University of Alberta

Evaluation of Concomitant Temozolomide Treatment in Glioblastoma Multiforme Patients in Two Canadian Tertiary Care Centers

by

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Dedicated to the memory of my father Mohammed Alnaami,

to my mother Majeedah,

my wife Tageyah and

my children Zubair, Musaab, and Hamzah.

Abstract

The study evaluated the survival of 364 glioblastoma multiforme (GBM) patients who received different modalities of treatment in two Canadian tertiary care centres. Retrospective and prospective databases were utilized to do a retrospective population based cohort study.

The thesis question was “among treated GBM patients in Edmonton and Halifax; does the survival rate differ with introduction of concomitant temozolomide and radiation therapy (RT) versus non concomitant treatment?”

Our results indicate that concomitant temozolomide with radiation therapy and surgery was associated with longer survival in comparison to radiation therapy with surgery. We also found that age; surgical resection and shorter time to radiation therapy are important factors for longer survival.

Acknowledgement

I would like to express my sincerest and deepest level of gratitude to Allah The Most Glorious The Most Exalted.

I owe my loving thanks to my mother Majeedah, my wife Tageyah, and to my children Zubair, Musaab, and Hamzah. Without their care, encouragement and understanding I would have not been able to complete my work.

I am deeply grateful to my supervisor and co-supervisor Professor Ambikaipakan Senthilselvan, PhD and Dr. Vivek Mehta, M.D, MSc respectively. Their knowledge, experience and personal guidance have been fundamental in helping me accomplish the present thesis.

I wish to express my warmest thanks to Dr. Sita Gourishankar, M.D, MSc and to Dr. Cian O'Kelly for their constructive comments, valuable advice and their important support throughout this work.

During this work I have collaborated with many colleagues and staff at Cross Cancer Institute , University of Alberta Hospital, Royal Alexandra Hospital, and Queen Elizabeth II Health Sciences Center in Halifax whom I have great regard, and I wish to extend my deepest thanks to all those who have helped me with my work.

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Chapter 1

Introduction

Brain tumors can be classified as non-aggressive (benign) or aggressive (malignant). Benign brain tumors usually originate from coverings of the brain (meningiomas) or cells associated with nerves coming from the brain (schwannomas and neurofibromas). There are two main types of malignant brain tumor: primary (arising from brain cells) and metastatic (having spread from tumors elsewhere in the body). The occurrence and growth of brain tumors are likely to be associated with a combination of genetic and environmental factors.(1) There are more than 120 types of brain tumors including benign and malignant.(2) Of these is glioblastoma multiforme (GBM) which is the most frequent primary malignant brain tumor in adults,(3) and the most aggressive brain tumour.(4)

The signs and symptoms of GBM, like other brain tumors, depend on their location and size. Brain tumors can cause either focal or generalized neurologic symptoms. The presentation of the disease varies: headache (50%), seizure (15-25%), hemiparesis (30-50%) and mental status changes (40-60%).(4) They can be located anywhere in the brain but usually affect the cerebral hemispheres.

GBM represent at least 80 percent of the malignant astrocytomas, (the anaplastic astrocytoma and GBM) with an annual incidence of 3 to 4 per 100,000 populations and the male-to-female ratio among affected patients is about 3:2. The peak age at onset of GBM usually present in the sixth or seventh decade.(4)

Despite available state-of-the-art multimodality treatments, the median survival of patients with GBM is 9 to 12 months.(5) In a population-based study conducted in Switzerland between 1980 and 1994, the survival rate of patients who had newly diagnosed GBM was 18% at 1 year and 3% at 2 years.(5) One of the major land marks in the history of GBM management was the introduction of adjuvant radiotherapy after surgery. Administration of adjuvant radiotherapy after surgery changed the survival from 14-22 weeks with surgery alone to 36-48 weeks.(6) Recently Stupp and colleagues published a study where they found the addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.(3) In this study, the median survival time was 14.6 months for patients receiving radiotherapy and temozolomide in comparison to 12.1 months with radiotherapy alone.(3) The greater benefit seen in the study has resulted in including radiation therapy with concomitant and adjuvant temozolomide after surgery in the management of glioblastoma,

