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Temporal Lobectomy for High Grade Gliomas: Impact on Outcomes and Implications for Postoperative Radiation Treatment Field Design

James C. Marsh[1], Julius V. Turian[2], Arnold M. Herskovic[1,2], Julie A. Wendt[3], Rohit Godbole[4] & Richard W. Byrne[5]

[1] 21st Century Oncology of Arizona, 9159 West Thurnderbird Road, Peoria, AZ, USA

[2] Rush University Medical Center, Department of Radiation Oncology, South Paulina, Chicago, IL, USA

[3] Allergy, Asthma & Immunolosy Associates, Ltd, Scottsdale, AZ, USA

[4] Rush Medical College, Chicago, IL, USA

[5] Department of Neurosurgery, Rush University Medical Center, Chicago, IL, USA

Correspondencr: James C. Marsh, M.D., 21st Century Oncology of Arizona, 9159 West Thurnderbird Road, Peoria, AZ, USA. 85381. Tel: 1-480-296-8514. Fax: 623-815-3380. E-mail: jmarsh@rtsx.com

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Conflicts of interest: none

Abstract

Objective: To review clinical outcomes for patients with high grade gliomas (WHO Grades 3 and 4) who have undergone temporal lobectomy or wide local excision (WLE) with particular attention to rates of recurrence within temporal lobectomy resection bed, and to assess the potential impact of this surgical approach on the design of postoperative radiotherapy treatment volumes. **Method:** We reviewed outcomes for 17 patients with diagnosis of high grade glioma located in temporal lobe who underwent either wide local excision (WLE, 18 procedures in 13 patients) or formal temporal lobectomy (5 procedures in 4 patients). Location of recurrence was identified for each, and classified as involving or not involving temporal lobectomy resection cavity. STANDARD and MODIFIED (temporal lobectomy resection cavity subtracted from CTV46Gy and CTV60Gy) treatment plans were generated for each patient with intensity modified radiotherapy (IMRT). Dosimetric data were collected for each plan and compared. **Results:** Only 1/5 of patients suffered recurrence following temporal lobectomy (none in temporal lobectomy resection cavity) with median follow up 27.3 months. 16/17 (94.1%) of recurrences after WLE involved temporal lobe). MODIFIED IMRT plans reduced dose to all critical organs versus while providing equivalent PTV coverage. **Conclusions:** Following temporal lobectomy, we identified no recurrences within the temporal lobectomy resection cavity, suggesting that this region might safely be excluded from postoperative radiotherapy planning treatment volumes. With IMRT, this improves ability to spare critical normal structures.

Keywords: temporal lobectomy, astrocytoma

1. Introduction

Although glioblastoma is generally considered an incurable disease, recent advances in treatment options have resulted in a 5 year overall survival rate of approximately 9.8% with maximum safe surgical resection followed by adjuvant therapy consisting initially of concurrent daily oral temozolamide and partial brain radiotherapy (PBRT), and then followed by temozolamide alone at higher doses every 4 weeks for 6 cycles (Stupp et al., 2005). We have anecdotally noted a group of patients treated at our institution with relatively long survivorship who share in common a temporal lobe location of their tumor and a surgical resection which consisted of formal temporal lobectomy rather than a standard tumor resection. Based on these anecdotal findings, we performed this retrospective analysis to assess the outcome for a group of patients diagnosed with temporal lobe high grade gliomas (World Health Organization [WHO] Grades 3 and 4) and treated at our institution with a variety of surgical approaches ranging from simple excision to formal temporal lobectomy. We hypothesize that in the setting of a high grade glioma restricted to the temporal lobe a formal temporal lobectomy followed by

appropriate adjuvant therapy will result in better outcomes than a more conservative surgical approach. We further hypothesize that after a formal temporal lobectomy high grade gliomas will not recur in the temporal lobectomy resection bed. It should therefore be unnecessary to include the temporal lobectomy resection bed as a target in the postoperative radiotherapy treatment field, and given the proximity of the antero-medial temporal lobe to a number of critical dose-limiting normal structures (optic nerves and chiasm, brainstem, retinae, and lenses) exclusion of the resection cavity from postoperative radiotherapy treatment fields should make it easier to spare these normal structures during treatment. Thus, in this retrospective review we will also ascertain whether any recurrences of high grade glioma have been identified in the region of the temporal lobe resection bed.

2. Materials and Methods

We identified 17 patients with a diagnosis of either anaplastic glioma (WHO Grade 3, 1 patient with an anaplastic oligo-astrocytoma) or glioblastoma multiforme (WHO Grade 4, 16 patients) who were treated at our institution with a gross total resection (R0) via either wide local excision (WLE) or formal temporal lobectomy, and for whom follow up information and imaging was available to ascertain the time interval to and location of tumor recurrences (if a recurrence had occurred). 9 patients had left-sided temporal lobe tumors and 8 patients had right-sided tumors. All patients were treated following initial resection (either WLE or formal temporal lobectomy) with 60 Gy of partial brain radiotherapy using a shrinking field approach and concurrent daily temozolamide (75Mg/m^2) followed by adjuvant temozolamide or other chemotherapy at thie discretion of their treating medical oncologist or neuro-oncologist. The initial 46 Gy in 23 fractions (2 Gy per fraction) was delivered to the preoperative gross enhancing tumor and peritumoral edema plus a 2cm margin. Subsequently the final 14 Gy in 7 fractions (2 Gy per fraction) was delivered to the preoperative gross enhancing tumor plus a 2cm margin for a total dose to the preoperatrive gross enhancing tumor of 60Gy in 30 fractions. Patients were treated with either 3-dimensional conformal radiotherapy (3DCRT) or imtensity-modulated radiotherapy (IMRT) at the discretion of their treating radiation oncologist. Patients were not re-treated with external beam radiotherapy after re-resection, but most were either re-treated with temozolamide or treated with bevicizumab or irinotecan, at the discretion of their treating medical oncologist or neuro-oncologist.

