Survival Analysis of Glioblastoma Multiforme

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Abstract

Introduction: To evaluate the survival of Glioblastoma Multiforme (GBM). Material and Methods: Patients with a pathological diagnosis of Glioblastoma Multiforme (GBM) between 1 January 1994 and 30 November 2013, were retrospectively reviewed. Inclusion criteria: 1) GBM patients with confirmed pathology, 2) GBM patients were treated by multimodality therapy. Exclusion criteria: 1) GBM patients with unconfirmed pathology, 2) GBM patients with spinal involvement, 3) GBM patients with incomplete data records. Seventy-seven patients were treated by multimodality therapy such as surgery plus post-operative radiotherapy (PORT), post-operative Temozolomide (TMZ) concurrent with radiotherapy (CCRT), post-operative CCRT with adjuvant TMZ. The overall survival was calculated by the Kaplan-Meier method and the log-rank test was used to compare the survival curves. A p-value of ≤ 0.05 was considered to be statistically significant. Results: Seventy-seven patients with a median age of 53 years (range 4-76 years) showed a median survival time (MST) of 12 months. In subgroup analyses, the PORT patients revealed a MST of 11 months and 2 year overall survival (OS) rates were 17.2%, the patients with post-operative CCRT with or without adjuvant TMZ revealed a MST of 23 months and 2 year OS rates were 38.2%. The MST of patients by Recursive Partitioning Analysis (RPA), classifications III, IV, V, VI were 26.8 months, 14.2 months, 9.9 months, and 4.0 months, (p <0.001). Conclusions: The MST of the patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group. RPA classification can be used to predict survival. Multimodality therapy demonstrated the most effective treatment outcome. Temozolomide might be beneficial for GBM patients in order to increase survival time.

Keywords: Glioblastoma multiforme- post-operative radiotherapy- median survival time- survival rate

Introduction

Glioblastoma Multiforme (GBM) or WHO grade IV, is a common malignant brain tumor in adults (Louis et al., 2007; Wen and Kesari, 2008). The GBM occurs in about 80% of the malignant gliomas (DeAngelis, 2001; Thakkar et al., 2014). The patients with GBM have poor prognosis and usually die rapidly if left untreated. Most of the patients die within 2 years and the overall survival time is less than a year from the diagnosed date (Laws et al., 2003; Minmanoff et al., 2006; Reardon and Wen, 2006; Wen and Kesari, 2008; Rock et al., 2012; Hanif et al., 2017). The prognostic factors affecting survival included age, Karnofsky performance status (KPS), chemotherapy administration, total dose of radiation, tumor location in the brain and ability of complete tumor resection (Nelson et al., 1988; Bleehen and Stenning, 1991; Simpson et al., 1993; Laws et al., 2003; Korsunov et al., 2005; Stummer et al., 2006; Pichlmeier et al., 2008; Scott et al., 2011, Okumus et al., 2012; Wang et al., 2012; Ahmadloo et al., 2013; Qin et al., 2015) The Radiation Therapy Oncology Group (RTOG) reported the “Recursive partitioning analysis” and categorized prognosis of the patients with GBM (Curran et al., 1993). Core treatment of the patients with GBM is to remove as much as possible or all of the tumor mass with fewest neurological complications. The only way to prevent major neurological deficits for deep location or infiltrative tumor is to perform either tumor debulking or biopsy (Li et al., 2009; Helseth et al., 2010). The patients who had complete tumor resection with post-operative brain radiation therapy had a 2-year survival of less than 15 % (Nelson et al., 1998; DeAngelis, 2001; Stupp et al., 2005; Stupp et al., 2006). The chemotherapy for adjuvant treatment after tumor resection plus PORT plays an important role on preventing local recurrence as well as distant metastases (Norden and Wen, 2006., Combs et al., 2008; Ohka et al., 2012). Stupp et al., (2005) and Stupp et al., (2009) studied a randomized control trial which demonstrated effectiveness of Temozolomide (TMZ) in post-operative GBM patients.