Chapter 2

Background

The idea of the study came from a famous landmark paper in glioblastoma multiforme (GBM) literature named (radiotherapy plus concomitant and adjuvant temozolomide for the treatment of GBM).(3) Stupp et. al. found that the addition of concomitant and adjuvant temozolomide is associated with increase survival for patients with GBM who received radiotherapy and temozolomide by 2 months. The survival of patients who received traditional radiotherapy alone was 12 months where in the gold standard treatment group, the survival was 14 months. This difference was statistically and clinically significant. Based on this trial, many international centers started to change their approach to GBM treatment to include temozolomide as concomitant and adjuvant chemotherapy (Figure 2.1).

There has always been an issue regarding the nature of the randomized control design in that their patients are always doing better for a variety of reasons which will be discussed later.(7, 8) Therefore, as concomitant and adjuvant temozolomide proved its efficacy in the ideal world, which is the randomized controlled trial atmosphere, we looked to this issue and evaluated the efficacy of this treatment from the real life perspective.

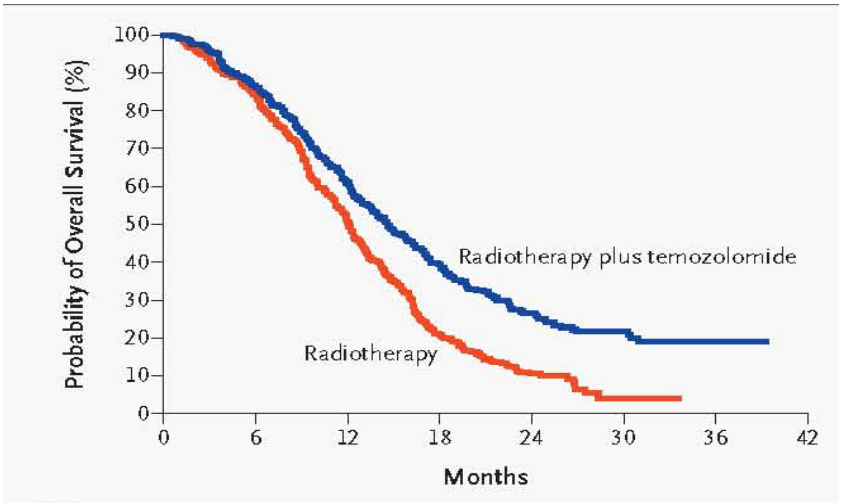


Figure 2.1: The survival curve of radiation plus temozolomide versus radiation therapy group in Stupp et.al trial.

Source: Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10; 352(10):987-96.

Research question and Hypothesis

The research question for the study is "Does survival differ with the introduction of temozolomide as concomitant and adjuvant treatment with radiotherapy versus non concomitant treatment among GBM treated patients in Edmonton and Halifax?"

The null hypothesis is that there is no difference in survival between GBM treated patients with concomitant and adjuvant temozolomide versus non-concomitant treatment in Edmonton and Halifax.

The alternative hypothesis that there is a difference in survival between GBM treated patients with concomitant and adjuvant temozolomide versus non concomitant treatment in the two cities.

Chapter 3

Review of Literature

The treatment of GBM remains difficult as there are no curative measures and the prognosis remains poor despite recent advances. The very nature of GBM, including tumor heterogeneity, tumor location in challenging locations and aggressive tumor relapse make the treatment of this disease challenging. Therefore, the treatment of patients with GBM still remains palliative and involves surgery, radiotherapy, and chemotherapy.

Surgery

The first successful removal of a glial tumor is credited to Bennett and Godlee in 1884.(9) The extent of surgery depends on a variety of factors, including the location of the tumor and the brain area grossly affected. Unfortunately, GBM cannot be cured with surgery since it is a highly infiltrating tumor and cannot be resected completely. Therefore, the goals of surgical resection include establishing a diagnosis, relieving mass effect and hopefully achieve a gross total resection to facilitate adjuvant therapy.(10)

Several studies do suggest a close inverse correlation between the survival and the amount of residual tumor observed on MRI scans post operatively.(11) An analysis of 28 studies found a mean duration of survival benefit for patients who had a total resection compared to those that had a subtotal resection for GBM disease (14 months vs. 11 months).(12, 13) Those who support radical resection

maintain several advantages, including good relief of intracranial pressure, reversal of some neurologic deficits and the lowering of seizure incidence. Others have argued against radical resection as GBM is inherently invasive and one cannot achieve a total resection anyway, the risk of new neurological deficits as well as a potential for tumor cell migration.

