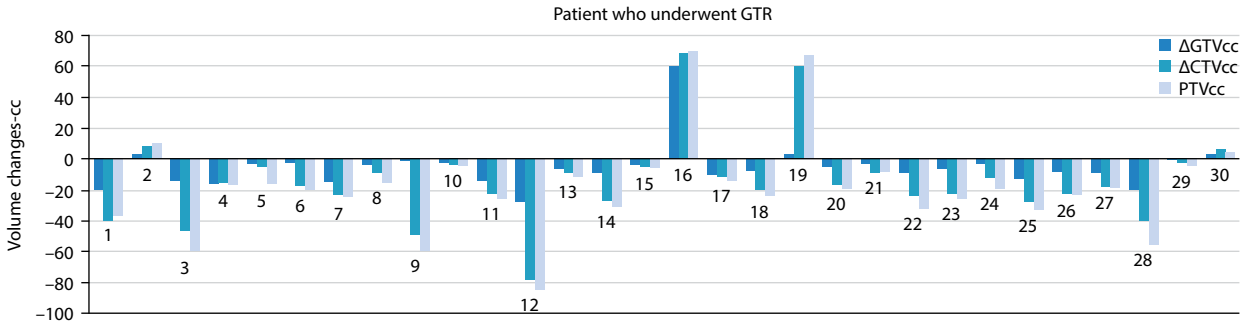

Fig. 1. Volume changes in patients with GTR. Volume change is observed in patients with (–) reduction in the direction of change and (+) in patients with growth.
GTR: Gross total resection; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume.

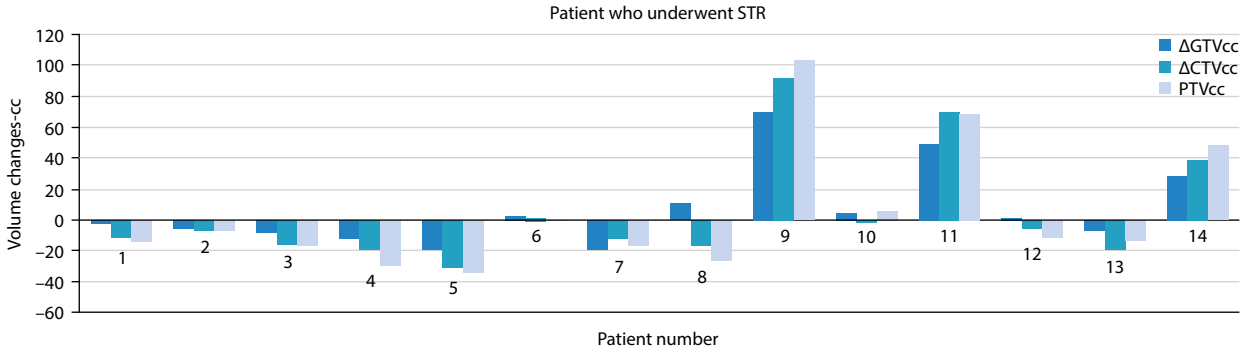

Fig. 2. Volume changes in patients who underwent STR. Volume change is observed in patients with (–) reduction in the direction of change and (+) in patients with growth.
STR: Subtotal resection; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume.

decreased at approximately the same rates. When the patients who underwent STR were evaluated in two separate groups as enlarging and shrinking target volumes, the changes in GTV, CTV, and PTV were found to be statistically significant (p=0.012) in eight patients whose volumes tended to decrease. In six patients with volume growth, the change in GTV volume was significant (p=0.028), while the change in CTV and PTV was not significant (p=0.345, p=0.138).

GTV shrank in two of the six patients (33%) who underwent biopsy, and a median shrinkage rate of (min-max) 11.61% (4.78%-18.44%) was found when compared to the initial GTV volume. GTV enlarged in four of the six (67%) patients who underwent biopsy with a median growth rate of 106.59% (12.2–256.54%). Figure 3 shows the graph of the differences in GTV, CTV, and PTV volumes for 6 patients who underwent biopsy. The change in GTV, CTV, and PTV between the two simulations was not statistically significant for all six patients who underwent

