

Improved Median Survival for Glioblastoma Multiforme Following Introduction of Adjuvant Temozolomide Chemotherapy

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Abstract

Introduction: The use of adjuvant temozolomide (TMZ) in patients managed with surgery and adjuvant radiation therapy (RT) for glioblastoma multiforme (GBM) has been demonstrated to improve median and 2-year survival in a recent large international multicentre study. To confirm this result in routine clinical practice, an audit of the management and outcome of patients with GBM at The Cancer Institute Radiation Oncology was performed. **Materials and Methods:** All patients with GBM managed radically at The Cancer Institute Radiation Oncology from May 2002 to 2006 were entered into a prospective database. Patient, tumour and treatment factors were analysed for association with the outcome of median survival (MS). Survival was calculated using the Kaplan-Meier technique and correlation was assessed using Cox proportional hazards regression. **Results:** Forty-one patients with GBM were managed with radical intent over the 4-year period. The median age was 54 years and 66% were Eastern Cooperative Oncology Group (ECOG) 0-1 performance status. Macroscopic, subtotal and biopsy alone procedures were performed in 61%, 29% and 10% of patients, respectively. The median time from surgery to RT was 26 days. Adjuvant TMZ was used in 44% of patients (n = 18). The MS of the total group was 13.6 months, with a 24% 2-year overall survival. The use of TMZ was associated with improved MS (19.6 versus 12.8 months; $P = 0.035$) and improved 2-year survival (43% versus 0%). A requirement of dexamethasone dose greater than 4 mg at the end of RT ($P = 0.012$) was associated with worse survival, but there was no association of MS with age, ECOG, tumour size or extent of surgery. **Conclusion:** The median and 2-year survival outcomes are comparable to the results of the European Multicentre Study and justify the continued use of TMZ in routine clinical practice.

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Introduction

WHO grade IV glioma or glioblastoma multiforme (GBM) is a highly aggressive primary brain tumour that accounts for 50% to 60% of intracranial glioma.¹ In patients who present with GBM, despite macroscopic debulking surgery and effective adjuvant radiation therapy (RT), the median survival (MS) is generally only 9 to 12 months with less than 15% of patients alive at 2 years post diagnosis.^{2,3} Measures to improve outcome such as RT dose escalation, nitrosurea-based chemotherapy and biological agents have generally had nil or limited benefit on 2-year survival.³⁻⁶

The best outcome has been achieved by attention to optimising the quality of neurosurgical and RT care, especially in patients with good performance status and tumours in non-eloquent areas of the cerebral cortex.^{7,8}

Temozolomide (TMZ) is an oral alkylating agent that was demonstrated in Phase II studies to improve the progression-free period of patients with relapsed high-grade glioma, and a lower toxicity profile than equivalent chemotherapy agents.^{9,10} In 2001 the presentation of Phase II data of TMZ to RT in the adjuvant therapy of GBM demonstrated a markedly improved 2-year survival rate

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compared to historical series.⁹ This was confirmed in a subsequent Phase III study, which reported an improvement in 2-year survival to 26% from 10% with RT alone.¹¹ These studies have significantly altered clinical practice; however, there are major health economic reasons for TMZ having restricted utilisation in initial therapy for GBM. In Singapore, the financial burden of therapy is high or prohibitive for many patients, and thus there is also a need to confirm the relevance of European data to Asian patients.

Materials and Methods

All adult patients diagnosed with GBM and referred to The Cancer Institute (TCI) Radiation Oncology from May 2002 to June 2006 were entered into a prospective database approved by the Institutional Ethics Review Board. Patients receiving adjuvant RT with radical intent, as defined by a RT dose of more than 50Gy, were included in this study cohort. The decision to manage patients with radical intent was assessed using performance status, extent of postoperative neurological dysfunction and patient informed consent to undertake 6 weeks of RT. Patients were managed at either TCI radiation oncology units at the National University Hospital or Tan Tock Seng Hospital. Follow-up was performed under a recommended protocol involving 3 monthly shared care reviews; with initial imaging for assessment of disease at 3 months post RT.

Neurosurgical Management

Patients were managed by multiple neurosurgeons across the 2 institutions, though a general surgical management philosophy existed. This involved initial preoperative magnetic resonance imaging (MRI) tumour localisation followed by image-guided resection. Aggressive debulking of tumours in non-eloquent areas was encouraged and biopsy was restricted to tumours in eloquent sites. Postoperative imaging to assess the extent of resection was left to the neurosurgeon's discretion. Extent of surgery was defined as biopsy, subtotal and near or gross total resection, as determined from the surgical report and postoperative imaging if performed.