Potential future direction in improving radical resection lies with careful pre-operative planning, use of intra-operative imaging modalities to aid the neurosurgeon in delineating the tumor and electrophysiological mapping to help preserve delicate areas. A recent study has also reported an increase in the median survival of GBM patients (17.7 months vs. 12.9 months) with the use of 5-aminolevulinic acid for influencing fluoresceine guided resections.(14) The use of robotic surgery in the treatment of GBM has not yet proved to have a survival benefit.(9)

Radiation Therapy

Early studies have shown that the addition of radiation therapy to surgery prolongs survival in patients with GBM compared to surgery alone. The addition of radiotherapy to surgery has been shown to increase survival from 3-4 months to 7-12 months.(15) Radiation therapy of GBM is also a dose dependent relationship, with significantly increased median in survival with a dose of 6000cGy compared to lower doses of radiation.

Whole brain radiation therapy does not improve survival when compared to the more precise and highly focused RT treatment modalities, including

stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (fSRT), and brachytherapy (with or without hyperthermia). Obviously, the goal of these highly focused irradiation techniques is to boost the delivery dose of conventional techniques while minimizing exposure to adjacent brain tissue in an effort to minimize side effects. Two large Phase III trials compared standard external beam radiation therapy (EBRT) alone versus EBRT plus low-activity ^{125}Iodine seed implants.

These trials showed no significant survival advantage by the addition of brachytherapy.(16, 17) However, two small cohort studies reported a statistically significant survival advantage with the addition of hyperthermia to brachytherapy compared to brachytherapy without hyperthermia. Despite these favourable results, no large scale randomized study has been performed to confirm these findings.

A new approach to brachytherapy is a balloon catheter system that delivers low-dose radiation focally to the GBM tumor site. The efficacy of this new approach was assessed in 24 patients with recurrent GBM, where the median survival duration was 9.1 months and was comparable to historical data.(20) Therefore, this approach has been shown to be feasible and safe in patients with recurrent GBM. However, there are no large scale studies or randomized clinical data to support these findings, and there are functional limitations to this approach including isolation of patient during the treatment as well as a second surgery to remove the system once the treatment has been completed.

The application of brachytherapy remains limited mainly due to its invasiveness, compared to SRS and fSRT that are virtually non-invasive. There are several retrospective studies that have reported that SRS is associated with a prolonged survival in patients with recurrent GBM, with median survival times ranging from 7.5 to 30 months.(21-23) some of the studies have also reported that patients with recurrent GBM treated with SRS required fewer surgical procedures along with the prolonged survival benefit as compared to untreated patients.

There have also been a few studies that focused on the combination of chemotherapy with SRS and fSRT for recurrent GBMs. One prospective study of SRS in conjunction with marimastat for recurrent GBM showed no survival advantage for patients with recurrent GBM.(16) Other trials have shown that the multimodality treatment of SRS, radiotherapy, and chemotherapy is feasible, well tolerated, and achieves survival times similar to those for other treatment modalities.(24-26)

Radiation therapy may have an increased therapeutic effect with the introduction of newer chemotherapeutic agents that include radiosensitizers, targeted molecular agents and anti-angiogenic agents.(27-29)

Nevertheless, adjuvant chemotherapy is a necessary part in the treatment of GBM as there are several limitations to RT that include the infiltrative nature of GBM, the risk of radiation necrosis, radiation-induced permanent neuronal damage, as well as the radio-resistance of some tumors.

