Effectiveness of adjuvant temozolomide treatment in patients with glioblastoma

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ABSTRACT

الأهداف: دراسة فيما إن كان العلاج المتزامن باستخدام التيموزولومايد يساعد في تحسين زمن البقاء وإثبات الجدوى في الحياة العملية خارج إطار البحث.

الطريقة: أجريت هذه الدراسة الاسترجاعية ل364 مريض تم تشخيصهم بالورم الدبقي الدماغي الرابع والذين خضعوا لطرق علاجية متعددة في مركزين طبيين بمدينتي أدمنتون وهليفاكس، كندا، خلال الفترة من عام 2006–2000م. النتيجة الأولية كانت زمن البقاء بعد العلاج.

النتائج: كانت معدلات المتغيرات المرتبطة بزيادة خطورة الوفاة كالتالي: نسبة الخطورة عند الاستئصال العام للورم 0.50 (نطاق الثقة عند 95%: 0.64–0.39) وكانت نسبة الخطورة في المجموعة الخاضعة للجراحة 5.2 (نطاق الثقة عند 95%: 7.06–3.85). وبلغت نسبة الخطورة لدى المجموعة العلاجية المثالية التي خضعت للجراحة والعلاج الإشعاعي وعقار التيموزولومايد 0.52 (نطاق الثقة عند 95%: 0.74–0.37). كذلك بلغت نسبة الخطورة عند المرضى الذين يعانون من تشنجات صرعية عند بداية الأعراض 0.88 (نطاق الثقة عند 95%: 0.89–0.55). وبلغت نسبة الخطورة عند المرضى المشاركين في الدراسات العلمية 0.74 (نطاق الثقة عند95%: 0.96–0.57)، وأخيراً بلغت نسبة الخطورة مع تقدم العمر 1.02(ونطاق الثقة عند 95%: 1.03–1.01) لكل سنة إضافية.

خاتمة: إن العلاج المتزامن بين عقار التيموزولومايد والعلاج الإشعاعي مع الجراحة للمرضى المشخصين بالورم الدبقي الدماغي الرابع يؤدي إلى زيادة زمن البقاء بعد العلاج مقارنة بالعلاج الإشعاعي مع الجراحة فقط. كذلك وجدنا أن صغر عمر المريض والاستئصال الجراحي ووجود التشنجات العصبية عند بداية الأعراض ومشاركة المرضى في الدراسات العلمية عوامل مهمة للحصول على زمن بقاء أطول.

Objective: To examine whether adjuvant temozolomide treatment improved glioblastoma patients' survival in a large Canadian cohort.

Methods: We retrospectively studied 364 glioblastoma patients who received different modalities of treatment in 2 Canadian tertiary care centers in Edmonton and Halifax, Canada, between January 2000 and December 2006. The primary outcome was survival following the treatment protocol.

Results: The following variables were associated with an increased risk of death: The hazard risk (HR) of on-gross total resection was 0.50 (95% confidence interval [CI]: 0.39-0.64). The HR for the surgery-only group was 5.2 (95% CI: 3.85-7.06). The standard treatment group (surgery, radiation therapy [RT], and temozolomide) had an HR of 0.52 (95% CI: 0.37-0.74). The HR for patients who presented with seizure or whose presentation included seizures was 0.88 (95% CI: 0.55-0.89). Patient entry into trials had an HR of 0.74 (95% CI: 0.57-0.96). Finally, the HR for age was 1.02 (95% CI: 1.01-1.03) for every extra year.

Conclusions: Concomitant temozolomide with RT and surgery was associated with longer survival compared with RT with surgery alone. We also found that younger age, surgical resection, seizure presence, and entry into trials are important prognostic factors for longer survival.

