Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Adjuvant treatment of Grade IV Glioma, outcomes at a UK tertiary centre

Louise Price (louise.price12@nhs.net)
Royal Stoke University Hospital
Charlotte Ziff
Royal Stoke University Hospital
Abdelfattah Elmasry
Royal Stoke University Hospital
Selvaraj Giridharan
Royal Stoke University Hospital

Research Article

Keywords: glioblastoma, Gliadel wafers, overall survival

Posted Date: May 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1606125/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Purpose

The 5 year overall survival (OS) for Glioblastoma multiforme (GBM) remains low.

Our cohort had a lower percentage completing adjuvant treatment than those reported in trials. We assess those not completing planned 6 cycles of adjuvant treatment.

We assess survival data for those who had Gliadel wafer insertion at the time of primary surgery. We go on to assess the combination of these factors on survival.

Methods

Cohort of 110 patients who had undergone neurosurgery followed by chemo-radiotherapy (CRT) 60 Gray in 30 fractions and adjuvant Temazolomide (TMZ) from 2007 to 2016.

Results

OS was 16 months and progression free survival (PFS) 11.9 months.

57% of patients completed 4-6 cycles of adjuvant TMZ 43% received 3 or less cycles of TMZ. Those unable to complete planned adjuvant TMZ had a poorer OS (10 vs 20 months, Cox analysis P-value 0.0003).

Those who had maximal safe debulking plus Gliadel wafer insertion, median OS was improved, 19.5 months P=0.06.

The group with the combination of significant factors, median OS was 2 months greater than those that did not receive Gliadel wafers and could not complete 4 cycles of adjuvant TMZ.

Conclusions

Survival outcomes were improved with Gliadel wafer insertion, completing 4-6 cycles of TMZ. Consequently the combination of these factors led to improved outcomes. Second-line chemotherapy improved OS at relapse regardless of second line surgery.

Background

Glioblastoma Multiforme (GBM) or Grade IV Glioma, is the most common primary central nervous system tumour. The incidence in England is 4.64 per 100,000 per year from 2005–2011 [1] and the leading cause of cancer related deaths in those under 40 years.

In the United Kingdom, established primary surgical management of glioblastoma is maximal safe de-bulking surgery. Where more than 90% of de-bulking is possible, carmustine implants (Gliadel wafers)

have been approved for insertion along the operative bed [2]. A meta-analysis of 513 patients demonstrated a survival advantage after Gliadel wafer insertion [3]. However, the use of Gliadel wafers varies within different neuro-surgical centres.

The standard of care for first line management is maximum safe debulking followed by radiotherapy to a dose of 60Gy in 30 fractions with concurrent temazolamide (TMZ) 75mg per metre squared and 6 cycles of adjuvant TMZ at 200mg per meter squared as per the landmark trial by Stupp et al, 2005 [4]. Within this trial median progression-free survival (PFS) was 6.9 months and median overall survival (OS) was 14.6 months. A minority, 9.8%, survived 5 years and beyond [4–5].

Within the first line setting the use of both vascular growth factor inhibitors (Bevazuimab) [6] and MTOR inhibitors Everolimus [7] have been trialled alongside chemoradiotherapy showing no significant effect on OS or PFS. Tumour treating fields (TTF) device use has shown some additional improvement of survival in those patients who do not have contraindications [8]. Its use is not approved by NICE NG99 [9–10].

In spite of these incremental improvements, median survival still remains poor, ranging between 14 and 21 months, especially in the MGMT unmethylated group. MGMT methylation is a predictive biomarker of response to TMZ [11] regardless standard treatment is 6 cycles TMZ.

More than 6 cycles of adjuvant TMZ has been investigated, without statistically significant improvement in PFS or OS [12]. A metanalysis confirmed extended maintenance TMZ beyond 6 cycles did not improve overall survival [13]. There are no studies, investigating effects of stopping TMZ early due to clinical complications before completing 6 cycles of adjuvant TMZ.

Aim

In this retrospective review, we investigated our tertiary neuro-surgical centre experience in the management of glioblastoma. We look at several outcome measures influencing overall survival and progression-free survival in relationship to Gliadel wafer insertion, number of adjuvant chemotherapy cycles completed, redo debulking surgery on relapse the usage of second-line chemotherapy. We also review the impact of both Gliadel wafer insertion and completing adjuvant TMZ on OS and PFS.