Chemotherapy

In attempts to further improve survival beyond that offered by RT, many chemotherapeutics have been tested for effectiveness in the treatment of GBM. Among these, alkylating agents have demonstrated some benefit. Either chloroethylating drugs like carmustine or methylating agents like temozolomide, are used in the majority of GBM clinical protocols.(30)

A major hindrance to the use of chemotherapeutic agents is the fact that the blood-brain barrier effectively excludes many agents from the CNS, resulting in dose-limiting side effects in order for such agents to adequately penetrate the CNS. Therefore, novel methods of intracranial drug delivery are being developed to deliver higher concentrations of the desired chemotherapeutic agent while minimizing the adverse systemic effects experienced.

In a landmark randomized trial, Stupp et al. reported that the addition of concomitant and adjuvant temozolomide is associated with an increase in the overall survival of patients with GBM who received radiotherapy and temozolomide by about 2 months compared to radiation therapy alone (14.6 months vs. 12.1 months). The median progression-free survival of GBM patients who received concomitant and adjuvant temozolomide was also improved by about 2 months compared to those who received radiation therapy alone (6.9 months vs. 5 months). The difference between the two groups was statistically and clinically significant. The survival of GBM patients who received

concomitant and adjuvant temozolomide with RT is superior to RT alone across all clinical prognostic subgroups.(3, 31) Based on this trial, many international centers started to change their approach to GBM treatment and started to include temozolomide as concomitant and adjuvant chemotherapy.

Currently, there are other experimental therapeutic modalities under investigation in an effort to improve outcomes for GBM patients. Such modalities include gene therapy, synthetic chlorotoxins, peptide and dendritic cell vaccines, and radiolabeled drugs and antibodies.(32-37)

Chapter 4

Methods

The conducted study is based on two Canadian cities: Edmonton and Halifax. In Edmonton we included GBM patients whom were treated at the University of Alberta Hospital, Royal Alexandra Hospital, and the Cross Cancer Institute. In Halifax we included the patients whom were treated at Queen Elizabeth II Health Sciences Center. The population of the study was all the patients whom were diagnosed with GBM in any hospital of the hospitals mentioned above. The intervention was concomitant and adjuvant temozolomide for GBM patients. The control group was GBM patients who received radiotherapy with or without chemotherapeutic agents other than concomitant and adjuvant temozolomide. The outcome was the overall survival in each group.

Study design

The study is conducted in Edmonton, Alberta was a retrospective cohort study based on chart and database review of GBM patients who were treated at University of Alberta Hospital, Royal Alexandra Hospital, Cross Cancer Institute (all in Edmonton) and Queen Elizabeth II Health Sciences Center in Halifax. The data in Halifax was prospectively collected while all the data in Edmonton was retrospectively collected. The time line of the study included GBM patients whom were treated between 2000 and 2006 in those centers. The diagnosis of GBM had to be confirmed by a tissue sample and was not based on only radiological suspicion.

The data collected included 130 GBM patients from Halifax and 216 GBM patients from Edmonton. The total number of patients (n=346) was classified into three groups based on the treatment they received. The first group composed of patients who had surgical intervention only (biopsy or resection). The second group of patients included the GBM patients who had both surgery (biopsy or resection) and radiation therapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide. The third group of patients included those who received the standard treatment, which is concomitant and adjuvant temozolomide with radiotherapy. The reason of combining the patients that received radiotherapy only and those that received any chemotherapeutic agent other than concomitant and adjuvant temozolomide into one group is based on the lack of evidence of any chemotherapeutic agent that showed any significant increase in the survival of GBM patients for the last two decades. Therefore, all chemotherapeutic agents other than concomitant and adjuvant temozolomide were considered as non-successful interventions and in 2001, the Medical Research Council trial concluded that no-chemotherapy control arms remain ethical in randomized trials in high-grade astrocytoma for lack of prolongation of survival with chemotherapeutic agents.(38)

Inclusion Criteria

- Patients who are 18 years or older.
- A tissue diagnosis of GBM must have been made (obtained either through biopsy or resection).

- Patients that were treated at University of Alberta Hospital, Royal Alexandra Hospital, and the Cross Cancer Institute in Edmonton and at the Queen Elizabeth II Health Sciences Center in Halifax.

