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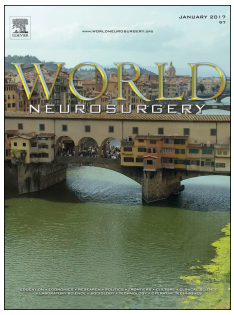

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Lessons Learned in Using Laser Interstitial Thermal Therapy (LITT) for Treatment of Brain Tumors: A Case Series of 238 Patients from A Single Institution

Jianning Shao, BA[1,2], Nathan R. Radakovich, BS,[1,2] Matthew Grabowski, MD[3], Hamid Borghei-Razavi, MD[3], Konrad Knusel, BS,[2] Krishna C. Joshi, MD[3], Baha'eddin A. Muhsen, MD[3,4], Lee Hwang, MD[3], Gene H Barnett, MD[1,3,4], Alireza M. Mohammadi, MD[1,3,4]

[1]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH
[2]Case Western School of Medicine, Case Western Reserve University, Cleveland, OH
[3]Department of Neurosurgery, Neurological Institute, Cleveland Clinic, Cleveland, OH
[4]Rose Ella Burkhardt Brain Tumor & Neuro-oncology Center, Cleveland Clinic, Cleveland, OH

Corresponding Author:
Alireza M. Mohammadi, MD
Assistant Professor of Neurosurgery
Cleveland Clinic Lerner College of Medicine at Case Western Reserve University
Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center
Cleveland Clinic CA-51 9500 Euclid Ave. Cleveland, OH 44195
Office: (216) 445-4290, Fax: (216) 444-0924
Email: mohamma3@ccf.org

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Disclosures and Conflicts of Interest Statements

Dr. Gene Barnett is a consultant for Monteris Medical, Inc.

Dr. Alireza Mohammadi is a consultant for Monteris Medical, Inc.

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ABSTRACT

Background: Laser interstitial thermal therapy (LITT) is a novel, minimally invasive alternative to craniotomy, and as with any new technology, comes with a learning curve.

Objective: We present our experience detailing the evolution of this technology in our practice in one of the largest patient cohorts to date regarding LITT in neuro-oncology.

Methods: We reviewed 238 consecutive brain tumor patients treated with LITT at our institution. Data on patient, surgery and tumor characteristics, and follow-up were collected. Patients were categorized into two cohorts: Early (<2014, 100 patients) and Recent (>2015, 138 patients). Median follow up for the entire cohort was 8.4 months.

Results: The indications for LITT included gliomas (70.2%), radiation necrosis (21.0%), and metastasis (8.8%). Patient demographics stayed consistent between the two cohorts, with the exception of age (Early: 54.3, Recent: 58.4, p=0.04). Operative time (6.6 versus 3.5, p<0.001) and number of trajectories (53.1% versus 77.9% with 1 trajectory, p<0.001) also decreased in the Recent cohort. There was a significant decrease in permanent motor deficits over time (15.5 versus 4.4%, p=0.005) and 30-day mortality (4.1% versus 1.5%) also decreased (not statistically significant) in Recent cohort. In terms of clinical outcomes, poor preoperative KPS (≤70) were significantly correlated with increased permanent deficits (p=0.001) and decreased overall survival (p<0.001 for all time points).

Conclusions: We observed improvement in operative efficiency and permanent deficits over time and also patients with poor preoperative KPS achieved suboptimal outcomes with LITT. As many other treatment modalities, patient selection is very important in this procedure.

Key Words: Laser Interstitial Thermal Therapy (LITT), Brain Tumor, Radiation Necrosis, glioma, brain metastasis, laser ablation, novel treatment

Running Head: LITT in neuro-oncology: lessons learned

INTRODUCTION

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical technique with progressively evolving utility and indications in the neurosurgical world.[1,2] Though first suggested by Bown in 1983, LITT was initially limited by technological restrictions, which did not permit real-time monitoring and control of thermal damage.[2-5] However, advances in recent years, in particular the development of MRI thermometry, have enabled precise monitoring and delivery of thermal energy to predetermined targets, thereby reviving LITT as a powerful and practical tool in the neurosurgical armamentarium.[2,3]

LITT achieves stereotactic tissue ablation via delivery of thermal energy to a designated brain region.[4,5] Specifically, a laser probe is inserted through a burr hole along a predetermined trajectory, and thermal energy is strategically delivered to induce hyperthermic damage of the target tissue while MR-thermometry facilitates real-time monitoring of the thermal energy being delivered.[1,2] Given its minimally invasive nature and ability to access lesions in problematic locations, LITT has been adopted for a variety of neurosurgical operations, including those for intracranial tumors, radiation necrosis, and epilepsy.[1,6-10]

LITT has long been recognized as a promising tool in neurosurgical oncology. While the current standard of care for high-grade gliomas is maximum safe resection with adjuvant therapy, gross total resection is sometimes unachievable due to neuroanatomical limitations and poor patient functional status.[1,11] It is well established that patients with tumors near eloquent areas or in deep seated regions that preclude safe aggressive resection face a worse prognosis.[6,11,12] In this setting, LITT may offer an alternative therapeutic approach that allows cytoreduction for difficult-to-access tumors that otherwise is infeasible with traditional surgery.[1,3,13-15] While there is no clear consensus on the optimal treatment methodology utilizing LITT for high-grade gliomas, several case series have described the utility and safety of LITT in this setting.[6,12,13,16-20] In addition, LITT has been utilized successfully in radiation necrosis from failed radiotherapy as well as a salvage treatment for metastatic brain lesions with promising results.[21-24]

Previous publications regarding the use of LITT suggest that it is a safe and well-tolerated modality of treatment for a variety of intracranial lesions, including malignant brain tumors.[1,6,13,21,25-27] As a relatively new procedure, however, there are several unanswered

questions concerning optimal patient selection and outcomes. Currently, there are no established guidelines regarding indications for LITT with respect to tumor size, pathology, or patient characteristics like age and functional status. We began using LITT for the treatment of brain tumors at our institution 10 years ago and conducted the first in-human study from 2009-2010.[28] As one of the earliest adopters of this technology, we have extensive experience with this technique and its development over the years. This study shows what we have learned from utilizing LITT in our practice over the past decade and the evolution of practices and outcomes over time in the largest single-center patient cohort to date.