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Glioblastoma is the most prevalent, and aggressive primary malignant brain tumor in adults.[1,2] Despite state-of-the-art treatment regimens, the mean survival of patients with glioblastoma is only 9-12 months.[3] Historically, the survival rate of patients who have newly diagnosed glioblastoma is 18% at one year, and 3% at 2 years.[3] One of the major therapeutic advances in the care of patients with glioblastoma was the introduction of adjuvant radiotherapy after surgery. The administration of adjuvant radiotherapy after surgery prolongs survival from 14-22 weeks with surgery alone to 36-48 weeks.[4] Recently, Stupp and colleagues[2] reported that the addition of temozolomide (Schering-Plough, Kenilworth, NJ, USA) to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity. In their study, the median survival time was 14.6 months for patients receiving radiotherapy and temozolomide in comparison with 12.1 months with radiotherapy alone.[2] This observation resulted in the acceptance of administering radiation therapy (RT), alongside concomitant and adjuvant temozolomide after surgery, in the management of glioblastoma as the gold standard. Although randomized controlled trials are considered the gold standard, many studies discussed how the external validity or generalizability of randomized trials is often neglected.[5,6] Many potential impediments to generalizing the results of randomized trials include the use of specialized centers, selected patients, and surrogate outcomes. Therefore, a potential role for an observational study is to assess the treatment effect observed in randomized controlled trials. Our study objective is to examine whether adjuvant temozolomide treatment improves glioblastoma patients' survival in a large Canadian cohort. This study will help in establishing the external validity and generalizability of the trial conducted by Stupp et al[2] to the Canadian population.

Methods.

Study design. We conducted our study in Edmonton, Alberta, Canada. It is a retrospective cohort study based on chart and database review of patients who were treated at the University of Alberta Hospital, Royal Alexandra Hospital, or the Cross Cancer Institute in Edmonton. The data of patients who were diagnosed and treated at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia, were prospectively collected from 2000. The study population included all glioblastoma patients treated between January 2000 and December 2006 at these centers. The diagnosis of glioblastoma was confirmed by a tissue biopsy. The intervention was concomitant and adjuvant temozolomide. The control group included patients who received radiotherapy with or without chemotherapeutic agents other than concomitant and adjuvant temozolomide, and a third group which includes patients who received surgery only. The primary outcome was the overall survival in each group.

Study population. Inclusion criteria. Patients who were 18 years or older and received a tissue diagnosis of glioblastoma (either through biopsy or resection) at one of the participating centers between January 2000 and December 2006 were included in this study. This study obtained the approval of each hospital's ethics committee/board.

The total population of patients was retrospectively classified into 3 groups based on the treatment they received. The first group of patients received surgical intervention only (biopsy or resection) (group A). The second group had both surgery (resection or biopsy), and RT; with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide (group B). The third group of patients received the standard treatment, which was concomitant and adjuvant temozolomide with radiotherapy after surgery (resection or biopsy) (group C).

As the partial resection of glioblastoma or debulking failed to prove major survival benefit when compared with biopsy, and due to existing literature of significant benefits of gross total removal when possible, all patients who received stereotactic biopsy, open biopsy or debulking, according to the operative report, were included in the biopsy group.[7-11] The rationale for combining the patients who received radiotherapy only, and those who received any chemotherapeutic agent other than concomitant and adjuvant temozolomide into one group was based on the lack of evidence of any chemotherapeutic agent providing any benefit to survival. Therefore, all chemotherapeutic agents other than concomitant and adjuvant temozolomide were considered non-successful interventions. In 2001, the Medical Research Council trial[12] concluded that no-chemotherapy control arms remain ethical in randomized trials for high-grade astrocytoma due to a lack of prolongation of survival with chemotherapeutic agents. Also, in the Stupp trial,[2] the comparison was concomitant temozolomide with RT versus radiotherapy alone for the same reason above. A modified WHO

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criteria was utilized to define tumor progression as per Stupp et al.[2]