Methods

Data was collected from 110 patients who completed standard treatment of surgery followed by adjuvant chemo-radiotherapy, 60 Gray in 30 fractions and had at least one cycle of adjuvant TMZ chemotherapy following neurosurgery from 2007 to 2016.

Data was reviewed from surgical and oncology records. Data was scrutinised using R-software V4.0.0 statistical package. Patients were followed up for at least 4.5 years.

Results

Within the cohort of 110 patients the median age was 60 years (see Table 1) with a PFS of 12 months with 95% Confidence interval (CI) of 9.5–13.7 months. *See* Fig. 1. The median OS is 16 months (95% CI 15–20 months). *See* Fig. 2. The 5 year survival rate is 7%.

Table 1
Baseline statistics of UHNM cohort N = 110

Characteristic	n
Median age	60 years (range 17–79 years)
Median time from diagnosis to start of radiotherapy	71 days (range 21–168 days)
Performance status:	
PS 0	33 (30%)
PS 1	73 (67%)
PS >/= 2	4 (3.6%)
Neurosurgery	
Maximal de-bulking	39 (35.4%)
Partially de-bulked	46 (41.8%)
Biopsy only	25 (22.7%)
Adjuvant Chemo-radiotherapy	
CRT plus completed 6 cycles of TMZ	63 (57.3%)

Maximal debulking was achieved in 35.5% (n = 39), partial de-bulking in 41.8% (n = 46) and 22.7% (n = 25) had biopsy only. Maximal debulking surgery alone was not a predictor of OS (Maximal debulking P-value 0.38). Patients who had maximal safe debulking plus Gliadel wafer insertion had an improved median OS of 19.5 months (95% confidence interval 14–30). For those without wafers median OS was 16 months (95% confidence interval 14–21), P = 0.06. 5 year OS was 6.25% for those with Gliadel wafer insertion and 5% for those without wafers. This was not a statistically significant difference (*See* Fig. 3*)*

On Cox regression analysis Gliadel wafer insertion was a statistically significant predictor of overall survival, P-Value, 0.008.

Median progression free survival with the insertion of Gliadel wafers was 12.2 months (95% CI 10.43–19.7 months) and 11.8 months (95% CI 8.93-15 months) without. This was not statistically significant (Log Rank test P value 0.5).

Of 110 patients 30% were Performance Status (PS) 0, 66% were PS 1 with only 3.6% being PS 2. (*See* Table 1*)*. 57% of patients completed adjuvant chemo-radiotherapy followed by 4–6 cycles of adjuvant

TMZ and 43% received 3 or less cycles of TMZ. Of those that did not complete treatment the highest dropout rate was seen after the initial cycle of TMZ.

Overall PFS was 12 months. Those that completed 4 or more cycles of adjuvant TMZ had an improved PFS (Log rank test P-value 0.001) versus those that completed 3 or fewer cycles. (*See* Fig. 4*)*

Median OS was 16 months for the whole group, but improved to 20 months for those completing 4 or more cycles of adjuvant TMZ. Median OS decreased to 10 months for those unable to receive 4 cycles on TMZ. *(See* Fig. 5*)* On Cox analysis the number of adjuvant cycles of TMZ significantly affects OS, P-value 0.0003. Figure 5 demonstrates the lack of census points to allow 5 year OS to be reported for those receiving less than 5 cycles of TMZ. *(See* Fig. 5*).*

Within subset of 12 patients who had at least 4 cycles of adjuvant TMZ and Gliadel wafer insertion, the median OS was 18 months. An improvement of 2 months compared to those who received less than 4 cycles and did not have Gliadel wafers inserted. (OS 18 months vs 16 months, log-rank test P-value 0.4).

Overall 5 year survival rates are 5%. 95% relapsed within 5 years; at relapse 20% underwent salvage surgery and similar numbers 25%, received second line chemotherapy. On Cox analysis we identified second line chemotherapy had a significant impact on OS (Cox model P-value 0.002) but salvage surgery was not a statistically significant predictor of OS (Cox-Model P-Value 0.23).

Discussion

We present data from long term follow up of 110 patents for our tertiary neuro-surgical centre in the North Midlands, United Kingdom (UK).

Our retrospective cohort includes those completing neurosurgery and chemoradiotherapy. We excluded those with surgical or radiotherapy complications from our cohort as this allowed us to look at the effects of completing adjuvant TMZ on survival outcomes.