METHODS

Patient Population

All patients (238 consecutive patients) who underwent LITT for brain tumor treatment at our academic institution between 2011-2018 were retrospectively reviewed in this case series. Cases in 2009-10 were excluded as they were used for the first human study for FDA approval in 2010. Patient data were collected through the middle of 2018, which explains the lower number of patients from 2018 in our cohort (figure 1). The patients were categorized into two groups: 1) Early, for those treated between 2011-2014 (100 patients) and 2) Recent, for those treated between 2015-2018 (138 patients). Differences in patient demographics, tumor characteristics, surgical approach, and outcomes between the Early and Recent cohorts served as the primary end point of our study. Patients with missing data and who were lost to follow-up were censored from survival analyses.

LITT

LITT was performed using the NeuroBlate® System (Monteris Medical, Plymouth, MN). All procedures in the cohort were performed by one of three surgeons at our institution in a manner consistent with previous descriptions in the literature.[29]

Data Collection and Analysis

This study was performed under the purview of an IRB committee, which approved retrospective data collection without requirement for patient consent prior to the start of this study. Data were collected on a variety of parameters, including patient demographics, tumor profile, operative

variables, complications, and postoperative outcomes. KPS scores were collected for all patients at four time points: the preoperative visit closest to LITT and at the 3-month, 6-month, and 12-month postoperative visits. All statistical analysis was performed in R (Version 3.5.1, The R Foundation for Statistical Computing, Vienna, Austria). To address and minimize bias within the retrospective study design, data collection was standardized with precise definitions for each variable and measure and validated by a second individual.

RESULTS

Patient Characteristics

A total of 238 patients were included; a detailed account of patient demographics across the entire cohort can be found in Table 1. Of the patients in our cohort, 50.8% were female and 49.2% were male. 55.5% of patients were under the age of 65 years. 79.4% had lobar tumors, 3.8% had posterior fossa tumors, and 16.8% had deep-seated tumors, defined as tumors in subcortical areas. The majority (70.2%) of patients had upfront or recurrent gliomas, while 21.0% of patients had radiation necrosis, and 8.8% of patients had intracranial metastases (Figures 1 and 2). Of the glioma patients, 84.4% had high-grade gliomas (HGG) and 15.6% had low-grade gliomas (LGG). Among the 167 patients with gliomas, 6 (3.5%) patients had WHO I astrocytoma, 20 (12.0%) had WHO II astrocytoma, and 37 (22.2%) patients had WHO III astrocytoma, 104 (62.3%) patients had glioblastoma. 112 patients (47.1%) were diagnosed upfront with biopsy at the time of LITT. Average surgical time, which was defined as time from incision to time to closing, was 4.7 ±2.6 hours (range: 1.0hr - 13.9hrs), and 67.7% were treated with single trajectories. 221 patients had preoperative Karnofsky Performanse scores (KPS) available, and the median preoperative KPS was 90. Median follow-up was 8.4 months, and 52% had progression during follow-up (31 patients were either lost to follow up or deceased prior to postoperative radiographical evaluation and were thus censored from this analysis). In our cohort, temporary complications occurred in 30.2% of patients, and permanent deficits occurred in 10.8% of patients, with an overall mortality of 2.16%. Tumor location was not found to have a significant effect on OS or PFS ($p=0.13$ and $p=0.11$, respectively).

Six patients had their procedures aborted due to equipment malfunction (3 patients) and absence of neoplasm (3 patients). A detailed list of the patients with aborted procedures can be found in table 2. There is not a statistically significant relationship between either patient cohort and procedure abortion in general (p=0.409). However, there was a trend towards decreased number of procedure abortion secondary to equipment malfunction in recent cohort (p=0.07). Since these patients did not complete the procedure, they were not included in the final QOL or survival analyses.

Outcome Analysis

Lesion Size

HGG patients who underwent LITT for large tumors (volume > $4cm^3$) had significantly worse OS (p<0.001) than HGG patients who underwent this procedure for small tumors (volume < $4cm^3$, Figure 3). This effect is apparent at the 12-month, 18-month, and 24-month postoperative time points (Table 3). At 12-months, only 36.9% of patients who underwent LITT for large HGG were alive, while 75% of patients with smaller HGG were alive (p<0.001). At 18 months, only 20.7% of LITT patients with large HGG were alive, while 54.8% of LITT patients with small HGG were alive at the same time point (p=0.001). Lastly, only 11.1% of LITT patients with large HGG were alive at 24 months, compared to 41.9% of patients with small HGG (p=0.001). HGG patients with large tumors also had significantly worse PFS than those with smaller tumors (p=0.015). Lesion size did not significantly affect OS or PFS for low-grade gliomas (LGG), metastatic lesions, or radiation necrosis.

Preoperative Functional Status

Poor preoperative KPS (≤70), were correlated with an increased number of permanent motor deficits compared to those with good preoperative KPS of 80-100 (17.6% vs. 2.3%, respectively, p<0.001, Table 4). Additionally, patients with poor preoperative KPS also had significantly decreased OS at 12 months (Poor Preoperative KPS: 33.8%; Satisfactory Preoperative KPS: 67.6%, p<0.001), 18 months (Poor Preoperative KPS: 23.5%; Satisfactory Preoperative KPS: 50%, p<0.001), and 24 months (Poor Preoperative KPS:14.7%; Satisfactory Preoperative KPS: 38.9%, p<0.001).