Statistical analysis. We used STATA 12 software (StataCorp LP., 2011 Stata Statistical Software: Release 12. College Station, TX, USA) for statistical analysis. Kaplan-Meier curves were used to describe the median survival of the 3 groups. Cox's proportional hazard models were used for the multivariate analysis. These methods allowed for the inclusion of censored data. The outcome of the survival analysis was death after intervention; where death was verified from hospitals records, and a case was censored if a patient did not die during the follow-up. The censored time was defined as the time between the date of the first CT or MRI at the time of diagnosis to the date when a patient was lost to follow-up or to the study end date (March 31, 2009). Two types of variables were collected: continuous and categorical. The continuous variables were age, duration of the symptoms (weeks), and time to surgery (days). The categorical variables were gender, presence of seizure (yes or no), type of surgery (resection versus biopsy), use of temozolomide (yes or no), center (Edmonton or Halifax), and entry into the clinical trial (yes or no). The time to surgery variable was considered as the time from the date of diagnosis, which was when the patient underwent the CT or MRI, to the date of surgery. T-test and chi square test were utilized to compare the distribution of the risk factors variables across the 3 treatment groups. Throughout the analysis, group B was considered the reference group. Purposeful model building was used upon running the multivariate analysis. The model building included the variables with p-values ≤0.2. While running the model, both the center variable (Edmonton versus Halifax) and the time factor variable (before versus after 2005) were kept in the model at all steps, as 2005 was the year of Stupp et al's study.[2]

Results.

Patient and treatment characteristics. A total of 346 patients were included in the study, of which 216 were from Edmonton (63%) and 130 (37%) from Halifax. Of the total number of patients, 329 (95%) patients died, and 17 (5%) were censored. The censored patients fell into 2 categories: 11 patients were lost to follow-up, and 6 patients were still alive. The mean and standard deviations of the ages of patients were comparable in both centers. The mean age of Edmonton patients was 61±12 years. The mean age of patients in Halifax was 60±11 years. The overall mean was 61±12 years. The mean overall symptom duration was 6 weeks ±8. In Edmonton, the mean symptom duration was 5 weeks ±6 and the mean in Halifax was 8 weeks ±9. The variability across the treatment groups is shown in **Table 1**.

There were a total of 216 male patients and 130 female patients. The gender distribution was similar in both centers. Regarding the presence of seizures in the patient's presentation, 238 (69%) presented without any seizures, which included 146 (68%) patients in Edmonton and 92 (71%) patients in Halifax. In terms of treatment type, 76 (21%) patients fell under group A, 221 (64%) under group B, and 49 (14%) under group C. In total, 226 (65%) patients underwent tumor resection with or without other interventions (radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide, or the standard treatment), and 120 (35 %) underwent biopsy. The mean time to surgery from the time of the first CT or MRI was 10 days ±14. In Edmonton, the mean was 11 days ±16. In Halifax, the mean time to surgery was 7 days ±11. **Table 2** illustrates the patients' characteristics according to the type of management. The median overall survival in patients in group C was 14 months, whereas in group B, the median survival was 10 months. In group A, the median survival was 3 months.

Table 1 - The median of age, symptoms duration, and time to surgery of the glioblastoma treatment groups.

Covariate	Group A	Group B	Group C
Age (years)	65	62	56
Symptoms duration (weeks)	4	4	4
Time to Surgery (days)	7	5	4

Table 2 - Characteristics of glioblastoma patients by treatment groups.

Covariate	Group A	Group B	Group C
		n (%)	
Gender			
Female	35 (10)	80 (23)	15 (4)
Male	41 (12)	141 (41)	34 (10)
Surgery type			
Biopsy	38 (11)	64 (19)	18 (5)
Resection	38 (11)	157 (45)	31 (9)
Seizure			
No	56 (17)	147 (42)	35 (10)
Yes	20 (6)	74 (21)	14 (4)
Trials			
No	72 (21)	155 (45)	23 (7)
Yes	4 (1)	62 (18)	25 (8)