We reviewed the patients' treatment charts to document their clinical course after resection, with particular attention to the timing and pattern/location of recurrences as documented by imaging studies and/or operative interventions. 5 patients underwent formal temporal lobectomy (4 at the time of initial resection, and 1 at time of recurrence in the setting of salvage surgery), while 13 patients underwent a total of 18 WLE (13 at time of initial resection, and 5 at time of salvage surgery for recurrence). A time to recurrence (TTR) was calculated in months for each patient, and mean TTR was calculated for the entire group. The site of each recurrence was categorized by the lobe of the brain in which the recurrence occurred.

We then randomly selected three patients who were resected via a formal temporal lobectomy at the time of initial resection for dosimetric plan evaluation. STANDARD and MODIFIED plans were generated for each patient using IMRT (intensity-modulated radiation therapy) techniques. These IMRT plans were prepared using the Eclipse ver. 8.1 (Varian Medical Systems, Palo Alto, CA.) treatment planning system. Our primary goal in planning was to maximize dosimetric sparing of the critical normal structures (OARs) while guaranteeing adequate coverage of the appropriate PTV (95% of each PTV was to receive the prescription dose, and 100% of each PTV was to receive 95% of the prescription dose).

For each of the plans, we calculated the V43.7Gy and V46Gy of the PTV46Gy (volumes within the PTV46Gy receiving 43.7Gy [95% of prescription dose] and 46Gy [100% of prescription dose]), and the V57Gy and V60Gyof the PTV60Gy (volumes within the PTV60Gy receiving 57Gy [95% of prescription dose] and 60Gy [100% of prescription dose]. For the critical normal structures, we calculated the V45Gy for each eye, the V10Gy for both lenses, the V54Gy for each optic nerve, the V54Gy for the optic chiasm, and the V54Gy for the brainstem, as well as the mean and maximum dose for each structure. These values were obtained for all treatment plans and for all 3 patients.

3. Results

The median TTR for all resections was 9.3 months (range 2 to 27 months). For patients undergoing initial WLE, the median TTR was 9.3 months (range 2 to 27 months), while for those undergoing initial temporal lobectomy the median TTR was 9.0 months (one patient with a recurrence at 9.0 months). Median TTR after first initial resection was 10 months (range 2 to 27 months), while median TTR after re-resection was 6.2 months (range 2 to 16 months).

Among the five patients who underwent temporal lobectomy at the time of initial resection, only one patient has sustained a documented recurrence. This recurrence occurred at the posterior edge of his temporal lobectomy site

9 months postoperatively and extended into the adjacent parietal lobe, but did not otherwise involve his temporal lobectomy site (Figure 1). For the other four temporal lobectomies, no documented recurrence has been noted with follow ups ranging from 14 to 54 months (median follow up 27.3 months). Three of these four temporal lobectomies were performed at the time of initial resection, while one was performed at the time of time of salvage re-resection (he had failed locally in the right temporal lobe 3 months after an initial WLE). No recurrence in this series has been documented that involves the temporal lobectomy cavity.

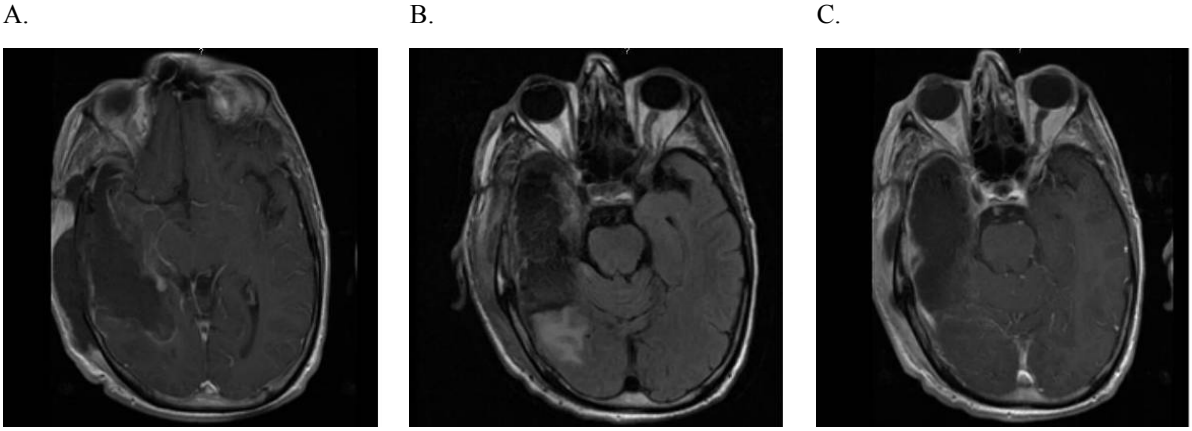


Figure 1. Temporal stump recurrence after temporal lobectomy with thin rim of enhancement and surrounding edema at posterior edge of prior resection bed as demonstrated on (A) axial T1 post-contrast MRI and (B) axial T2 FLAIR MRI sequences. Images (C) demonstrates lack of involvement of anterior resection bed

Sites of recurrence after initial WLE were as follows: ipsilateral temporal + frontal lobe (1 patient), ipsilateral parietal lobe (1 patient), ipsilateral temporal + parietal lobe (1 patient), ipsilateral temporal + occipital lobe (2 patients), and temporal lobe alone (12 patients). One patient with a left temporal GBM underwent a generous WLE (but not formal temporal lobectomy) and remained free of documented recurrence at 41 months postoperatively. Figure 2 demonstrates a typical temporal lobe recurrence after WLE.