Glioma Patient Survival: Subset Analysis

All 6 patients with grade I glioma were alive at 12, 18, and 24 months. The OS for patients with WHO II astrocytoma was 100% (20/20) at 12 months, 85% (17/20) at 18 months, and 85% (17/20) at 24 months. OS for patients with WHO III astrocytoma were 78% (29/37) at 12 months, 62% (23/37) at 18 months, and 54% (20/37) at 24 months. Finally, OS for patients with glioblastoma was 47% (49/104) at 12 months, 36% (37/104) at 18 months, and 29% (30/104) at 24 months.

Comparative Analysis: Early vs. Recent Cohort

Patient Indications and Selection

There was a trend towards utilizing LITT for radiation necrosis in the past two years at our institution (Figure 1). With the exception of age, there were no significant differences in patient demographics between the two cohorts (Table 5). The average age of patients in the Early cohort was 54.3±15 years (range: 19-87 years), while the average age of patients in the Recent cohort was 58.4±15 years (p=0.040, range: 17-88 years). Of note, we did not find any trend towards using LITT based upon the size (volume or maximum diameter) or location (deep versus lobar) in early versus recent cohort.

Operative Efficiency

There was a significant reduction in operation time, from 6.67±2.66hrs in the Early cohort, to 3.57±1.75hrs in the Recent cohort ($p<0.001$, table 6, figure 4). The number of trajectories utilized also decreased such that 77.9% of patients in the Recent cohort underwent only one trajectory to achieve satisfactory ablation, compared to 53.1% in the Early cohort ($p<0.001$, Table 6). Univariate analysis identified radiation necrosis and recurrent tumors as variables significantly correlated with shorter operation time ($p=0.02$ and $p=0.012$, respectively). Furthermore, univariate also found operation time was significantly decreased in cases performed after 2013 ($p<0.001$). In contrast, upgraded tumors were associated with significantly longer operation time ($p=0.013$). Multivariable analysis identified cases performed after 2013 to be correlated with significantly shorter operation time ($p<0.001$).

Complications

Temporary motor complication rate did not significantly differ between the two cohorts (Early: 23.9%; Recent: 19.1%, p=0.493). Patients with temporary deficits had larger edema size compared to patients without temporary motor deficits (7.39 cm vs. 7.18cm), though this relationship was not significant (p=0.63). There was a statistically significant decrease in permanent motor deficits over time, occurring in 15.5% of patients in the Early cohort compared to 4.4% of patients in the Recent cohort (p=0.005, Table 7, Figure 5). Our study was not powered to detect significant differences in rare complications due to their low incidence, but we did observe trends towards a decrease in postoperative hemorrhages necessitating surgery (Early: 3, Recent: 0), lower infection rate (Early: 3.1%; Recent: 0%), and a reduction in 30-day mortality (Early: 4.1%; Recent: 1.5%) between the two cohorts, although these changes did not reach statistical significance. Neither univariate nor multivariate analysis identified any specific predictors of postoperative complications.

DISCUSSION

With optimal preoperative planning and patient selection, LITT provides a minimally invasive method of ablating designated intracranial targets with minimal damage to surrounding structures.[17,27] Recently, Kamath and colleagues published a case series of 133 patients demonstrating that LITT was safe and effective at treating a variety of intracranial lesions.[27] Of these 133 patients, 88.3% had gliomas, and 3.8% had radiation necrosis from radiosurgery failure.[27] They reported a complication rate of 12% and a perioperative mortality rate of 2.2%.[27] Similar to our study, this report noted a decrease in operative time (average: 3.75hrs±1.83hrs) and an association between large tumor size (maximal diameter > 3cm) and increased complications (p=0.056).[27] Another study performed by Patel and colleagues in 2016 also demonstrates the safety and efficacy of LITT, though the authors stress the importance of appropriate patient selection and rigorous surgical approach in achieving optimal outcomes.[30] In their cohort, 49% of patients had gliomas and 36.3% had radiation necrosis. They reported an overall complication rate of 26.5% and a neurological complication rate of 13.7%.[30] Similar to our study, they reported a decrease in operative time with experience (average: 2.8hrs±0.6hr) and emphasized the potential of LITT after overcoming the learning curve. Several other reports have also corroborated the safety and efficacy of this treatment modality for intracranial lesions.[1,6,16,23,25]

In our cohort, we observed a 46% reduction in operative time with a significant increase in the number of patients requiring just one trajectory for complete ablation over time ($p<0.001$, table 6). The decrease in operation time can likely be attributed to increased surgical proficiency as well as advances in laser technology. For instance, a new generation of the laser ablation system with more efficient lasers was released in 2013, leading to reduced ablative times and fewer trajectories. Recent evolution in LITT technology have led to increased precision of thermal energy delivery, decreased collateral damage to adjacent brain structures, and greater control over the thermal energy delivered.[2,4,5,22,25,31-35] Our results also support this conclusion, as multivariate analysis confirmed that cases performed after 2013, during which the new generation of NeuroBlate® was introduced, were independently correlated with shorter operation time ($p<0.001$). These ongoing technological advances have led to increased safety and efficacy in LITT.[2,6,21,27]

We also noted an increased average age of our patients by 4 years between the two time periods, which may reflect our expanding patient selection in the Recent cohort due to increased experience with LITT. When we first adopted this technique, we were more selective and operated on patients with fewer comorbidities to decrease confounding. This was often accompanied by younger age. In the Recent cohort, with increased surgical expertise and established outcomes in certain pathologies, we expanded our patient selection to include a broader range of prognoses and corresponding ages.