The result of t-test comparing the distribution of age across the 3 treatment groups, revealed a significant difference between the treatment groups A and B; p=0.02, and the same significant difference for the same variable between groups B and C; p=0.02. T-test for the distribution of symptoms duration, and time to surgery variables, showed no significant differences between the treatment groups. For the symptoms duration variable, the p-value was 0.4 between groups A and B, and 0.13 between groups B and C. The time to surgery variable revealed the same p-value of 0.3 between groups A and B, and between groups B and C. Chi square test comparing the distribution of categorical variables across the 3 treatment groups, revealed no significant difference regarding gender variable between groups A and B (p=0.12), and between groups B and C (p=0.4). The presence of seizure at presentation variable was insignificant between all the treatment groups. The p-values were 0.2 between groups A and B, and 0.5 between groups B and C. The type of surgery variable showed a significant difference between the groups. This variable revealed that more patients in group A received biopsy only compared with group B (p=0.001), whereas there was no significant difference between groups B and C.

Univariate analysis. The descriptive analysis using the Kaplan-Meier survival curves in the survival distribution showed no significant difference between the 2 centers, with a hazard ratio (HR) of 1.00 (95% CI: 0.80-1.26; p=0.8). Older age was negatively associated with survival: there was a 2% increase in the risk of death for every one-year increase in age (HR 1.02, 95% CI: 1.01-1.03; p<0.001). The presence of seizure in the patient's presentation was protective: there was a 22% reduction in the risk of death for patients with seizure in comparison with those without seizure (HR 0.78, 95% CI: 0.61-0.97; p=0.02). Patient involvement in trials showed a survival benefit compared to non-involvement (HR 0.56, 95% CI: 0.43-0.71; p<0.0001). **Figure 1** shows the effects of the type of management. There was a significant difference among the 3 groups, when group B was deemed the reference group. The patients in group A had an HR of 5.5 (95% CI: 4.11-7.28; p<0.0001), whereas the patients in group C had an HR of 0.59 (95% CI: 0.42-0.82; p=0.002). Resection had a significant protective effect over biopsy (HR 0.52, 95% CI: 0.41-0.65; p<0.0001). The variables of gender (p=0.79), time to surgery (p=0.08), and duration of symptoms (p=0.13) were not significantly associated with survival. However, time to surgery and duration of symptoms were carried into the multivariate analysis, as their p-values were ≤0.2, as per our statistical analysis protocol.

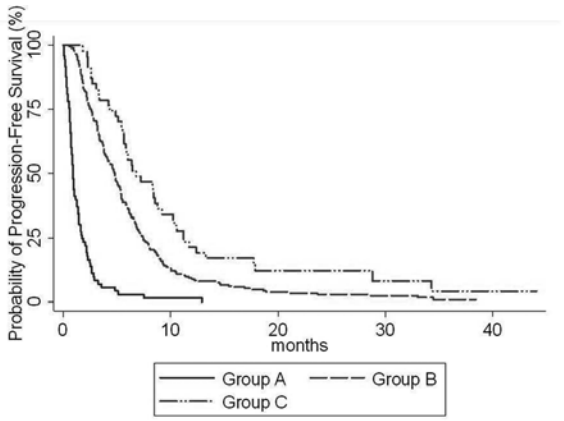

Figure 1 - Kaplan Meier estimates of survival by type of management of glioblastoma patients.

Table 3 - Significant predictors of survival among glioblastoma patients from the multivariate analysis

Covariate	Hazard ratio and %	95% CI	*P*-value
Age	1.02 (-)	1.00-1.023	0.02
Seizure	0.88 (31)	0.55-0.89	0.004
Surgery type	0.50 (65)	0.39-0.64	<0.0001
*Type of management**			
Group A	5.20 (22)	3.85-7.06	<0.0001
Group C	0.52 (14)	0.37-0.74	<0.0001
Trials	0.74 (27)	0.57-0.96	0.02