The retrospective cohort from 2007 yielded mature OS and PFS outcomes. However the historical time frame led to heterogenous data due to the evolution of practice over time. So, firstly, we excluded those who received reduced fractionation regimes. Our cohort began before the publications by NCBTSG 2012 and Perry et al trials [14–15] which have since led to more standardised hypofractionation radiotherapy practices for patients over 60 years and with performance status 2.

Secondly, MGMT, IDH, 19q16p codeletion and ATRIX biomarkers were not consistently carried out across this time period within the UK so data was not recorded. It is known those who are MGMT methylated have an improved prognosis and response to treatment [11].

Overall we demonstrate median PFS of 11.9 months and median OS of 16 months. PFS data has significant positive skewness 3.21, due to the statistical limitations of long-term retrospective cohorts.

The median OS was 14.6 months within the Stupp trial with analysis taken from the intention to treat population [4]. A more recent retrospective cohort of GBM treated between 2007–2011 found a comparable median OS of 14.9 months in those receiving maximal treatment [1].

The age range within our cohort is 17– 79 years, with a median age of 60 years. 4% of our cohort had a performance status of 2. This gives a real life data of GBM patients and makes direct comparisons to trial populations limited. However within the Stupp trial population (those aged under 18–70 years and PS 2 or less) 85% completed planned chemoradiotherapy and adjuvant TMZ [4]. Our real world non-trial data demonstrated 57% of patients completed 6 cycles of TMZ following chemoradiotherapy. Patients did not complete 6 adjuvant cycles of TMZ for a variety of reasons, including infection, deterioration in performance status, toxicities and progression.

We demonstrate for the first time those patients receiving 4 or more cycles of adjuvant TMZ had an extra 10 months median OS compared to those who received less than 4 cycles of adjuvant TMZ. This is a significant clinical and statistical difference. As clinically expected if patients discontinued adjuvant TMZ it was most likely after the first cycle.

A second key finding was, in our centre Gliadel wafer insertion improved OS by a median of 3.5 months, demonstrating those who do not have complications from Gliadel wafer insertion such as post-operative infection, incur a benefit.

Within our cohort we saw those who have Gliadel wafer insertion and receive 4 or more adjuvant cycles of TMZ both have improved OS. Therefore we went on to hypothesize the combination of both factors would give maximal OS. Indeed, OS was improved by 2 months in this group. Statistical significance was not reached on log-rank test (P-value 0.4) likely due to the small sample size of 12 patients.

95% of our cohort progressed despite primary standard treatment. At progression 20% underwent re-do surgery and 25% had second line chemotherapy with the majority opting for best supportive care (55%). This is comparable to the Stupp trial where 23% underwent surgery and 24% chemotherapy at relapse [4].

Using Cox analysis we demonstrate second-line chemotherapy had a significant impact on OS whereas re-do surgery did not significantly effect OS however there are complex factors to consider. This measure does not account for patients' quality of life which is an important factor in decision making. However this gives an overview of practices within our centre which are in-line with large European randomized controlled trials.

This review of data gives us meaningful data to explain outcomes in our centre and beyond.

Conclusions

- Overall we demonstrate median PFS of 11.9 months and median OS of 16 months in the whole cohort.

- Those receiving at least 4 cycles of adjuvant Temozolomide have improved overall survival by a margin of 10 months
- Gliadel wafer insertion, following at least 90% de-bulking at primary surgery, improves overall survival by a median of 3.5 months
- The combination of both Gliadel wafer insertion and receiving at least 4 cycles of adjuvant Temazolomide improves overall survival but was not significant, maybe due to small numbers
- Second-line chemotherapy improved OS at relapse regardless of second line surgery.

Statements & Declarations

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

The authors have no relevant financial or non-financial interests to disclose.

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

This is a retrospective observational study using clinical records therefore ethical approval was sought.

References

1. Andrew, Brodbelt et al (March 2015) Glioblastoma in England: 2007–2011. Eur J Cancer Volume 51(4):533–542
2. NICE, TA121 Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma. Technology appraisal guidance. Published: 27 June 2007. WWW[www.nice.org.uk/guidance/ta121]
3. Xing et al (2015) The role of Gliadel wafers in the treatment of newly diagnosed GBM: a meta-analysis. Drug Des Devel Ther 9:3341–3348
4. Stupp R et al (2005) Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. The new england journal of medicine. 987.
5. Stupp R, 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(Article). The Lancet Oncology. Volume 10, Issue 5, May et al (2009) Pages 459–466
6. Gilbert MR et al (2014) A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma. N Engl J Med 370:699–708
7. Chinnaiyan P et al (2018) A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: Results of NRG Oncology RTOG 0913. Neurooncology 20:666–673