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Materials and Methods

Patients with Glioblastoma Multiforme (GBM) at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, between 1 January 1994 and 30 November 2013, were retrospectively reviewed. The study was approved by the Ethics Committee for Human Research of Khon Kaen University, HE 561484. Inclusion criteria: 1) GBM patients with confirmed pathology, 2) GBM patients were treated by multimodality therapy. Exclusion criteria: 1) GBM patients with unconfirmed pathology, 2) GBM patients with spinal involvement, 3) GBM patients with incomplete data records. Operating definitions: a) Eloquent area refers to temporo-parietal, parieto-occipital, thalamus, parietal, temporal, hypothalamus, fronto-temporal, basal ganglion, fronto-parietal lobe. b) Non-eloquent area refers to frontal and occipital lobes. c) Survival was calculated from the date of surgical management to the date of death. d) The patients who were treated with post-operative CCRT had to take TMZ orally with the dose of 75 mg/m\(^2\) one hour before each radiation fraction. e) Adjuvant chemotherapy with TMZ was prescribed in some cases starting at 4 weeks after complete radiation treatment with the dose of 150-200 mg/m\(^2\)/day for 5 days every 28 days for 6 cycles. f) The titrational dose technique was usually used with whole brain radiation therapy (WBRT) in some cases with extensive brain edema to avoid brain herniation. The dose per fraction was gradually escalated from a low dose such as 50 cGy to 1 Gy, 1.5 Gy, 1.8 Gy and 2 Gy on the consecutive days.

Patient data were collected from the hospital and radiotherapy unit records in combination with the cancer registry of Srinagarind Hospital. Biographical data and social status of some patients were obtained from the Department of Provincial Administration, Ministry of Interior, Thailand. Statistical analysis was performed by using the STATA software version 10.1. Overall survival was calculated by the Kaplan-Meier method and the log-rank test was used to compare the survival curves. A p-value of \(\leq 0.05\) was considered to be statistically significant.

Results

Patients and treatment characteristics

This study consisted of 112 cases diagnosed with GBM. Thirty-five patients were excluded from the study. There were 7 patients with unconfirmed pathological results, 3 patients with spinal involvement, 20 patients with incomplete data records and 5 patients were lost to follow-up. There were 77 out of 112 cases who met the inclusion criteria. The most frequent tumor region was in the eloquent area (79.2%). In types of surgery, 41 patients underwent partial tumor removal (53.2%), 23 cases had total tumor removal (29.9%) and the rest only had tissue biopsies (16.9%). There were 51 out of 77 cases (66.2%) who received a total radiation dose of 54-60 Gy. Dose fractionation was used as follows: 57 cases (74.0%) were treated with a dose per fraction of 1.8-2 Gy/day, while 20 cases (26.0%) were treated with the WBRT (titrational dose technique). In cases of combined treatment of surgery plus TMZ, 14 cases were treated with post-operative CCRT, another 6 patients received post-operative CCRT plus adjuvant TMZ. Although 4 cases had a complete adjuvant TMZ, the other 2 cases failed to have complete adjuvant TMZ because of tumor progression during treatment and also loss of follow-up.

Sixty-one out of 77 cases (79.2%) received two phases of radiation treatment. Either whole brain radiotherapy (WBRT) or 3D-CRT (3 dimension conformal radiotherapy) technique was used in the first phase of radiation while the second phase was tumor boosting with 2-dimensional radiotherapy (2D) or with 3D-CRT local field external beam radiotherapy( EBT) technique.

Regarding RPA classification, 32 out of 77 cases (41.5%) were classified as class IV and 21/77 cases (27.3%) were class V. The patient and treatment characteristics are summarized in Table 1.

Survival

The median survival time (MST) of all GBM patients in this study was 12 months (n = 77; 95% confidence interval [CI], of 9.9-14 months). The 2 and 5 year overall survival rates were found to be 21.3% and 13.8% as shown in Figure 1.

The patients who underwent surgery plus PORT alone had a median survival time of 11 months (95% confidence interval [CI], 8.8-13.2 months) while in patients treated...
with CCRT with or without adjuvant TMZ was found to be 23 months (95% confidence interval [CI], 13.7-32 months, \( p = 0.03 \)). The patients who underwent surgery plus PORT alone had 2 and 5 year-survival rates of 17.2% and 11.8% while in patients treated with CCRT with or without adjuvant TMZ of 38.2% and 19.1% were as shown in Figure 2.

In sub-group analysis, there were 4 sub-groups, 1) post-operative CCRT + complete adjuvant TMZ, 2) post-operative CCRT, 3) post-operative CCRT + incomplete adjuvant TMZ, 4) PORT alone. Median survival times of each sub-group were 22.7, 20.9, 15.5 and 10.9 months (\( p = 0.181 \)) as shown in Figure 3.