*Group B was the reference group, CI - confidence interval

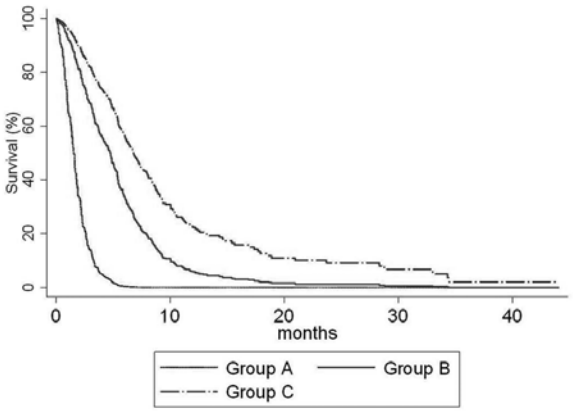

Figure 2 - Adjusted estimates of survival from Cox's proportional hazards regression of the overall study patients.

Multivariate analysis. For multivariate analysis, age, duration of symptoms, seizure presence, type of surgery, type of management, involvement in trials, and the time to surgery were considered. The results from the multivariate analysis are shown in **Table 3**. Older

age remained a significant factor (HR 1.02, 95% CI: 1.00-1.023; p=0.02). The presence of seizure revealed an HR of 0.88 (95% CI: 0.55-0.89; p=0.004), in those who presented with seizure or whose presentation included seizure compared with patients who had no seizures at presentation. Surgery type had an HR of 0.5 (95% CI: 0.39-0.64; p<0.0001), for patients who had resection compared to those who had biopsy. Regarding the type of management received, group B again was considered the reference group. Therefore, the patients in group A had an HR of 5.2 (95% CI: 3.85-7.06; p<0.0001), while the patients in group C had an HR of 0.52 (95% CI: 0.37-0.74; p<0.0001). The factor of trial involvement was also significant in the multivariate analysis (HR 0.74, 95% CI: 0.57-0.96; p=0.02) (**Figure 2**).

Discussion. A few randomized controlled trials have shown clinical and statistical significance in the improvement of survival in glioblastoma patients. Since the publication of the results of Stupp et al in early 2005,[2] care centers around the world have started to change their practices in the treatment of glioblastoma to include surgery, RT, and concomitant and adjuvant temozolomide therapy. Our results validate the Stupp trial and protocol in indicating that concomitant and adjuvant temozolomide provides a survival benefit for patients with glioblastoma.

Our retrospective cohort study also found multiple factors that affect and assist in predicting the overall survival of patients. The overall results in both centers show that older age is a significant poor prognostic factor for survival. These results confirm previous reports.[13] The presence of seizures at the time of presentation, whether the only symptom at presentation or part of the patient's overall presentation, showed a protective effect, with a 12% HR reduction compared with those patients who did not have seizures. Possible explanations for this factor's significance may be based on the fact that the seizures may bring the patients to medical care facilities earlier than those patients who do not present with seizures.[14] Despite that, controversies still exist, where other studies concluded that presence of seizure had no impact and did not offer a survival benefit for glioblastoma patients.[14]

The type of surgery (biopsy versus resection) showed a protective mechanism for patients who underwent resection compared with those underwent biopsy only. Despite that near total resection patients were classified as biopsy patients in our study, the significance of this factor in predicting survival was high.[15-17] Due to recent advances in surgical techniques and adjunct treatments of glioblastoma, more publications are now advocating that more surgical resection whenever possible, is an independent positive prognostic factor.[16]

The entry into trials is a contentious factor in the current literature. Patient involvement in trials can be a positive prognostic factor because patients feel well supported and perceive a heightened degree of medical care.[18,19] However, other studies argue against this finding, and report that patient involvement in trials is not associated with any improvement of survival.[20] Our study found that patients' involvement in trials reduced the hazard ratio by 26%. We confirmed previous findings that surgery alone without pursuing other types of treatments is associated with short survival time. Patients in group B showed significantly higher survival times than group A patients who received surgery alone,[21] whereas group C patients had significantly better survival compared with the reference group, which also supports the findings of previous studies.[2,15] The increase in survival by 4 months in the group of patients who received RT with concomitant and adjuvant temozolomide after surgery is well supported by the literature.[2,22]