Additionally, we observed a trend over time towards utilizing LITT for radiation necrosis. This was likely motivated by the emergence of strong evidence on the efficacy of LITT for this indication. For instance, a multi-site, open-label phase II study on 39 patients with radiosurgery failure, 20 of whom had radiation necrosis, by Ahluwalia and colleagues demonstrated PFS in 100% of patients at the 12-week follow up appointment.[26]

We also found a significant decrease in permanent motor deficits between the two cohorts (Early: 15.5%; Recent: 4.4%, $p=0.005$). This can be attributed to an important change in preoperative surgical planning. Work previously performed at our institution showed a significant association between overlap of hyperthermic fields with corticospinal fibers during LITT and postoperative permanent motor deficits.[21] Indeed, Sharma et al. demonstrated that even minimal overlap of the corticospinal fibers with thermal damage threshold (TDT) lines led

to increased permanent motor deficits.[21] As such, we began routinely tracing and uploading important motor fibers (using MRI diffusion tensor fiber tracking) to the image guidance software, thereby giving the neurosurgeon direct visualization of these critical regions and preventing off-target thermal damage, leading to a significant decrease in permanent motor deficits.

In our cohort, there was a clear correlation between tumor size and survival in HGG, such that smaller HGG (volume < 4cm^3) had significantly improved OS and PFS compared to their larger counterparts ($p<0.001$ and $p=0.015$, respectively). While the authors recognize that many factors may contribute to this association, previous reports suggest the correlation between tumor size and survival may be partially due to more favorable laser coverage in smaller tumors, since a single laser trajectory has a maximal diameter of 4cm. Indeed, a multicenter study on HGG patients treated by LITT demonstrated that smaller tumors (<10 cm^3) had more favorable TDT coverage compared to their larger counterparts, which in turn was correlated with significantly improved PFS ($p=0.02$).[6] Another multi-center study showed a significant association between the extent of laser coverage and disease specific OS and PFS as well as a correlation between favorable coverage and tumor size[25] Despite this, we do not observe a trend towards operating in smaller tumors, even in HGG. This is partially due to the usage of LITT as a conjunctive therapy in combination with minimally invasive surgical debulking strategies to decrease mass effect in large tumors.[33,34]

Finally, our data show a significant association between poor preoperative KPS (≤70) and increased PMDs and decreased OS. This is in accordance with previously published data on the correlation of preoperative KPS with outcomes. For instance, a report by Stark and colleagues found a significant decrease in median survival between patients with KPS of 50-70 compared with patients with KPS with a KPS of 80 or higher ($p<0.0001$).[36] While unsurprising, this suggests that LITT may not be well suited for patients who are significantly functionally compromised before surgery. Patients with poor preoperative KPS scores were often not candidates for conventional surgery and received LITT for a variety of reasons, including inability to tolerate chemotherapy and failure of adjuvant therapy.

As a novel technology, LITT has tremendous potential as a tool in the neurosurgery armamentarium, but appropriate use and patient selection are paramount for optimal outcomes. A

key benefit of LITT is its minimally invasive approach that reduces damage to nearby structures compared to conventional open surgery. As such, tumors that may otherwise be difficult to access or inoperable due to their anatomical location or close proximity to eloquent structures could be ablated utilizing LITT. However, LITT is not without risks. For one, as reported by Mohammadi and colleagues, thermal damage can occur to corticospinal tracts, leading to postoperative motor deficits. As such, meticulous preoperative trajectory mapping with intraoperative visualization of adjacent motor fibers using image guidance software is critical in all operations involving LITT.[21] As such, based on our experience, we recommend against the use of LITT as the sole treatment modality for large tumors with significant mass effect, as this has been associated with postoperative complications. However, LITT can still serve as an adjunctive treatment in conjunction with surgical debulking in these cases for residual tumor in difficult-to-access regions. Based on previous reports from our group, we would recommend LITT as a treatment modality for radiation necrosis, as LITT has been shown to be highly effective in prolonging OS and PFS in these patients.[23,26,33]

While the past decade of experience with LITT at our institution has significantly increased our understanding of this technique and its indications, our study is not without its limitations. Importantly, the retrospective nature of this study predisposes it to selection bias; in particular, patients who received LITT were often those who were not good candidates for conventional open resection due to factors like poor functional status, which is associated with poor outcomes.[6,11,12,36] Thus, our results may not completely reflect outcomes of LITT in the brain tumor patient population at large. Additionally, only 112 (47.1%) of the patients were diagnosed with biopsy at the time of LITT, which also introduces selection bias to the result. Due to the study design, tumor profiles were also constrained by the patient population, which primarily consisted of supratentorial and lobar lesions. Additionally, as our patients are from a single institution, the results could be affected by institution-specific practices, and due to the relatively recent introduction of LITT, only 232 patients were included in the final analysis. As such, the study was not sufficiently powered to detect significant differences in rare occurrences, such as 30-day mortality, between the patient cohorts. Moreover, since our study was designed as a case series to examine changes in trends over time, there is no reference group with which to compare outcomes following LITT. These limitations provide a useful platform for future endeavors, which could include multi-center prospective studies on the efficacy of LITT in defined patient

groups in comparison with other surgical modalities. Such a study would include a higher patient volume, increased statistical power, and a reference group that allows head-to-head comparisons of outcomes and indications. We did not have access to the complete molecular profiles of the tumors in this study, but as the heterogeneity of many tumors treated in our cohort, in particular HGG, and its effect on survival and tumor progression are well established, it would be interesting to examine the relationship between molecular profile and LITT outcomes in a future investigation.[37-40]

CONCLUSION

LITT provides a minimally invasive method of photocoagulating defined targets via thermal energy with minimal compromise of adjacent structures. Recent developments in technology and experience have allowed us to both improve the efficiency and safety of this surgery, as evidenced by the reduction in permanent motor deficits. LITT appears to be more effective in the treatment of smaller tumors (volume <4cc), an effect that is particularly salient HGG. As with all treatment modalities, patient selection plays an important role, and our results suggest poor preoperative KPS is correlated with worse outcomes. Future large-scale studies are necessary to further elucidate the indications for LITT in the management of patients with brain tumors.