8. Fabian D et al (2019) Treatment of Glioblastoma (GBM) with the Addition of Tumor-Treating Fields (TTF): A Review, vol 11. Cancers, p 174
9. Brain cancer: glioma. NG99. NICE Pathways bring together everything NICE says on a topic in an interactive flowchart. NICE Pathways are interactive and designed to be used online. [WWW] http://pathways.nice.org.uk/pathways/brain-tumours-and-metastases. 07 December 2021
10. NICE guideline [NG99] (2018) Brain tumours (primary) and brain metastases in adults. Published date: 11 July 2018
11. Lin N et al (2014) Prevalence and clinicopathologic characteristics of the molecular subtypes in malignant glioma: a multi-institutional analysis of 941 cases. PLoS ONE 9:e94871
12. Bhandari M (2017 May) Comparative Study of Adjuvant Temozolomide Six Cycles Versus Extended 12 Cycles in Newly Diagnosed Glioblastoma Multiforme. J Clin Diagn Res 11(5):XC04–XC08
13. Blumenthal et al (2017) Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. Neuro-Oncology, Volume 19, Issue 8, Pages 1119–1126. https://doi.org/10.1093/neuonc/nox025
14. Malmström A, Grønberg BH, Marosi C et al (2012) Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 13:916–926
15. Perry et al (2017) Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma 2017. N Engl J Med 376:1027–1037