Gender, the duration of symptoms, and the time to surgery were not significant factors in the prediction of survival. The insignificance of the time to surgery might have been related to the short time between the diagnoses of glioblastoma by CT or MRI to the time of operation. These findings in comparing pre and post temozolomide era are similar to the findings published recently by Johnson and O'Neill.[23] Their study is by far the largest study for glioblastoma patients. It analyzed the data of more than 13,000 patients from the Surveillance, Epidemiology, and End Results (SEER) program in the United States. The major study limitation was the assumption that all patients received chemotherapy, as there were no data on chemotherapy in the SEER program. The rationale for publishing those data was the same concern of limited representation of the enrolled population in those trials.[23]

Strengths of the study. The most important strength was addressed in the introduction section, in regards assessing the effectiveness of randomized control trial results from a real life prospective. Second, is the relatively large number of patients involved in the study. The number of the patients in most of the retrospective glioblastoma studies found in the literature is in the range of 100 to 300 patients.[24-26] Few cohort glioblastoma papers have been published with more than 400 patients.[9,27,28] However, randomized controlled trials have a higher number of patients on average, often reaching 500 or more.[2,24] Therefore, our

total patient population of 346 is considered a relatively large sample size. Additionally, conducting the study in 2 Canadian tertiary care centers brings us closer to generalizing the findings to the entire Canadian population. Although it is difficult to conclude that our findings are generalizable solely based on 2 cities, we hope to encourage other Canadian centers to publish their experiences with concomitant and adjuvant temozolomide treatment.

Limitations. The first limitation of this study lies in its retrospective nature. Observational research often systematically over-estimates the benefits of heath interventions compared with randomized trials.[29,30] However, other studies have challenged these results, finding that well-designed observational studies did not overestimate treatment benefit, which was attributed to better recognition and avoidance of design bias and improved statistical models for risk adjustment.[31,32] The second limitation is the lack of complete data. We faced this issue in both the prospectively and retrospectively collected data. This created limitations in including some of the variables, or excluding them from the study based on the availability of the data. The unavailability of the Karnofsky score in the charts was also a limiting factor. The Karnofsky score is an important functional evaluation of the patients and consistently has been identified as an important prognostic factor for patients with glioblastoma.[15,33] As this study is retrospective in nature; selection bias was present as well, in many aspects. First, bias could have been introduced by the neurosurgeon that saw the patient and decided what type of surgical intervention was warranted (biopsy or resection). This is explained by the fact that more patients in group A received biopsies only. It was also present in the decision of the radiation oncologist whether the patient required radiotherapy as an intervention, and if so, what type of radiotherapy (curative versus palliative). From the neuro-oncologist's point of view, the decision whether to offer chemotherapeutic agents could have introduced bias. Recall bias was also present in 2 variables, the presence of seizure and the duration of symptoms prior to the presentation. In addition to the above, population-based studies cannot be used to provide prognosis for individuals, rather providing an overall trend over a period of time.[23] The last limitation is the dual nature of the data that were collected, as the data from Halifax were prospectively collected, while the data from Edmonton were retrospectively collected.

In conclusion, our observational study showed the effectiveness of Stupp protocol[2] in providing survival benefits for glioblastoma patients outside randomized control trials. Surgical resection, when possible is an independent factor in predicting survival of glioblastoma patients. We also found that younger age, the presence of seizures in the patient's presentation, and involvement in trials are also important factors for improved survival.

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ETHICAL CONSENT

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed. Research papers not involving human or animal studies should also include a statement that approval/no objection for the study protocol was obtained from the institutional review board, or research ethics committee.