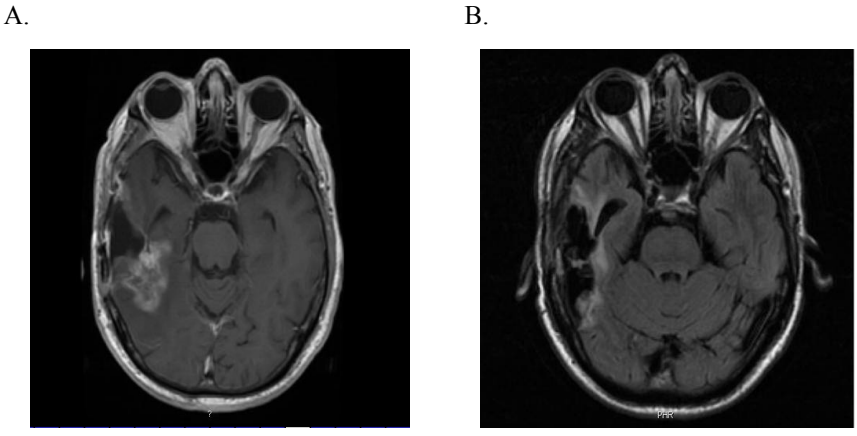


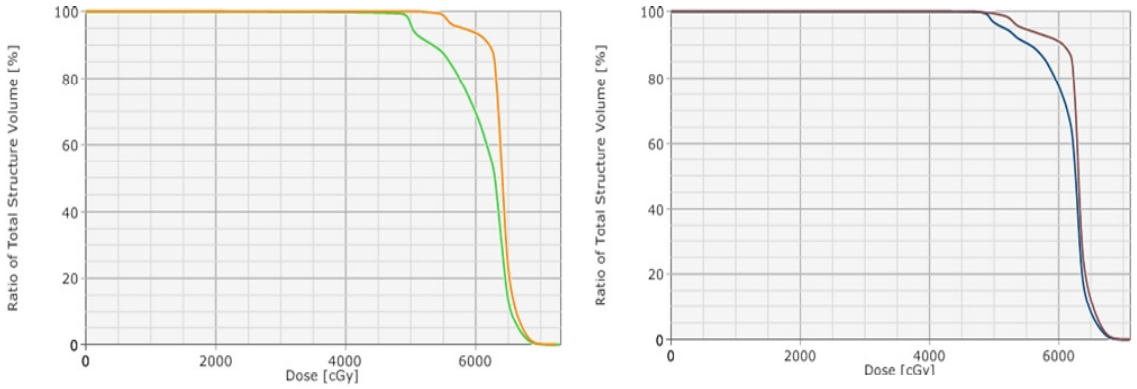
Figure 2. Temporal lobe recurrence after wide local excision (WLE) as demonstrated on (A) axial T1 post-contrast MRI and (B) axial T2 FLAIR MRI sequences

We found a significant benefit to the use of our modified PTV contours in terms of dose reduction to the organs-at-risk (OARs: ipsilateral eye, ipsilateral lens, ipsilateral optic nerve, optic chiasm, and brainstem), a reduction in the maximum dose delivered to the treatment targets (PTVs), and an improvement in the V60 Gy for the PTV 60Gy, while overall PTV coverage was the same in both plans.

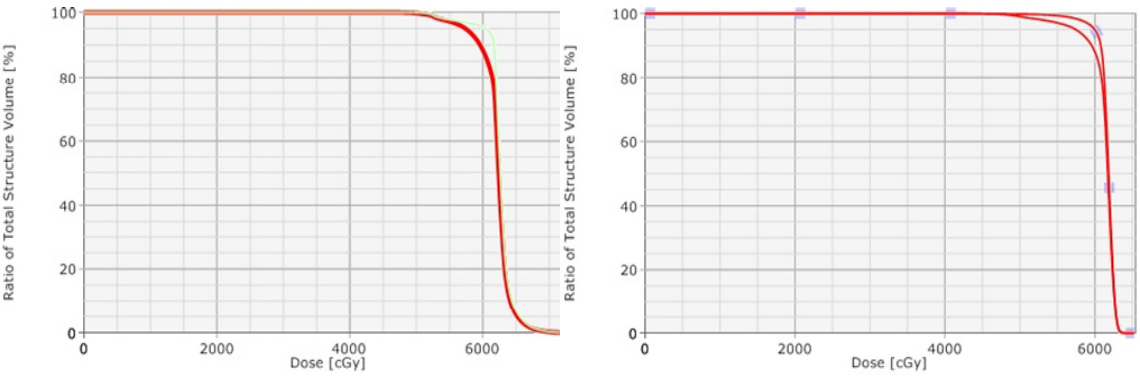
Mean and maximum doses to the OARs for the STANDARD and MODIFIED IMRT plans, respectively, were: ipsilateral eye 21.4 Gy and 40.3 Gy versus 21.0 Gy and 38.6 Gy, ipsilateral lens 9.9 Gy and 12.7 Gy versus 9.8 Gy and 13.0 Gy, ipsilateral optic nerve 48.2 Gy and 55.1 Gy versus 44.0 Gy and 52.7 Gy, optic chiasm 50.0 and 54.7 Gy versus 48.3 Gy and 53.1 Gy, and brainstem 39.5 Gy and 58.0 Gy versus 35.3 Gy and 55.6 Gy. This amounts to a relative reduction of mean dose to the ipsilateral eye, ipsilateral lens, ipsilateral optic nerve, optic chiasm, and brainstem in the MODIFIED IMRT plans of 1.9%, 1.5%, 8.6%, 3.4%, and 10.5%, respectively. The corresponding reductions in maximum dose were 4.1%, -1.0%, 4.3%, 2.9%, and 4.2%.

Maximum doses to the PTV 46Gy in the STANDARD versus MODIFIED plans were 72.5 Gy versus 67.5 Gy (mean values), while the corresponding values for the PTV 60Gy were 72.3 Gy and 67.4 Gy (mean values). This amounts to a 7.0% reduction in maximum dose to PTV 46Gy, and a 6.7% reduction in maximum dose to PTV 60Gy, in both cases favoring the MODIFIED IMRT plans. V60 Gy for the PTV 60Gy was 90.5% in the STANDARD IMRT plans versus 95.0% in the MODIFIED IMRT plans (mean values). This amounts to a 5.0% improvement in the V60 Gy favoring the MODIFIED plans.