Radiation Oncology Management

Depending on the institution, patients were referred to either the Neuro-Oncology Multidisciplinary Tumour Clinic or to the radiation oncologist on call. The majority of patients were ultimately managed by 1 radiation oncologist who counselled them on the role of radical or palliative therapy. Once the decision to proceed with radical intent using adjuvant RT was made, a discussion regarding the additional benefits of adjuvant chemotherapy was facilitated by the radiation oncologist and subsequently the neuro-oncologist or medical oncologist. All patients receiving adjuvant RT with radical intent were counselled and offered

adjuvant chemotherapy using TMZ, though the decision to accept therapy was dependent on patient-related issues.

RT was delivered under a uniform TCI Radiation Oncology Protocol based on the European Organisation for Research and Treatment of Cancer (EORTC) guidelines. All patients were immobilised, computed tomography (CT) planned with either intravenous contrast or MRI fusion and managed with 3D conformal RT. The planning target volume (PTV) was based on the preoperative MRI enhancing mass with a 20-mm expansion to surrounding tissues or anatomical boundary. Unnecessary delays prior to RT were minimised to prevent regrowth at the tumour bed. The standard RT prescription was 60Gy in 30 fractions over 6 weeks delivered to the PTV.

Chemotherapy Management

Patients received adjuvant chemotherapy strictly under the EORTC TMZ protocol with an initial 6-week "concurrent" phase with RT (75 mg per m²) and second "adjuvant" phase commencing 4 weeks post RT with an optimal 6 monthly cycles (150 to 200 mg per m² delivered for days 1 to 5 every 28 days).¹¹ Patients without progression after 6 months of adjuvant phase were offered continuation of therapy. No nitrosurea-based regimens were offered.

Follow-up Management

Patients receiving chemotherapy generally had a MRI scan performed 4 weeks post RT immediately prior to the adjuvant phase for baseline assessment; however, the initial response scan was generally considered at 3 months post RT. Subsequently, MRI imaging was performed on a 3-monthly basis or earlier if symptomatic.

At progression, patients were assessed on their individual characteristics and offered further surgery, re-irradiation, second-line chemotherapy or supportive care alone.

Statistical Considerations

All patients had their data entered on an Access database at the TCI Radiation Oncology and updated for outcome events. The major study endpoint chosen was overall survival calculated from the date of surgical diagnosis to death. Date of death was obtained from medical records or family contact at the time of bereavement. If the date of death was unavailable, these patients were censored as dead at last review if they had evidence of radiological progression. The MS was calculated using the Kaplan-Meier method.

Analysis was performed using Cox proportional hazards regression for the relationship of potential prognostic factors with MS duration. These factors were patient-related [age, gender, Eastern Cooperative Oncology Group (ECOG) performance status], tumour-related (size of enhancing

tumour, dexamethasone dose required at the end of RT and treatment-related (extent surgical resection, time from surgery to RT, use of TMZ).

To determine if selection bias existed for patients receiving chemotherapy, the association of TMZ use with these prognostic factors was also analysed using Chi-square analysis.

Results

A total of 50 adult patients with GBM were managed at the TCI Radiation Oncology during the study period. Of this group, 41 patients were managed with radical intent and form the basis of the study cohort. The 9 patients who were excluded were managed with palliative RT as defined by a prescribed dose of <50Gy. The median follow-up time of the radically-treated study group was 10.5 months (2.6 to 33.2), while for surviving patients it was 10.5 months (5.2 to 27.6). Two patients had incomplete follow-up due to foreigner residency status. Patient details are outlined in Table 1.

The median age was 54 years and 66% were ECOG 0-1. All patients had pathology categorised as WHO grade IV or GBM. Surgical resection was determined to be more than 90% resection in 61%, while 10% had biopsy only. RT was completed as prescribed in all patients. Adjuvant chemotherapy with TMZ was administered in 44% of patients.

Overall Survival

The MS for the total group was 13.6 months and the 2-year survival rate was 24.4% (Fig. 1). Three patients survived into the third year after diagnosis, and 8 patients were in their second year at the time of the study analysis.