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FIGURE LEGENDS

Figure 1. Tumor Profile of Entire Cohort Over The Years

Figure 2. Primary Pathology

Figure 3. Overall Survival With Respect to Tumor Size

Figure 4. Operative Time Across The Years

Figure 5. Permanent Deficits Between Two Cohorts

Abbreviations

FDA: Food and Drug Administration

GBM: Glioblastoma

HGG: High grade glioma

IRB: Institutional Review Board

KPS: Karnofsky Performance Scale

LGG: Low grade glioma

LITT: Laser interstitial thermal therapy

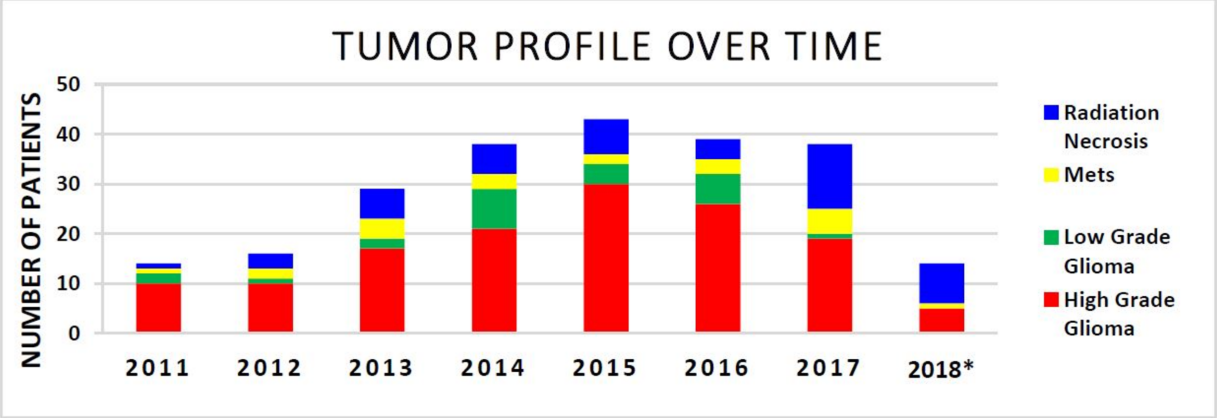
MR: Magnetic Resonance

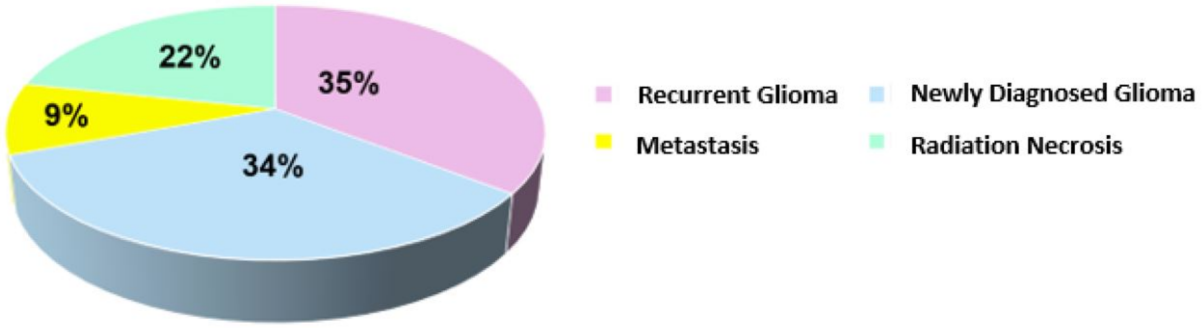
OS: Overall survival

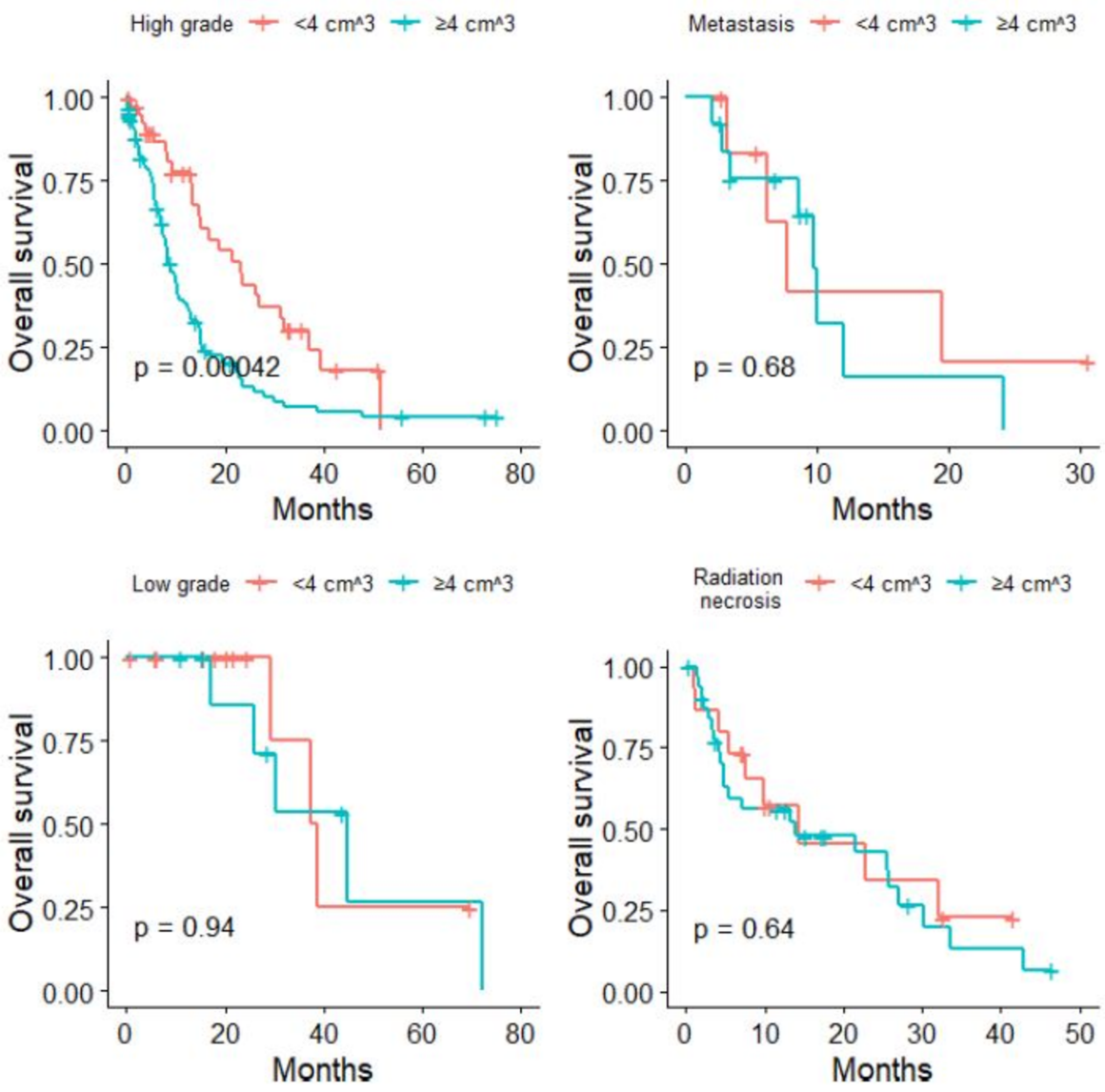
QOL: Quality of life

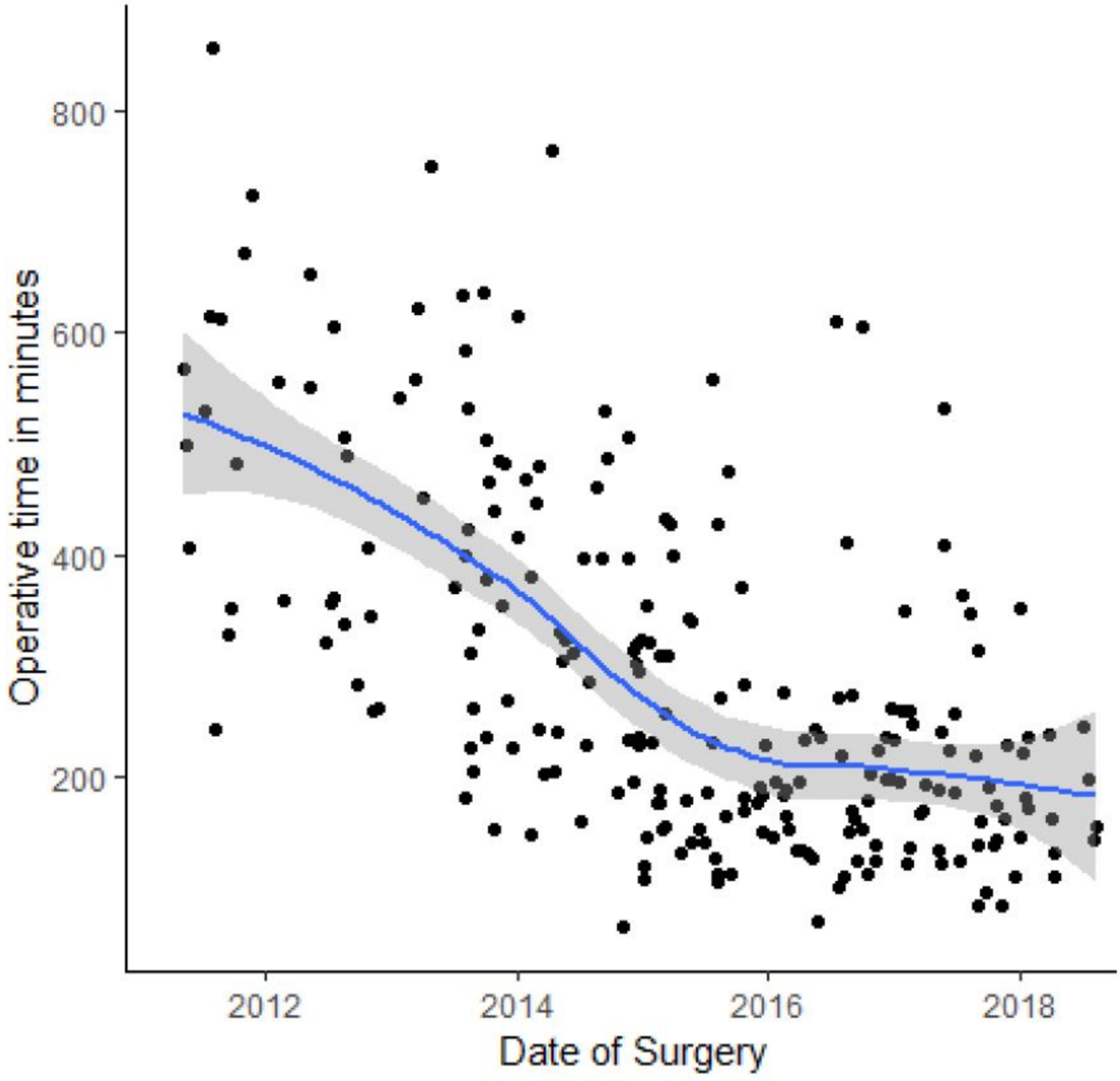
PFS: Progression free survival