Patient 1: STANDARD PTV60Gy (left, orange), STANDARD PTV46Gy (left, green), MODIFIED PTV60Gy (right, brown), MODIFIED PTV46Gy (right, dark blue)



Patient 2: STANDARD PTV60Gy (left, light green), STANDARD PTV46Gy (left, red), MODIFIED PTV60Gy (right, dark pink), MODIFIED PTV46Gy (right, red)



Patient 3: STANDARD PTV60Gy (left, blue), STANDARD PTV46Gy (left, teal), MODIFIED PTV60Gy (right, dark pink), MODIFIED PTV46Gy (right, red)

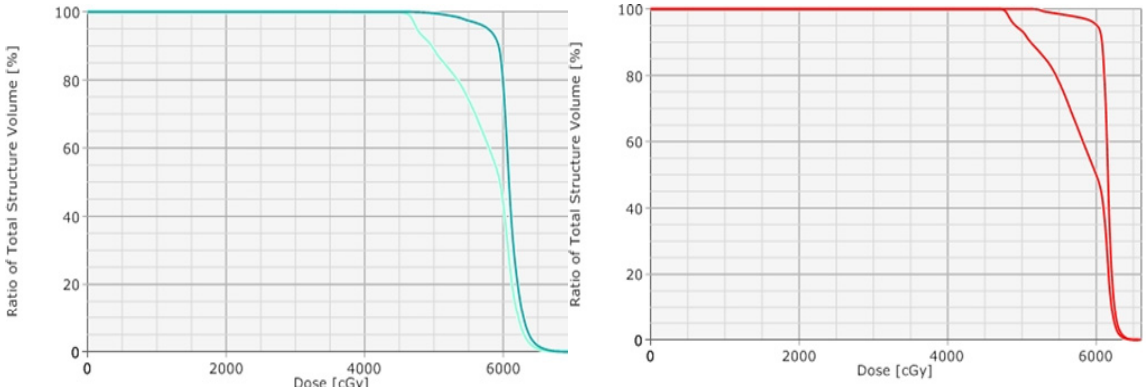
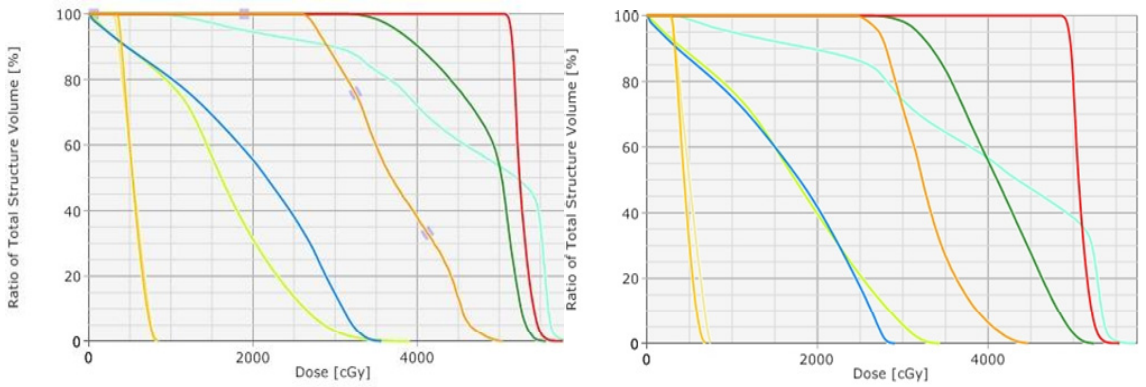


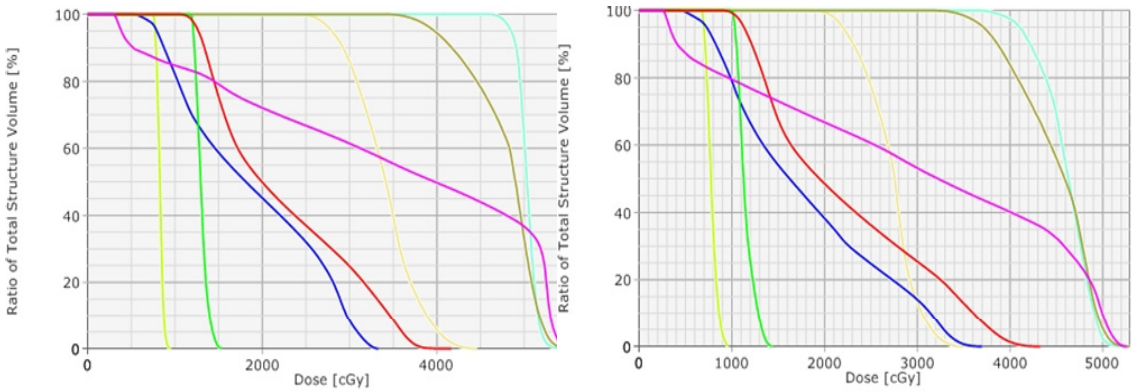
Figure 3. Comparative cumulative DVH for IMRT STANDARD plan (left) versus MODIFIED plan: PTV coverage (right)

Figure 3 shows a comparative cumulative DVH for the PTV46Gy and PTV60Gy in the STANDARD and MODIFIED IMRT plans for each patient. Figure 4 shows a comparative cumulative DVH for the OARs (ipsilateral eye, ipsilateral optic nerve, optic chiasm, and brainstem) in the STANDARD and MODIFIED IMRT plans for each patient. Figure 3 shows representative isodose distributions for STANDARD and MODIFIED treatment plans. IMRT dosimetric data are shown in Table 1.