Analysis

Kaplan Meir curves were used to describe the survival experience of the three groups. Cox's proportional hazard models were used for the multivariate analysis. These methods allowed for inclusion of censored data. The outcome for the survival was death after surgery and if a patient did not die during the follow-up it was considered as censored. The censored time was defined as the time between the date CT or MRI to the date when patient lost to follow up or patient being alive at the end of study (March 31,2009).

The variables that were collected are two types: continuous and categorical. The continuous variables were age, duration of the symptoms (weeks), time to surgery (days), time to radiotherapy (days). The categorical variables are gender, presence of seizure (yes or no), type of surgery (biopsy vs. resection), use of temozolomide (yes or no), time of entry (before or after 2004), centre (Edmonton or Halifax), and entry into clinical trial (yes or no).

The time to surgery variable was considered as the time from the date of diagnosis, which is when the patient had computed tomography (CT) or magnetic resonance imaging (MRI), to the date of surgery. The time to radiation therapy was from the date of diagnosis, which again is the date of CT or MRI, to the date where radiotherapy was started. Also, regarding the time factor, we dichotomized

this variable into two categories: the first category is before 2004 and the second category is after 2004. The reason for having 2004 as the cut-off point in the time factor variable is based on the date of initial publication of the Stupp trial where most of the international centers started to change their practice based on that study.(39) Therefore, we dichotomized the time factor variable to avoid any bias that may occur due to the change in practice that was experienced.

Purposeful model building was used upon running the multivariate analysis where we included the variables with p-values ≤ 0.2.

Chapter 5

Results

There were 346 patients included in the study; 216 were from Edmonton (63%) and 130 (37%) patients were from Halifax (Figure 5.1A). Of the total number of the patients, 329 (95%) patients died and 17 (5%) patients were censored (Figure 5.1B). The censored patients fell into two categories: 11 patients were lost to follow up and 6 patients are still alive. The mean and median age of patients was comparable in both centers. The mean age of patients in Edmonton was 61 years and standard deviation of 12 years, with a median age of 63 years (IQR=18 years). The mean age of patients in Halifax was 60 years and standard deviation was 11 year, with a median age of 61 years (IQR=13). The mean number of GBM symptoms duration in patients was 5 weeks where SD was 6 weeks in Edmonton with a median of 3 and IQR of 4 weeks whereas the mean of symptom duration in patients in Halifax was 8 weeks where SD was 9 weeks with a median of 4 weeks and IQR of 6(Table 5.1 and Figure 5.8).

With regards to patients' gender, there were 216 male patients and 130 female patients. In Edmonton, there were 135 (62%) male patients and 81 (38%) female patients In Halifax there were 81 (62%) male patients (62%) and 49 (38%) female patients (Figure 5.1C).

Regarding the presence of seizures in the patient's presentation, 146 (68%) patients in Edmonton presented without any seizure, while 70 (32%) patients presented with seizures as their main symptom or had seizures as part of their

presentation. In Halifax 92 (71%) patients presented without any seizures, while 38 (29%) patients presented with seizures as their main symptom or had seizures as part of their presentation (Figure 5.1D).

Stratifying patients based on the type of intervention received revealed that 53 (25%) patients in Edmonton underwent only the surgical intervention (resection or biopsy). The majority of patients in Edmonton, 128 (59%) patients, had the second category of intervention, receiving radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide. In total, 35 (16%) patients underwent the gold standard treatment, i.e. surgery, radiotherapy and concomitant and adjuvant temozolomide in Edmonton. Again, the percentages were comparable between the two centers with 23 (18%) patients receiving surgical intervention in Halifax, In Halifax, 93 (71%) patients received underwent radiation therapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide and 14 (11%) patients received the gold standard treatment (Figure 5.1E).

In Edmonton, 143 (66%) patients underwent surgical resection of their GBM. This number was comparable to the percentage of patients that underwent resection in Halifax, where 83 (64%) patients underwent surgical resection. The patients who underwent biopsy only included 73 (34%) patients in Edmonton and 46 (36.2%) patients in Halifax (Figure 5.1F).

In Edmonton, the mean time to surgery, which was calculated from the time of diagnosis on CT or MRI to the date of surgery, was 11 days (SD=16) and

median time was 6 days. In Halifax the mean and median time of surgery was 7, 5 days respectively (SD=11).