TDT: Thermal damage threshold






High grade <4 cm^3 ≥4 cm^3
Overall survival
1.00
0.75
0.50
0.25
0.00
p = 0.00042
0
20
40
60
80
Months
Metastasis <4 cm^3 ≥4 cm^3
Overall survival
1.00
0.75
0.50
0.25
0.00
p = 0.68
0
10
20
30
Months
Low grade <4 cm^3 ≥4 cm^3
Overall survival
1.00
0.75
0.50
0.25
0.00
p = 0.94
0
20
40
60
80
Months
Radiation necrosis <4 cm^3 ≥4 cm^3
Overall survival
1.00
0.75
0.50
0.25
0.00
p = 0.64
0
10
20
30
40
50
Months


800
600
400
200
Operative time in minutes
2012
2014
2016
2018
Date of Surgery

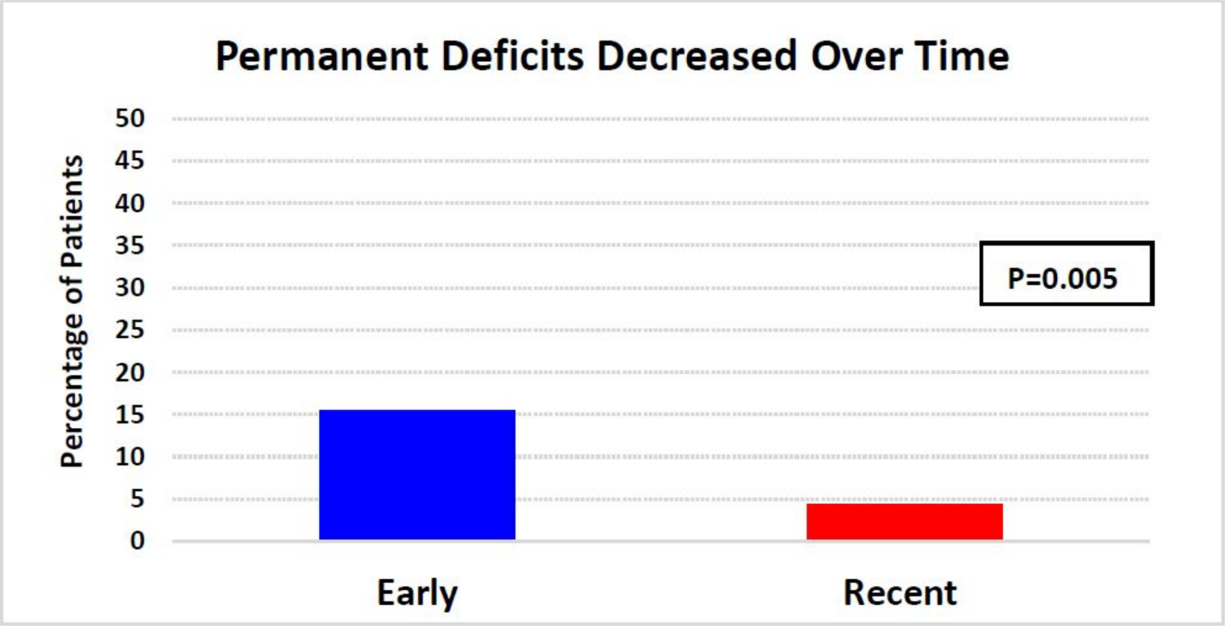


Table 1. Cohort Overview

Patient Characteristics		**Number of Patients (%)**
Gender	Male	117 (49.2%)
	Female	121 (50.8%)
Age	≥65 years	106 (44.5%)
	<65 years	132 (55.5%)
Functional Status	Preoperative KPS	**Median Score**
		90 (Range: 50-100)
Tumor Characteristics		**Number of Patients (%)**
Pathology	Glioma (Total)	167 (70.2%)
	High Grade Glioma	141 (59.3%)
	Low Grade Glioma	26 (10.9%)
	Metastases	21 (8.8%)
	Radiation Necrosis	50 (21.0%)
Location	Lobar	189 (79.4%)
	Deep-Seated	40 (16.8%)
	Posterior Fossa	9 (3.8%)
Surgical Parameters		**Hours**
Operative Variables	Average Operation Time	4.7±2.6 (Range: 1.0 – 13.9 hrs)
	1 Trajectory	**Number of Patients (%)**
		157 (67.7%)
	2 Trajectories	60 (25.9%)
	3+ Trajectories	15 (6.4%)
Outcomes and Follow-Up		**Number of Patients (%)**
Complications	Temporary Deficits	70 (30.2%)
	Permanent Deficits	25 (10.8%)
Survival and Follow-Up	Overall Mortality	5 (2.16%)
	Overall Survival	**Months**
		13.6
	Progression-Free Survival	5.5
	Median Follow-Up	8.4