Figures

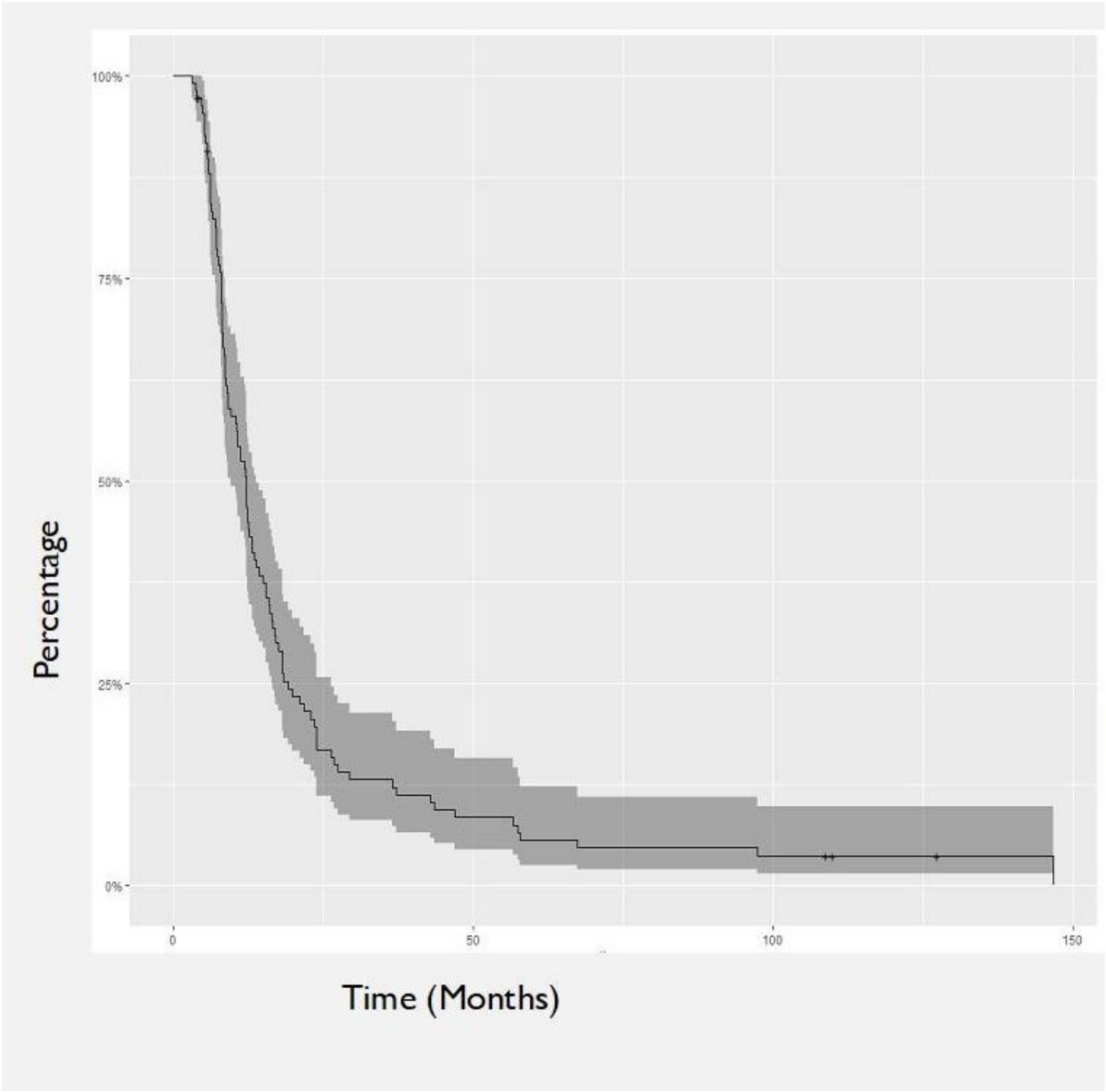
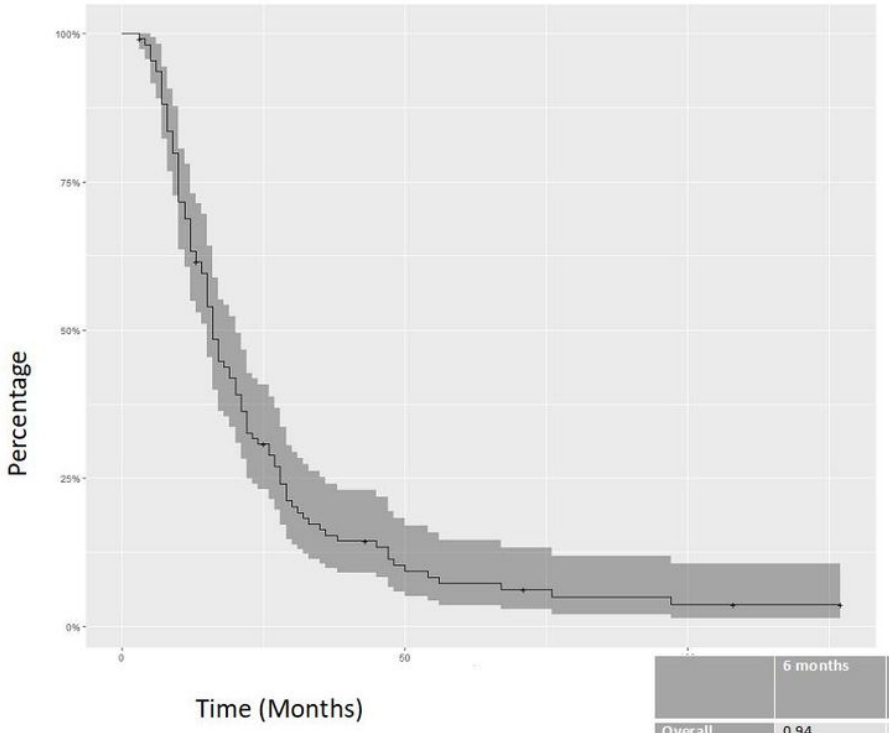


Figure 1

Kaplan–Meier plot to show PFS for GBM at UHNM



Medial Overall survival 16 months. Table to show Overall Survival probability at time periods (years)

	6 months	1 year	2 years	3 years	4 years	5 years
Overall Survival	0.94	0.63	0.31	0.15	0.10	0.07

Figure 2

Kaplan–Meier plot to show overall survival for GBM at UHNM.