Patient 1: brainstem (teal), optic chiasm (red), ipsilateral optic nerve (green), contralateral optic nerve (burnt orange), ipsilateral eye (blue), contralateral eye (yellow), ipsilateral lens (orange), contralateral lens (light orange)



Patient 2: brainstem (pink), optic chiasm (teal), ipsilateral optic nerve (brown), contralateral optic nerve (skin), ipsilateral eye (red), contralateral eye (blue), ipsilateral lens (green), contralateral lens (yellow)



Patient 3: brainstem (burnt orange), optic chiasm (teal), ipsilateral optic nerve (lavender), contralateral optic nerve (pink), ipsilateral eye (blue), contralateral eye (red), ipsilateral lens (yellow), contralateral lens (green)

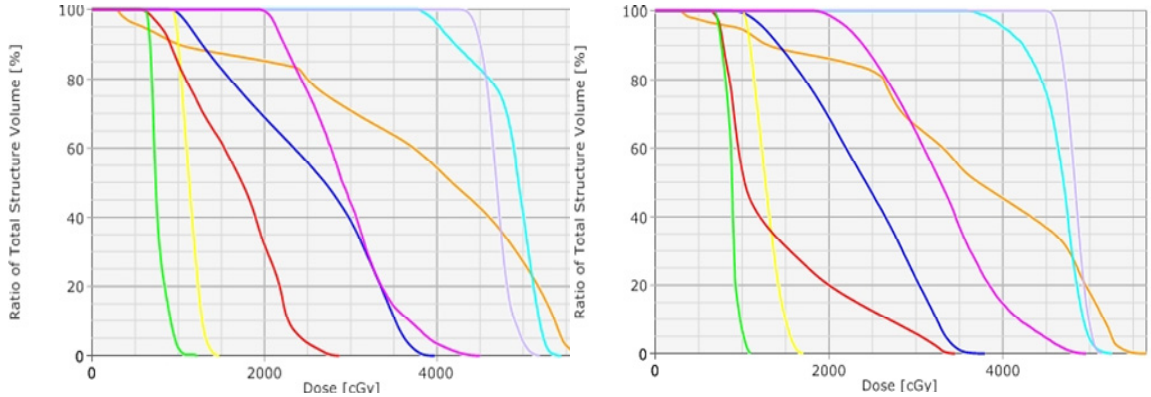


Figure 4. Comparative cumulative DVH for IMRT STANDARD plan versus MODIFIED plan): organs at risk (OAR)

Table 1. Dosimetric comparison: Standard versus Modified IMRT plans

TARGET	**STANDARD**	**MODIFIED**
PTV 46 Gy		
V43.7 Gy (95% IDL)	100%	100%
V46 Gy (100% IDL)	100%	100%
Maximum Dose (cGy)	7251	6746
PTV 60 Gy		
V57 Gy (95% IDL)	96%	96.60%
V60 Gy (100% IDL)	90.50%	95%
Maximum Dose (cGy/%IDL)	7225/120%	6743/112%
NORMAL	**STANDARD**	**MODIFIED**
Brainstem		
Mean Dose (cGy)	3945	3530
Max Dose (cGy)	5803	5559
V54Gy (%)	18.4	1.2
Optic Chiasm		
Mean Dose (cGy)	5000	4833
Max Dose (cGy)	5472	5313
V54Gy (%)	4.3	0.1
Left Optic Nerve		
Mean Dose (cGy)	4816	4402
Max Dose (cGy)	5508	5271
V54Gy (%)	1.4	0
Right Optic Nerve		
Mean Dose (cGy)	3360	3090
Max Dose (cGy)	4669	4327
V54Gy (%)	0	0
Left Eye		
Mean Dose (cGy)	2138	2097
Max Dose (cGy)	4026	3860
V45Gy (%)	0	0

Right Eye		
Mean Dose (cGy)	1842	1613
Max Dose (cGy)	3267	3361
V45Gy (%)	0	0
Left Lens		
Mean Dose (cGy)	993	978
Max Dose (cGy)	1274	1303
V10Gy (%)	61.5	66.7
Right Lens		
Mean Dose (cGy)	713	702
Max Dose (cGy)	1011	928
V10Gy (%)	0.7	2.2

IDL: IsoDose Line

4. Discussion

The current standard treatment regimen for high grade gliomas in patients with good performance status consists of maximum safe surgical resection followed by postoperative partial brain radiation therapy with concurrent and adjuvant temozolamide, based on a prospective randomized trial from the EORTC and NCIC (Stupp et al., 2005). The goal of surgery is to resect all gross visible disease that can be safely removed without producing severe and unacceptable neurological deficits, based on a body of literature which clearly shows that the extent of surgical resection correlates with median survival in this patient population (Nitto & Sato, 1995; Simpson et al., 1993). The standard dose of radiation for these patients is 60Gy, using a conedown boost after 46Gy to the gross preoperative tumor plus a margin of approximately 2cm (Walker, Strike, & Sheline, 1979; Bleehen & Stenning, 1991). The initial 45-46Gy is delivered to a field which includes the preoperative tumor and surrounding edema plus a margin of 2-2.5cm, based on studies which have shown that the area of edema surrounding the gross tumor frequently contains microscopic foci of tumor, and that most recurrences (up to 78%) occur within 1-2cm of the initial resection bed (Halperin, Burger, & Bullard, 1988; Hochberg & Pruitt, 1980; Wallner, 1991; Kelly et al., 1987; Fiveash et al., 2007). The current RTOG 08-25 study, which is randomizing patients to standard therapy with postoperative radiotherapy and concurrent and adjuvant temozolamide (as described above) with or without concurrent beviczumab stating on day 22 of radiotherapy, utilizes postoperative imaging rather than pre-operative imaging for delineation of radiotherapy treatment volumes and includes the postoperative resection bed in both the 46 Gy and 60 Gy treatment volumes rather than the preoperative gross enhancing tumor volume [RTOG.org].