In the aspect of RPA classification, class III cases showed the longest median survival time (MST) of 26.8 months (95% CI, 10.9-NA months) while class IV cases showed MST of 14.2 months (95% CI, 9.2-18.1 months), class V cases showed MST of 9.9 months (95% CI, 8.4-14.0 months) and class VI cases showed the MST of 4.0 months (95% CI, 1.8-10.8 months) with CCRT with or without adjuvant TMZ was found to be 23 months (95% confidence interval [CI], 13.7-32 months, \( p = 0.03 \)). The patients who underwent surgery plus PORT alone had 2 and 5 year-survival rates of 17.2% and 11.8% while in patients treated with CCRT with or without adjuvant TMZ of 38.2% and 19.1% were as shown in Figure 2.

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The patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group (\( p < 0.030 \)) in this present study. In sub-group analysis, there were 4 groups of patients; 1) Surgery plus complete CCRT and adjuvant TMZ (4 cases, 5.2%), 2) Surgery plus complete CCRT (TMZ) (8 cases, 10.4%), 3) Surgery followed by complete CCRT with incomplete adjuvant TMZ (2 cases, 12.9%) and 4) Surgery plus PORT (63 cases, 81.8%). The first group showed the longest MST of 22.7 months. The second, third and fourth groups revealed MSTs of 20.9, 15.5 and 10.9 months (\( p = 0.181 \)). This present study showed better results in post-operative CCRT cases with or without adjuvant TMZ. The data from RTOG classifications reported that MST of patients with RPA class III, IV, V and VI were 17.9, 11.1, 8.9 and 4.6 months and 2-year OS rates were 35%, 15%, 6% and 4% (Curran et al., 1993). This study revealed similar results as the RTOG trial. The patients with RPA class III, IV, V and VI showed the MSTs of 26.8, 14.2, 9.9 and 4.0 months (\( p < 0.001 \)) and 2-year OS rates were 62.2%, 19.9%, 13.9% and 0%. The RPA class III had a longest MST and the best 2-year OS rate.

In conclusion, the MST of the patients who had post-operative CCRT with or without adjuvant TMZ was better than the PORT group. The RPA classification can be used to predict survival. While multimodality therapy demonstrated the most effective treatment outcome. Temozolomide might be beneficial for GBM patients in order to increase survival time.

**Conflicts of interest**

None.

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**References**

Ahmadloo N, Kani AA, Mohammadianpanah M, et al (2013). Treatment outcome and prognostic factors of adult glioblastoma multiforme. *J Egypt Natl Cancer Inst*, 25, 21–30.

Bleehen NM, Stenning SP (1991). A medical research council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. *Br J Cancer*, 64, 769–74.

Binabaj MM, Bahrami A, ShahidSales S, et al (2018). The prognostic value of MGMT promoter methylation in glioblastoma: A meta-analysis of clinical trials. *J Cell Physiol*, 233, 378–86.

Combs SE, Wagner J, Bischof M, et al (2008). Postoperative treatment of primary glioblastoma multiforme with radiation and concomitant temozolomide in elderly patients. *Int J Radiat Oncol Biol Phys*, 70, 987–92.

Curran WJ Jr, Scott CB, Horton J, et al (1993). Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst*, 85, 704–10.