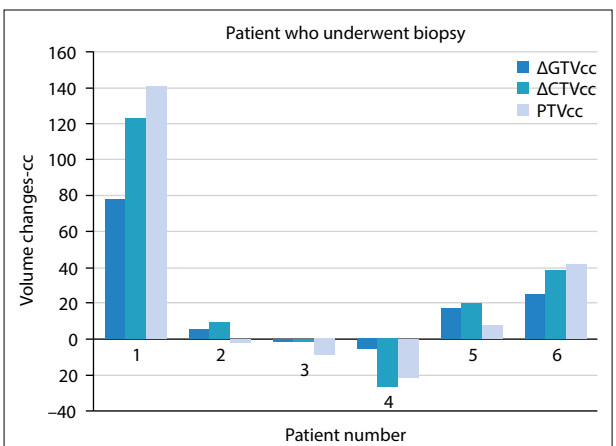

Fig. 3. Volume change in patients with biopsy. Volume change is observed in patients with (–) reduction in the direction of change and (+) in patients with growth.
GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume.

Table 3 Volume changes and p values for patients with STR

Volume changes	STR median (min-max) p			
Cc	Growth (n=6)	p	Shrinkage (n=8)	p
ΔGTV	19.05 (2.4–69.6)	**0.028**	-8.9 ([-0.7]–[-19.3])	**0.012**
ΔCTV	18.85 ([-17.4]–[91.7])	0.345	–14.4 ([-6.3]–[-31.1])	**0.012**
ΔPTV	26.2 ([-27.5–102.9])	0.138	–15.9 ([-8.1]–[-34.5])	**0.012**

For Δ TV, (–) values show decreasing volumes, (+) values show increasing volumes. STR: Subtotal resection; GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume

Table 4 Volume changes and p values for patients with biopsy

Volume changes	Biopsy median (min-max) p			
Cc	Growth (n=4)	p	Shrinking (n=2)	p
ΔGTV	21.75 (6.1–78.5)	0.068	-3.5 ([-1.2]–[-5.9])	0.18
ΔCTV	29.1 (9.4–123)	0.068	-13.75 ([-1.2]–[-26.3])	0.18
ΔPTV	24.8 ([-1.5]–140.7)	0.144	-15.1 ([-9.1]–[-21.1])	0.18

For Δ TV, (–) values show decreasing volumes, (+) values show increasing volumes. GTV: Gross tumor volume; CTV: Clinical target volume; PTV: Planning target volume

biopsy; p values were found to be 0.116, 0.249, and 0.600, respectively. The volume changes and p values for patients who underwent biopsy are shown in Table 4. When all six patients who underwent biopsy were evaluated, the change was not significant. GTV and CTV changes were both close to significance (p=0.068), but PTV change was not significant (p=0.144) for four patients with a growth tendency. Two patients with a shrinking tendency to target volume change were not significant (p=0.18).

DISCUSSION

Several studies have shown that the cavity and edema volume changes might occur during RT treatment in GBM patients. Therefore, the boost volumes defined on pretreatment MR scans are subject to change resulting in larger or smaller than actual boost volumes being radiated. This study showed the boost GTV, CTV, and PTV volumes changed during RT and a repeat CT/MR simulation performed around the 20th fraction might compensate for these changes.

We found a relation between the volume changes and the extent of surgical resection; patients who underwent GTR had significantly decreased volumes most probably due to post-operative cavity shrinkage, while patients with STR and biopsy were more likely to experience volume enlargement. Considering the results from this study, one might argue more generous margins as recommended by RTOG should be able to compensate for the volume changes during RT if the main concern was under treatment. However, it is a subject for further studies to investigate whether the volumetric changes occurred in a symmetrical margin. In the low resources setting, it might not be possible to obtain a second MR scan before the boost phase for all patients; however, the extent of resection can be considered to define the patient who will most likely benefit from repeat imaging.

The previous studies also reported that wide margins against the possibility of tumor recurrence would cause more brain tissue irradiation with an undesired loss of brain functions.[10–13] In the study of Gebhardt et al.,[14] 95 documented relapses had an on-site component of treatment failure in 77 (81%), a marginal component in 6 (6%), and a distant component in 27 (28%). Although the international group trials recommended 2–2.5 cm CTV margins to account for microscopic disease, most recent MRI-based studies utilized margins smaller than 2cm and they reported similar recurrence patterns. According to the results of this study, using the same symmetrical margin, approach for all patients is not reflecting the actual reality, since patients undergoing GTR require smaller margins while STR and biopsy patients demand for wider margins to avoid over and undertreatment of boost volumes. Appropriate imaging and adaptive treatment planning for limited field RT might have clinical significance for the avoidance of geographic misses and reduced toxicity. Similar to our study, Kim et al.[8] also reported that patients with GTR also would most likely experience.