Table 2. Aborted Procedures

Patient	Date of Scheduled Procedure	Cohort	Rationale for Procedure Abortion	p-Value
1	9/15/2011	Early	Equipment malfunction	0.409
2	12/27/2011	Early	Equipment malfunction	
3	7/23/2013	Early	Equipment malfunction	
4	7/1/2014	Early	No tumor present/Abscess	
5	1/23/2015	Recent	No tumor present/Abscess	
6	3/24/2015	Recent	No tumor present/Abscess	

Table 3: Patient Demographics across Both Time Periods

Characteristic	Category	Time period		P-value
		Early, 2011-2014 n=100	Recent, 2015-2018 n=138	
Age, n (%)	Mean±STD	54.3±15	58.4±15	**0.040**
	<65	62 (62.0%)	70 (50.7%)	0.084
Sex, n (%)	Female	55 (55.0%)	66 (47.8%)	0.275
KPS, Mean ± SD	Preoperative	85±9.7	83.2±11	0.213
	6 month follow-up	72.5±14.3	75±13.6	0.320
Recurrence, n (%)	Newly diagnosed	51 (51.0%)	68 (49.3%)	0.793
	Recurrent	49 (49.0%)	70 (50.7%)	
Location	Lobar	80 (80.0%)	109 (79.0%)	0.133
	Posterior fossa	1 (1%)	8 (5.8%)	
	Deep-seated	19 (19.0%)	21 (15.2%)	
Lesion type, n (%)	High grade glioma	60 (60.0%)	81 (58.7%)	0.280
	Low grade glioma	14 (14.0%)	12 (8.7%)	
	Metastasis	10 (10.0%)	11 (8.0%)	
	Radiation necrosis	16 (16.0%)	34 (24.6%)	

Table 4. Operative Characteristics across Both Time Periods

Characteristic	Category	Time period		P-value
		Early, 2011-2014, n=96	Recent, 2015-2018, n=136	
Operative time, n (%)	Mean ± SD	6.67±2.66 hrs	3.57±1.75 hrs	**<0.001**
	Prolonged	20 (21.1%)	4 (2.9%)	**<0.001**
Trajectories, n (%)	1	51 (53.1%)	106 (77.9%)	**<0.001**
	2	36 (37.5%)	24 (17.6%)	
	3	8 (8.3%)	5 (3.7%)	
	4	1 (1%)	1 (0.7%)	
Tumor volume, n (%)	Mean ± SD	12±11.9	10.7±16.5	0.492
	≥3cc	74 (77.9%)	92 (67.6%)	0.120
	≥4cc	67 (70.5%)	85 (62.5%)	0.261
	Range	0.092cc – 59.7cc	0.176cc – 127.1cc	

Table 5. Outcome Comparison between Time Periods

Characteristic	Category	Time period		P-value
		Early, 2011-2014 n=96	Recent, 2015-2018 n=136	
Temporary deficits, n (%)	Motor	23 (23.9%)	26 (19.1%)	0.493
	Sensory	3 (3.1%)	0 (0%)	**0.071**
	Seizures	0 (0%)	2 (1.5%)	0.512
	Other	10 (10.4%)	6 (4.4%)	0.113
Permanent deficits, n (%)	Motor	15 (15.5%)	6 (4.4%)	**0.005**
	Sensory	2 (2.1%)	2 (1.5%)	1.000
Hemorrhage, n (%)	None	19 (19.6%)	29 (21.3%)	0.103
	Small Blood products	61 (62.9%)	95 (69.9%)	
	large hemorrhage	14 (14.4%)	12 (8.8%)	
	Need Surgery for ICH	3 (3.1%)	0 (0%)	
Infection, n (%)	Yes	3 (3.1%)	0 (0%)	**0.071**
Length of stay, n (%)	Mean ± SD	2.3±2.2	2.5±3.7	0.801
30-day mortality, n (%)	Yes	4 (4.1%)	2 (1.5%)	0.241

Table 6. Outcomes According to Tumor Volume

Characteristic	Time period	Size of tumor		P-value
		<4 cm^3	≥4 cm^3	
High grade glioma				
Overall survival	12 months	75% (57.9-86.7)	36.9% (27.4-47.6)	**<0.001**
	18 months	54.8% (37.8-70.8)	20.7% (13.4-30.7)	**0.001**
	24 months	41.9% (26.4-59.2)	11.1% (6-19.8)	**0.001**
Progression free survival	12 months	20% (9.5-37.3)	8.4% (4.1-16.4)	0.103
Low grade glioma				
Overall survival	24 months	100% (56.6-100)	85.7% (48.7-97.4)	1.000
Progression free survival	24 months	33.3% (6.1-79.2)	25% (4.6-69.9)	1.000
Metastasis				
Overall survival	12 months	40% (11.8-76.9)	25% (7.1-59.1)	1.000
Progression free survival	12 months	0% (0-43.4)	0% (0-35.4)	1.000
Radiation necrosis				
Overall survival	12 months	45.5% (21.3-72)	53.6% (35.8-70.5)	0.731
Progression free survival	12 months	10% (1.8-40.4)	12.5% (4.3-31)	1.000

Table 7. Outcomes According to Preoperative KPS

Characteristic	Category	KPS		P-value
		≤ 70, n=91	80-100, n=130	
Permanent deficits, n (%)	Motor	15 (17.6%)	3 (2.3%)	**<0.001**
	Sensory	2 (2.4%)	2 (1.5%)	0.686
Overall survival	12 months	24 (33.8%)	69 (67.6%)	**<0.001**
	18 months	16 (23.5%)	47 (50%)	**<0.001**
	24 months	10 (14.7%)	35 (38.9%)	**0.001**
Progression free survival	12 months	9 (12.5%)	14 (16.9%)	0.691