Table 1. Comparison of Potential Patient Prognostic Factors Managed with Adjuvant RT Alone and Adjuvant RT/TMZ

	Total group	RT alone (n = 23)	RT/TMZ (n = 18)	Level of significance
Age <55 years	51%	44%	61%	<i>P</i> = 0.35
Gender Male	68%	70%	67%	<i>P</i> = 0.55
GBM size <5cm	51%	48%	56%	<i>P</i> = 0.43
Gross/Near total resection	61%	65%	56%	<i>P</i> = 0.42
ECOG Performance Status 0,1	66%	52%	83%	<i>P</i> = 0.05
Time from surgery to RT (days)	26 days	28 days	25 days	<i>P</i> = 0.22
Dexamethasone at end RT <4 mg	56%	48%	67%	<i>P</i> = 0.34

GBM: glioblastoma multiforme; RT: radiation therapy; TMZ: temozolomide

The association of potential prognostic factors with the MS is outlined in Table 2. The use of TMZ was associated with improved MS (19.6 versus 12.8 months; *P* = 0.035) and improved 2-year survival (43% versus 0%) (Fig. 2). A requirement of dexamethasone dose >4 mg at the end of RT (*P* = 0.012) was associated with worse survival, but there was no association of MS with age, ECOG, tumour size, extent of surgery or time from surgery to RT.

Factors Associated with the Use of TMZ

To determine potential selection bias in patient selection for chemotherapy, the association of potential prognostic factors was analysed for the use of chemotherapy (Table 1). Patients receiving chemotherapy had better performance status (ECOG 0 or 1 status in 83% versus 52%; *P* = 0.051); however, the other potential prognostic factors were equivalent in both groups.

TMZ-related Treatment Toxicity

Detailed toxicity specifically relating to TMZ therapy was not recorded in the database. However, Common Terminology Criteria (CTC v3.0) grade 4 acute toxicity during the concurrent chemoradiation treatment was recorded, and there were no haematological or gastrointestinal toxicity grade 4 events occurring in this patient cohort.

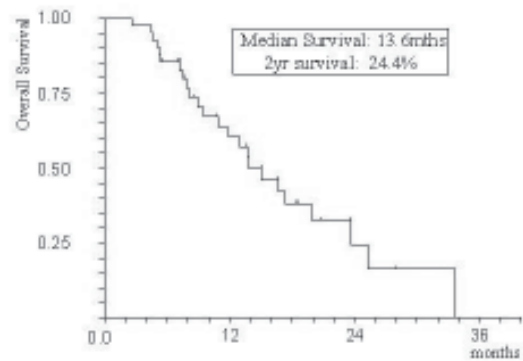


Fig. 1. Overall survival for total group (n = 41).

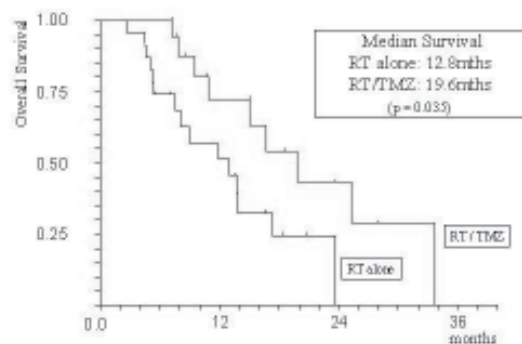


Fig. 2. Overall survival for radiation therapy (RT) alone (n = 23) and RT/temozolomide (TMZ) (n = 18) groups.

Table 2. Relationship Between Potential Patient Prognostic Factors and Median Survival

	Hazard ratio	95% confidence interval	Level of significance
Age	1.00	0.95-1.05	$P = 0.91$
GBM size	1.02	0.33-3.06	$P = 0.98$
Gross/near total resection	1.17	0.09-14.77	$P = 0.90$
ECOG Performance Status 0,1	0.83	0.17-4.14	$P = 0.83$
Time from surgery to RT	1.03	0.92-1.15	$P = 0.59$
Dexamethasone at end RT >4 mg	6.47	1.50-27.89	$P = 0.012$
Chemotherapy use	0.45	0.22-0.95	$P = 0.035$

GBM: glioblastoma multiforme; RT: radiation therapy

Discussion

The outcome from this local cohort of radically-treated patients with GBM confirms the experience of the large EORTC study with improved MS associated with the use of TMZ chemotherapy in addition to adjuvant RT.¹¹ Although this retrospectively analysed local data is non-randomised in its selection of patients for chemotherapy, the results achieved are still significantly improved over local patients with similar tumour characteristics as well as improved over international historical controls.⁵

The results of this local cohort of patients managed with adjuvant TMZ demonstrate a MS of 19.6 months and a 2-year survival rate of 43.3%, which is similar to the large EORTC study outcome of 14.6 months MS and 2-year survival rate of 26.5%.¹¹ A subsequent publication from the EORTC trial performed a subgroup analysis on patients with the best prognostic features (age <50, complete resection and ECOG 0) and demonstrated a 2-year survival rate of 43%, which was significantly improved over patients with similar good prognostic features managed with adjuvant RT alone.¹² In counselling patients for the role of TMZ, these clinical selection factors may become more important to attempt to determine which patients will receive clinically significant benefits for the additional financial cost. Biological predictors of TMZ response, such as methylation of the MGMT repair gene, are evolving with further subgroup analysis from the EORTC study.¹³