The temporal lobe, particularly the medial temporal lobe, is located adjacent to a number of critical normal structures whose tolerance lies well below 60Gy; specifically, these structures include the globe of the eye, optic nerves, optic chiasm, brainstem, cochlea, pituitary, and lenses (Emami et al., 1991; Hall & Giaccia, 2006). The proximity of these critical structures to the temporal lobe complicates treatment planning, as the standard treatment fields used in the treatment of high grade gliomas will invariably overlap these structures when the tumor is located in the temporal lobe. One possible solution to this problem would be to resect such tumors via a formal temporal lobectomy rather than a simple wide local excision as would otherwise be performed.

A formal temporal lobectomy consists of a resection of the tumor infiltrated lateral neocortex, amygdala and hippocampus to the level of the ambient cistern. Resections to 4.5 cm on the dominant hemisphere or 5.5 cm on the non dominant hemisphere are usually well tolerated in patients with tumor replacing normal cortex. In some cases a larger tumor resection into the occipital area is appropriate and well tolerated.

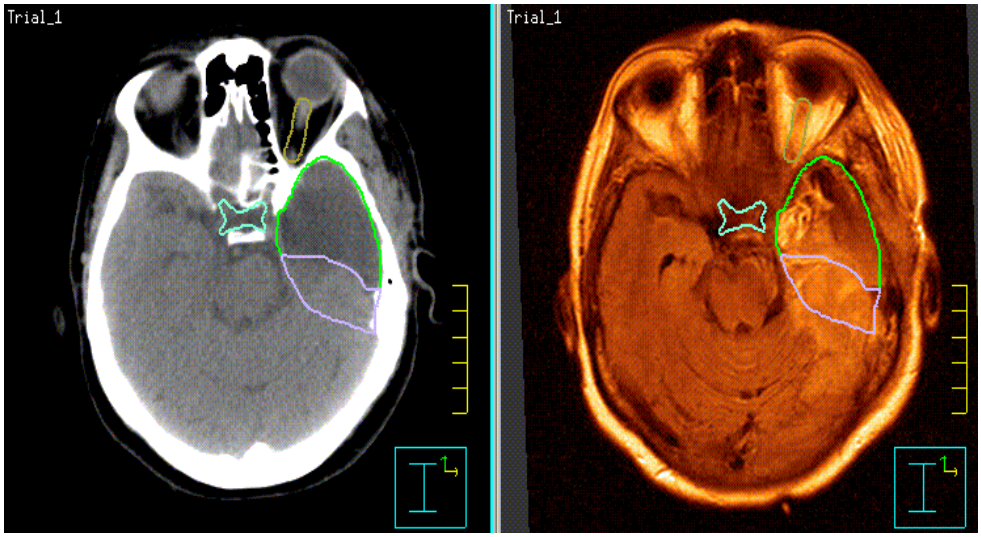


Figure 5. Axial postoperative CT (left) and preoperative MRI (right) showing the STANDARD CTV46Gy (green + purple) and MODIFIED CTV46Gy (purple) as well as their relationship to the optic chiasm (blue) and ipsilateral optic nerve (yellow)

Such an operation essentially amounts to an amputation of the anterior temporal lobe, and will leave a large resection cavity on the floor of the middle fossa (Figure 5). Gliomas would not be expected to recur in this resection cavity, as removal of the temporal lobe removes both the normal brain tissue and blood supply necessary to support tumor growth in this area, and leaves behind only dura and overlying calvarium, both very rare sites for glioma growth (Rainov et al., 1996; Gheyi et al., 2004; Wu et al., 2011; Arnautovic, Husain, & Linskey, 2000; Reifenberger et al., 1996; Hsieh et al., 2009; Brandes et al., 1998). The results of our study confirm this theory, as no recurrences involving the temporal lobectomy cavity have been documented after temporal lobectomy with follow up as long as 54 months. In contrast, 17 temporal lobe recurrences were noted after the 18 WLE reviewed. Only 1 recurrence after WLE did not involve the temporal lobe as a component of failure.

Other investigators have recently reported an approach to postoperative field planning after resection of glioblastoma multiforme which involves using the temporal bone as a margin for generating radiotherapy treatment volumes, and concluded that such an approach would allow for adequate target coverage while preserving the optic apparatus (Bokstein et al., 2008). Their rationale was that the temporal bone represents a natural barrier to the growth of high grade astrocytomas, and that it was therefore reasonable to not expand the CTV (46 Gy or 60Gy) into the temporal bone (Bokstein et al., 2008). This reasoning is supported by other studies which have documented the relative rarity of bony involvement by glioblastoma (Rainov et al., 1996; Gheyi et al., 2004). However, while we agree with the rationale behind such an approach, we also recognize that such an approach will not spare the brainstem and may not spare the optic chiasm, which is situated above the sellar diaphragm and therefore will not be spared from the high dose region by simply trimming the 60Gy CTV off of the temporal bone. Sparing of the optic apparatus and brainstem is critical, as the clinical consequences of excessive irradiation of these structures are severe and permanent (Mayo, Yorke, & Merchant, 2010; Mayo et al., 2010). We believe that an operative approach which includes resection of the anterio-medial temporal lobe, preferable via a formal temporal lobectomy, will more completely allow for sparing of the brainstem and optic apparatus by allowing for exclusion of the temporal lobectomy cavity from the postoperative radiotherapy treatment volumes. This will in turn (1) remove the retina, optic nerve, optic chiasm, and part of the brainstem from the high dose region during treatment, and (2) allow for better coverage of the areas that are at risk for recurrence, particularly the residual posterior temporal lobe and adjacent parietal and occipital lobes, without fear of exceeding critical normal tissue tolerances in the region [figure 6-7]. This approach should provide a dosimetric advantage whether preoperative or postoperative imaging is employed to generate treatment volumes.