Ciammella P, Galeandro M, D’Abbiere N, et al (2013). Hypo-fractionated IMRT for patients with newly diagnosed
glioblastoma multiforme: a 6 year single institutional experience. Clin Neurol Neurosurg, 115, 1609-14.
DeAngelis LM (2001). Brain tumors. N Engl J Med, 344, 114-23.
Illic R, Somma T, Savic D, et al (2017). A survival analysis with identification of prognostic factors in a series of 110 patients with newly diagnosed glioblastoma before and after introduction of the stupp regimen: A single-center observational study. World Neurosurg, 104, 581-8.
Hanif F, Muzaffar F, Perveen K, et al (2017). Glioblastoma Multiforme: A Review of its epidemiology and pathogeneses through clinical presentation and treatment. Asian Pac J Cancer Prev, 18, 3-9.
Hegi ME, Diserens AC, Gorlia T, et al (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med, 352, 997-1003.
Hegi ME, Liu L, Herman JG, et al (2008). Correlation of O6- methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. J Clin Oncol, 26, 4189-99.
Helseth R, Helseth E, Johannesen TB, et al (2010). Overall survival, prognostic factors, and repeated surgery in a consecutive series of 516 patients with glioblastoma multiforme. Acta Neurol Scand, 122, 59-67.
Korshunov A, Sycheva R, Golanov A (2005). The prognostic relevance of molecular alterations in glioblastomas for patients age < 50 years. Cancer, 104, 825-32.
Kesari S, Schiff D, Henson JW, et al (2008): Phase II study of temozolomide, thalidomide, and celocoxib for newly diagnosed glioblastoma in adults. Neuro Oncol, 10, 300-8.
Laws ER, Parney IF, Huang W, et al (2003). Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Gliomas Outcome Project. J Neurosurg, 99, 467-73.
Li SW, Qiu XG, Chen BS, et al (2009). Prognostic factors influencing clinical outcomes of glioblastoma multiforme. Chin Med J, 122, 1245-9.
Louis DN, Ohgaki H, Wiestler OD, et al (2007). The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol, 114, 97-109.
Mirimanoff R, Gorlia T, Mason W, et al (2006). Radiotherapy and temozolomide for newly diagnosed glioblastoma: Recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol, 24, 2563–9.
Nelson DF, Diener-West M, Horton J, et al (1988). Combined modality approach to treatment of malignant gliomas- re- evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: A joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. NC1 Monogr, 6, 279-84.
Norden AD, Wen PY (2006) Glioma therapy in adults. Neurologist, 12, 279-92.
Ohka F, Natsume A, Wakabayashi T (2012). Current trends in targeted therapies for glioblastoma multiforme. Neuro Res Int, 2012, 878425.
Okumus NO, Gursel B, Meyndan D, et al (2012). Prognostic significance of concomitant radiotherapy in newly diagnosed glioblastoma multiforme: a multivariate analysis of 116 patients. Ann Saudi Med, 32, 250-5.
Pichlmeier U, Bink A, Schackert G, et al (2008). Resection and survival in glioblastoma multiforme: An RTOG recursive partitioning analysis of ALA study patients. Neuro Oncol, 10, 1025-34.
Prados MD, Chang SM, Butowski N, et al (2009). Phase II study of Erlotinib plus Temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. J Clin Oncol, 27, 579-84.
Qin J-J, Liu Z-X, Wang J-M, et al (2015) Prognostic factors influencing clinical outcomes of malignant glioblastoma multiforme: Clinical, immunophenotypic, and fluorescence in situ hybridization findings for 1p19q in 816 Chinese cases. Asian Pac J Cancer Prev, 16, 971-7.
Reardon DA, Wen PY (2006). Therapeutic advances in the treatment of glioblastoma: rationale and potential role of targeted agents. Oncologist, 11, 52-64.
Rock K, McArindle O, Forde P, et al (2012). A clinical review of treatment outcomes in glioblastoma multiforme: the validation in a non-trial population of the results of a randomised Phase III clinical trial: has a more radical approach improved survival?. Br J Radiol, 85, e729-33.
Scott J, Tsai Y-Y, Chinnaiyan P, Yu H-HM (2011). Effectiveness of radiotherapy for elderly patients with glioblastoma. Int J Radiat Oncol Biol Phys, 81, 206-10.
Simpson JR, Horton J, Scott C, et al (1993). Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys, 26, 239-44.
Stummer W, Pichlmeier U, Meinel T, et al (2006). Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. Lancet Oncol, 7, 392-401.
Stupp R, Mason WP, van den Bent MJ, et al (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 352, 987-96.
Stupp R, Hegi ME, van den Bent MJ, et al (2006). Changing paradigms-an update on the multidisciplinary management of malignant glioma. Oncologist, 11, 165-80.
Stupp R, Hegi ME, Mason WP, et al (2009). Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized Phase III study: 5-year Analysis of the EORTC-NCIC trial. Lancet Oncol, 10, 459-66.
Thakkar JP, Dolecek TA, Horbinski C, et al (2014). Epidemiologic and molecular prognostic review of Glioblastoma. Cancer Epidemiol Biomarkers Prev, 23, 1985-96.
Teo M, Martin S, Owusu-Agyemang K, et al (2014). A survival analysis of GBM patients in the West of Scotland pre- and post-introduction of the Stupp regime. Br J Neurosurg, 28, 351-5.
Wang Y, Li S, Zhang Z, et al (2012). Surgical extent impacts the value of the established prognosticators in glioblastoma patients: a prospective translational study in Asia. Head Neck Oncol, 4, 80.
Wen PY, Kesari S (2008). Malignant gliomas in adults. N Engl J Med, 359, 492-507.
Yang LJ, Zhou CF, Lin ZX (2014). Temozolomide and radiotherapy for newly diagnosed glioblastoma multiforme: a systematic review. Cancer Invest, 32, 31-6.
Zarnett OJ, Sahgal A, Gosio J, et al (2015). Treatment of elderly patients with glioblastoma: a systematic evidence-based analysis. JAMA Neurol, 72, 589-96.