While TMZ demonstrates this significant MS benefit and an acceptable toxicity profile, the high financial burden of therapy and the eventual poor 3-year survival associated with GBM generally limits its funding from public healthcare providers. Thus, the patient population that may actually receive the potential benefits of therapy is limited. As TMZ has demonstrated activity in relapsed disease, the option of reserving TMZ until the time of initial tumour

progression may defer the financial costs of therapy.¹⁰ However, as demonstrated in the EORTC study, this approach results in a less favourable outcome. Almost half of patients in this study who were randomised to RT alone did receive TMZ at relapse, but still experienced a reduced median overall survival compared to upfront therapy.¹¹ Alternative approaches with other chemotherapeutic agents, such as more affordable nitrosurea-based regimens, are associated with greater toxicity and less efficacy.^{5,10} Similarly, other measures to improve outcome in GBM, such as RT dose escalation, stereotactic radiosurgery boosts and biological agents, have not resulted in significant survival benefits over standard RT alone.³⁻⁶ Thus, the results obtained with TMZ are considered as a major breakthrough in high-grade glioma, and ongoing clinical studies are emerging to further improve upon outcome. These include utilising targeted biological agents such as cetuximab in addition to TMZ,¹⁴ and strategies to overcome the MGMT effect such as a combination of TMZ and other drugs (BCNU, Procarbazine, O6-benzylguanine).¹³

With the improved 2-year survival rate of patients with GBM, there is a need to optimise the clinical and technical quality of local therapies of surgery and RT to maximise tumour control and minimise treatment-related morbidity. The expanded utilisation of digital technology in diagnostic imaging has improved the targeting capabilities of neurosurgical and RT techniques, with a potential for greater tumour resection or coverage and reduction in normal tissue damage.¹⁵

Clinical studies have demonstrated improved outcomes in patients whose tumours have been aggressively debulked to greater than 90% of the initial volume.⁷ Image-guided resections using ultrasound, stereotactic localisation or intraoperative CT or MRI may potentially allow for more complete resections. Preoperative MRI tractography allows localisation of eloquent cerebral regions to avoid in the pathway of surgical resection. Awake craniotomy, which is more commonly utilised in low-grade tumours where the normal brain tumour interface is poorly defined, may also be utilised in high-grade gliomas adjacent to eloquent areas. These techniques, along with the surgeon's level of experience, may determine which patients are suitable to attempt maximal debulking surgery.

Similarly, RT techniques have been dramatically altered with the incorporation of 3D digital imaging technology into the RT planning systems.^{8,16} RT dose calculation is still determined on CT imaging based algorithms; however, fusion techniques allow preoperative MRI imaging to be used to more accurately determine target volumes in relation to the postoperative planning CT scan. CT-MRI fusion with 3D dosimetry was routinely used in the planning of adjuvant RT of the study cohort, thus minimising risks of

geographical target miss or normal tissue toxicity. Advanced MRI techniques using MR spectroscopy may accurately determine areas of viable tumour in the postoperative tumour bed that can be “dose painted” to receive a higher RT dose via intensity modulated radiation therapy (IMRT).¹⁷⁻¹⁹ This sophisticated RT delivery can reduce the dose to surrounding normal brain structures, whilst maintaining or escalating the dose to the target. Similarly, biological imaging, such as PET, can be fused with RT plans to demonstrate potentially more resistant areas of tumour that can be targeted with IMRT dose escalation. These techniques are currently available; however, their clinical efficacy is yet to be determined.

At present, local and international data demonstrate that TMZ can significantly improve median and 2-year survival in patients with GBM. Given the economic burden of therapy, methods to improve patient selection may be utilised to isolate the group of patients most likely to obtain a clinically significant improvement in 2-year survival. This may be based on clinical prognostic factors or by identifying reliable biomarkers to response.¹³ Further data are required to determine the reliability of these markers and to have the confidence to withhold TMZ or introduce alternative therapies in patients without these factors.

Conclusion

The median and 2-year survival outcomes of this study population of Asian patients with GBM are comparable to the results of the large European Multicentre Study and justify the continued use of TMZ in routine clinical practice. Methods to reduce the financial burden of TMZ therapy or improve patient selection via biomarkers should be explored.

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