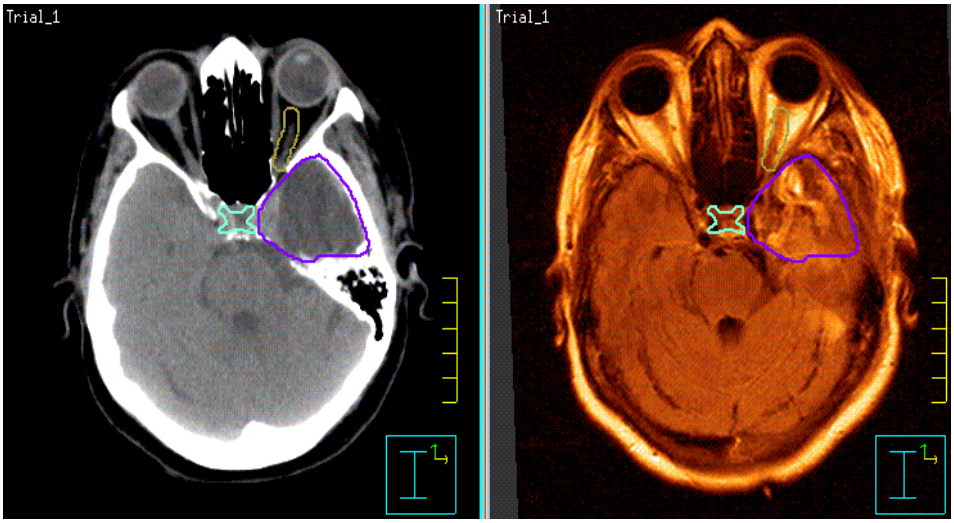


Figure 6. Axial postoperative CT (left) and preoperative MRI (right) showing the STANDARD CTV60Gy (purple) as well as its relationship to the optic chiasm (blue) and ipsilateral optic nerve (yellow). For this patient, the temporal lobectomy resection cavity was sufficiently large that the MODIFIED CTV60Gy did not approach these structures on any axial MRI slice

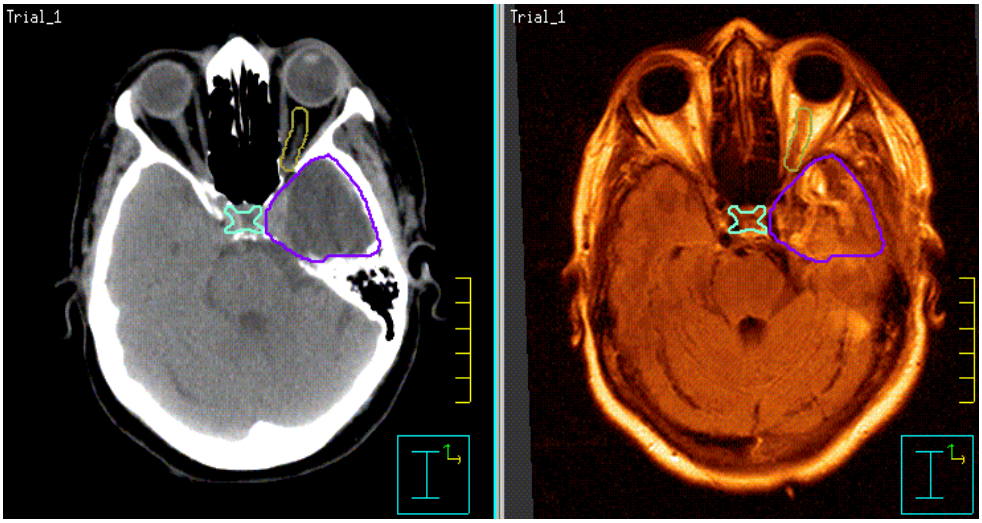


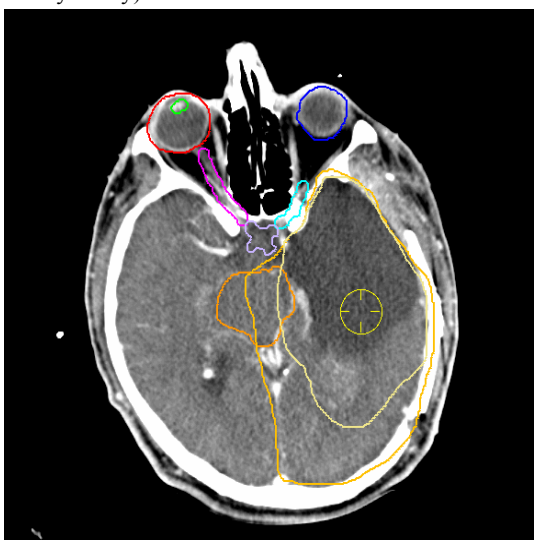
Figure 7. Axial postoperative CT (left) and preoperative MRI (right) showing the STANDARD CTV60Gy (purple) as well as its relationship to the optic chiasm (blue) and ipsilateral optic nerve (yellow). For this patient, the temporal lobectomy resection cavity was sufficiently large that the MODIFIED CTV60Gy did not approach these structures on any axial MRI slice

Such an operative approach is, of course, not technically feasible for all patients and this procedure should only be perfomed by a surgeon experienced in the technique. The decision to proceed with formal temporal lobectomy rather than a standard WLE should only be made after careful discussion of the risks and benefits of this operative approach with the patient. We would also not universally recommend the use of this approach to generating postoperative radiation treatment fields in patients whose tumors are noted on imaging or at the time of operative resection to involve the uncinate fasciculus, as involvement of this white matter bundle would provide a means for tumors to grow directly from the temporal lobe into the frontal lobe. While it should still be reasonable to exclude the temporal lobectomy cavity from the treatment volumes in such cases, one would still need to treat several centimeters of frontal lobe in such cases, and this would negate much of the dosimetric advantage our approach provides.