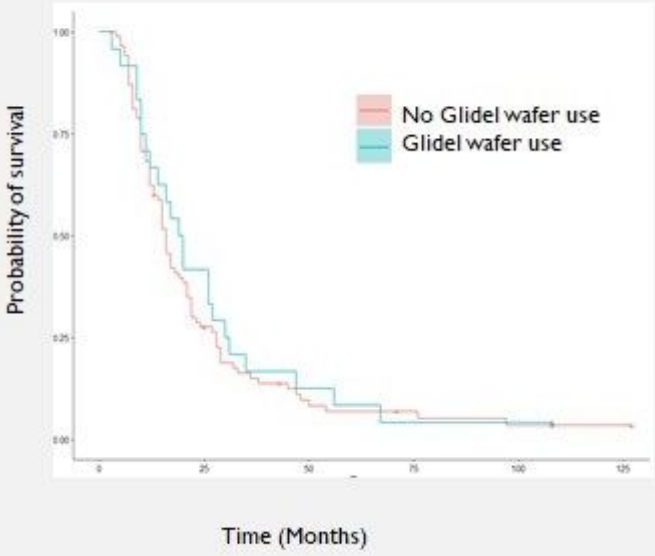


Table to show Cox regression analysis

Variable	COX-Model P-Value
Gliadel wafer	0.008
Age	0.04

Figure 3

Kaplan–Meier plot to show OS for GBM resection with or without intra-operative Gliadel wafers

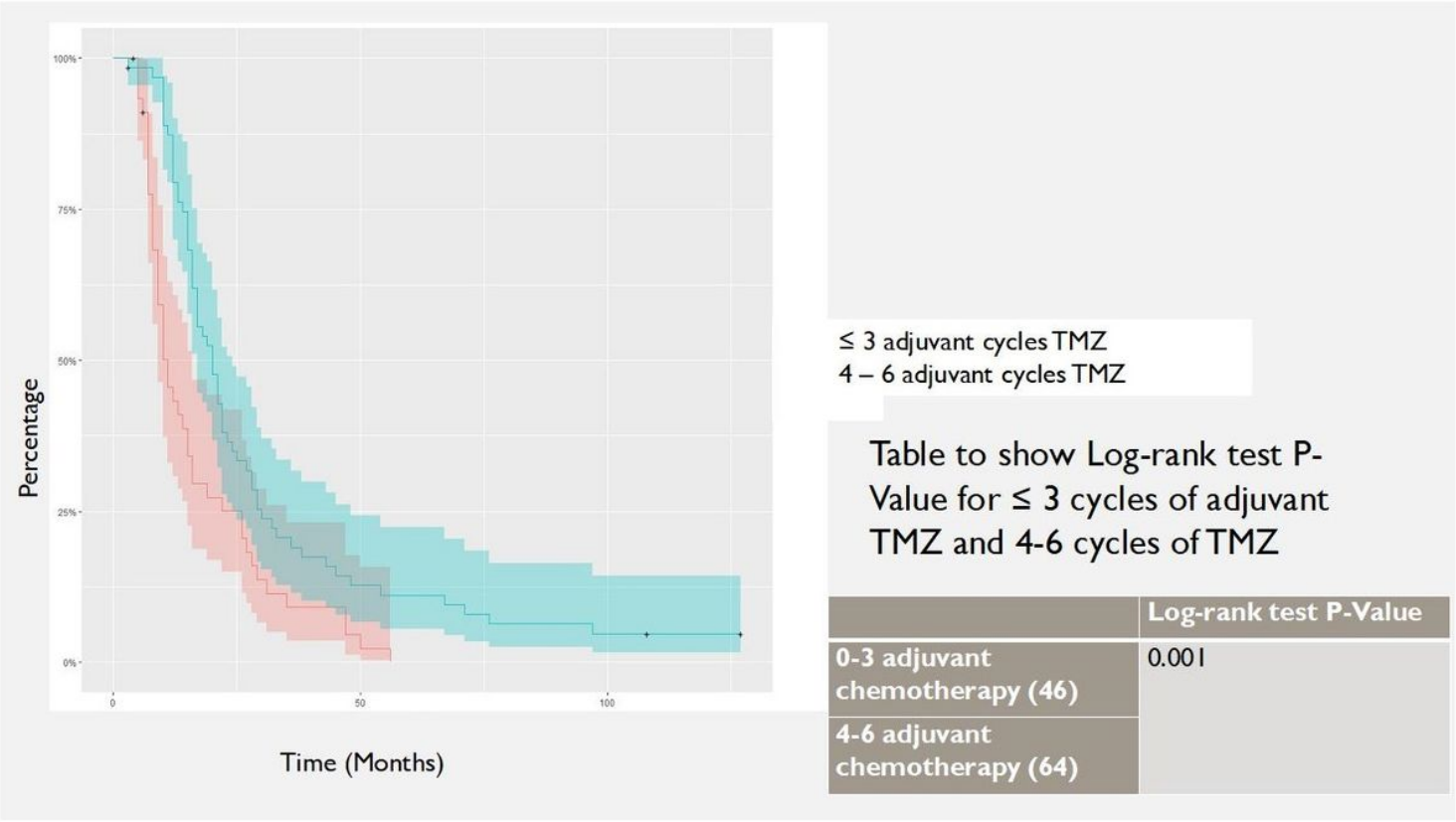


Figure 4

Kaplan–Meier plot to show PFS for GBM treated with ≤ 3 cycles of adjuvant TMZ and 4-6 cycles of TMZ at UHNM.