Several previous studies have shown that the target volume did not receive sufficient dose in the enlarged group, and the extra irradiated normal tissue dose in the shrinking group caused unnecessary radiation damage and the intended dose distribution can be achieved with adaptive RT.[7,15–17]

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CONCLUSION

Our study showed that there were considerable radiological changes occurring during RT for GBM patients. The boost volume variations occurring during RT require repeat CT/MRI for the second phase of RT. Adaptive MRI might be beneficial to reduce the boost volume for GTR patients who have shrinkage of operation cavities and boost volumes while avoiding undertreatment of STR and biopsy patients with GTV volumes enlarged during RT. Extent of surgical resection should be considered while generating CTV volumes when an adaptive MR scan cannot be performed.

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REFERENCES

1. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10(5):459–66.
2. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery 2008;62(4):753–266.
3. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 1989;16(6):1405–9.
4. Chan JL, Lee SW, Fraass BA, Normolle DP, Greenberg HS, Junck LR, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol 2002;20(6):1635–42.
5. RTOG 0825: Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant temozolomide plus bevacizumab versus conventional concurrent chemoradiation and adjuvant temozolomide in patients with newly diagnosed glioblastoma; 2011. Available at: www.rtog.org. Accessed Ap 5, 2021.
6. Manon R, Hui S, Chinnaiyan P, Suh J, Chang E, Timmerman R, et al. The impact of mid-treatment MRI on defining boost volumes in the radiation treatment of glioblastoma multiforme. Technol Cancer Res Treat 2004;3(3):303–7.
7. Tsien C, Gomez-Hassan D, Ten Haken RK, Tatro D, Junck L, Chenevert TL, et al. Evaluating changes in tumor volume using magnetic resonance imaging during the course of radiotherapy treatment of high-grade gliomas: Implications for conformal dose-escalation studies. Int J Radiat Oncol Biol Phys 2005;62(2):328–32.
8. Kim TG, Lim DH. Interfractional variation of radiation target and adaptive radiotherapy for totally resected glioblastoma. J Korean Med Sci 2013;28(8):1233–7.
9. Şenkesen Ö, Tezcanlı E, Abacıoğlu MU, Özen Z, Çöne D, Küçücük H, Göksel EO, Arifoğlu A, Şengöz M. Limited field adaptive radiotherapy for glioblastoma: changes in target volume and organ at risk doses. Radiat Oncol J 2022;40(1):9–19.
10. Duan C, Yang R, Yuan L, Engelbach JA, Tsien CI, Rich KM, et al. Late effects of radiation prime the brain microenvironment for accelerated tumor growth. Int J Radiat Oncol Biol Phys 2019;103(1):190–4.
11. Duchstein S, Gademann G, Peters B. Early and late effects of local high dose radiotherapy of the brain on memory and attention. Strahlenther Onkol 2003;179:441–51.
12. Archibald YM, Lunn D, Ruttan LA, Macdonald DR, Del Maestro RF, Barr HW, et al. Cognitive functioning in long-term survivors of high-grade glioma. J Neurosurg 1994;80(2):247–53.
13. Bosma I, Vos MJ, Heimans JJ, Taphoorn MJ, Aaronson NK, Postma TJ, et al. The course of neurocognitive functioning in high-grade glioma patients. Neuro Oncol 2007;9(1):53–62.
14. Gebhardt BJ, Dobelbower MC, Ennis WH, Bag AK, Markert JM, Fiveash JB. Patterns of failure for glioblastoma multiforme following limited-margin radiation and concurrent temozolomide. Radiat Oncol 2014;9:130.
15. Champ CE, Siglin J, Mishra MV, Shen X, Werner-Wasik M, Andrews DW, et al. Evaluating changes in radiation treatment volumes from post-operative to same-day planning MRI in High-grade gliomas. Radiat Oncol 2012;7:220.

16. Yang Z, Zhang Z, Wang X, Hu Y, Lyu Z, Huo L, et al. Intensity-modulated radiotherapy for gliomas: Dosimetric effects of changes in gross tumor volume on organs at risk and healthy brain tissue. Onco Targets Ther 2016;9:3545–54.

17. Mehta S, Gajjar SR, Padgett KR, Asher D, Stoyanova R, Ford JC, et al. Daily tracking of glioblastoma resection cavity, cerebral edema, and tumor volume with MRI-guided radiation therapy. Cureus 2018;10(3):e2346.