The use of IMRT allowed us to create steep dose gradients between the treatment targets (MODIFED and STANDARD PTV46Gy and 60Gy for the MODIFIED and STANDARD plans, respectively), which correlated

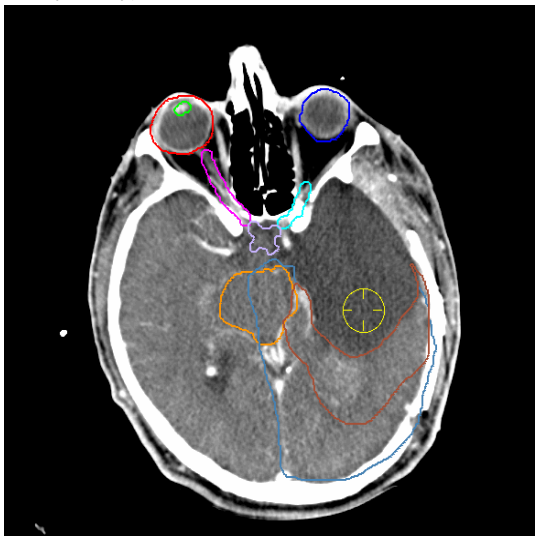
to improved PTV coverage and simultaneously improved dosimetric sparing of our OARs with IMRT as compared to 3DCRT (Table 1). This dosimetric advantage is readily explained by the increased distance between the treatment target (MODIFIED PTV46Gy and PTV60Gy) and the ipsilateral eye, optic pathway, and part of the brainstem afforded by the temporal lobectomy resection cavity, as demonstrated in Figure 8 which shows representative images of the STANDARD and MODIFIED CTV46Gy and CTV60Gy from 2 patients as they relate to these structures. This advantage could be further augmented with the use of daily image guidance (IGRT), which allows for a reduction in the necessary expansion from CTV to PTV to allow for daily setup error. In this study we expanded the CTV by 3mm to generate the treatment PTV. This negated some of the extra distance afforded by the temporal lobectomy cavity between the PTVs and OARs. An expansion of 1-2mm rather than 3mm, for example, might be possible with daily IGRT and would likely further accentuate the dosimetric difference between our STANDARD and MODIFIED plans.

a. Standard postoperative treatment volumes (include temporal lobectomy cavity)

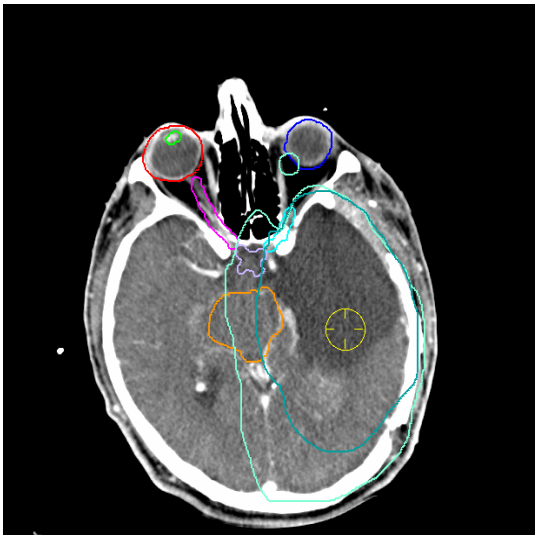


White: standard ctv60Gy, yellow/orange: standard ctv46gy

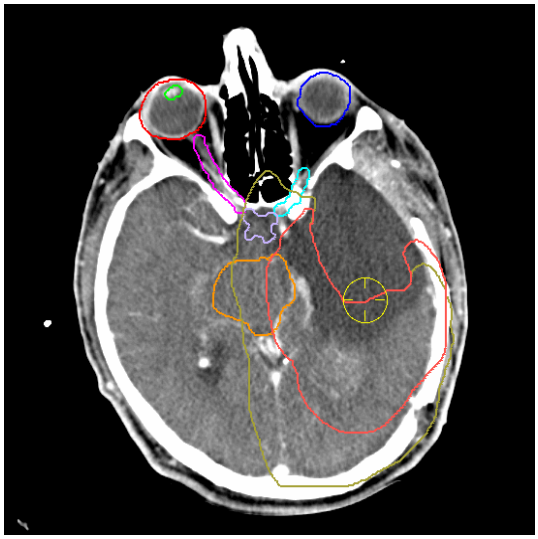
b. Modified postoperative treatment volumes (exclude temporal lobectomy cavity)



Brown: modified ctv60Gy, cornflower blue: modified ctv46Gy



Blue/green: standard ptv60Gy, aquamarine: standard ptv46Gy



Tomato: modified ptv60Gy, yellow/green: modified ptv46Gy

Figure 8. Postoperative 46 Gy and 60 Gy radiotherapy treatment volumes after temporal lobectomy using preoperative imaging for target delineation: relationship to critical normal structures with (a) and without (b) inclusion of the temporal lobectomy. Overlap of ptv60Gy with optic chiasm and left optic nerve is eliminated. Normal structure key utilized in all images is detailed below

Teal: left optic nerve, pink: right optic nerve, lavender: optic chiasm, orange: brainstem, blue: left eye, red: right eye, white: standard ctv60Gy, yellow/orange: standard ctv 46gy

5. Conclusion

The results of our study suggest that for patients presenting with high grade astrocytomas involving the temporal lobe alone, and whose tumors can technically be gross totally resected via temporal lobectomy, a temporal lobectomy may be considered. Such a procedure has the potential to reduce local recurrences when compared to a standard WLE, and also improves the ability of the radiation oncologist to adequately treat the necessary postoperative target to full dose while simultaneously sparing critical normal structures. The significance of these findings is limited by the small size and retrospective nature of our study, and should be validated in the context of a larger series or prospective study before being implemented into routine clinical practice.

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