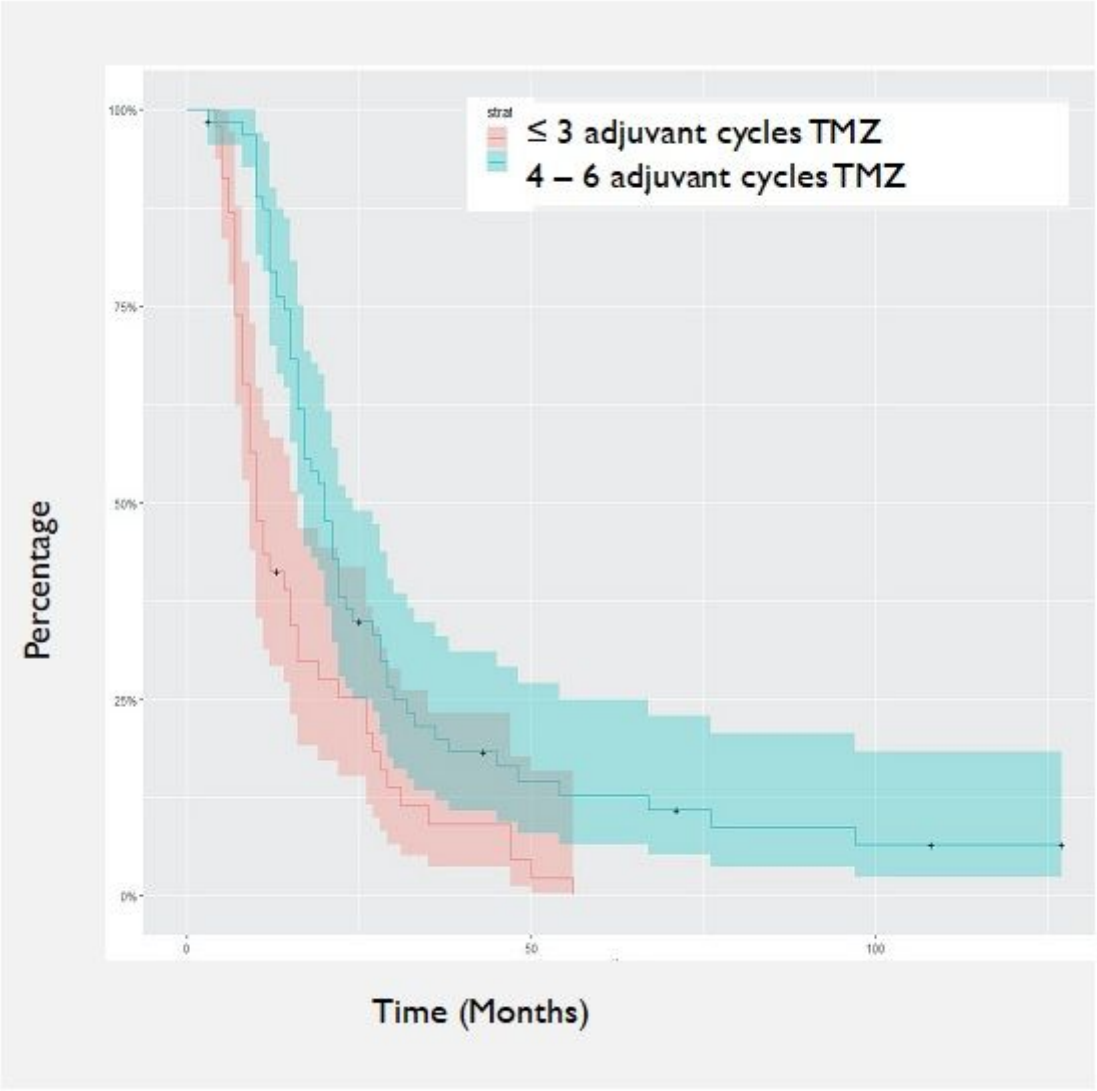


Figure 5

OS by Number of Adjuvant cycles received, Table to show log-rank test