Further description of the data, based on the type of management is illustrated in Tables 5.2 and 5.3.

Univariate analysis

The descriptive analysis using the Kaplan Meir survival curves (Figure 5.2) in the survival distribution showed no significant difference between the two centres (HR 1.00, 95% CI: 0.80-1.26). There was also no statistical significance in the survival distribution between the male and females (HR 1.03, 95% CI 0.82-1.28) which is also described by Kaplan-Meier curves (Figure 5.3). Patients' age was found to be significantly associated with survival with 2% increase in the risk of death for one year increase in age (HR 1.02, 95% CI: 1.01-1.03).

As shown in Figure 5.4, The presence of seizure in patient's presentation showed a protective effect with 22% reduction in the risk of death for patients with seizure in comparison to those without seizure (HR 0.78, 95% CI: 0.61-0.97). As shown in Figure 5.5, patient involvement in trials showed statistical significance in survival distribution for those who participated in trials compared to those who did not (HR 0.56, 95% CI: 0.43-0.71). The time to surgery and duration of symptoms were not significantly associated with survival distribution.

In regards to type of management, KM curves (Figure 5.6) showed significant difference between the 3 groups as we considered the group of patients that received radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide to be the reference group. Therefore, the patients who received surgery only had a (HR of 5.5, 95% CI: 4.11-7.28), where the patients who received standard treatment of concomitant and adjuvant temozolomide (HR 0.59, 95% CI: 0.42-0.82).

As shown in Figure 5.7, The nature of the surgical intervention showed statistically significant difference between the biopsy and resection groups where the resection was found to have a protective mechanism vs. underwent biopsy (HR 0.52, 95% CI: 0.41-0.65).

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 5.4).

The factor of age was not different from the univariate analysis (HR 1.02, 95% CI: 1.00-1.023). The presence of seizure revealed a (HR 0.88, 95% CI: 0.55-0.89) in those who presented with seizure or being part of their presentation vs. patients who had no seizures at presentation. The surgery type had an (HR 0.5 95% CI: 0.39-0.64) for patients who had resection compared to those who had biopsy. Regarding the type of management received, the group of patients that

received radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide was considered to be the reference group. Therefore, the patients who received surgery only had a (HR of 5.2, 95% CI: 3.85-7.06), where the patients who received standard treatment of concomitant and adjuvant temozolomide the (HR 0.52, 95% CI: 0.37-0.74). The factor of trial involvement also showed significance in the multivariate analysis (HR 0.74, 95% CI: 0.57-0.96). While running the model, both the center variable (Edmonton vs. Halifax) and the time factor variable (before and after 2004) were kept in the model at all steps. Both factors were not significant and did not affect the significance of the variables mentioned above.

The mean of the overall survival in patients who received radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide in Edmonton was 380 days, with a median of 288 days. In Halifax, the mean of the overall survival of the same group was 348 days, with a median of 264 days. In Edmonton, the mean of overall survival in the group that received standard treatment was 574 days, with a median of 505 days. In Halifax, the mean of overall survival in the same group was 524 days with a median of 335 days. In regards to patients who had surgery only as their intervention, their mean of survival in Edmonton was 89 days and the median was 51 days where in Halifax the mean was 81 days and the median was 77 days.

Table 5.1 Distribution of age, symptoms duration and time to surgery.

covariate	Mean	Median	Standard Deviation
Age (years)			
Edmonton	61	63	12
Halifax	60	61	11
Symptoms duration(weeks)			
Edmonton	5	3	6
Halifax	7	4	9
Time to Surgery (days)			
Edmonton	11	6	16
Halifax	7	5	9

Table 5.2 Median of covariates by the type of management.

Covariate	Surgery Only	Surgery, RT +/- others *	Surgery, RT, TMZ†
Age (years)	65	63	56
Symptoms duration (weeks)	4	4	4
Time to surgery (days)	7	5	4

* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

Table 5.3: Characteristics of patients by treatment groups.

covariate	Surgery Only	Surgery, RT+/- others*	Surgery, RT, TMZ†
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)

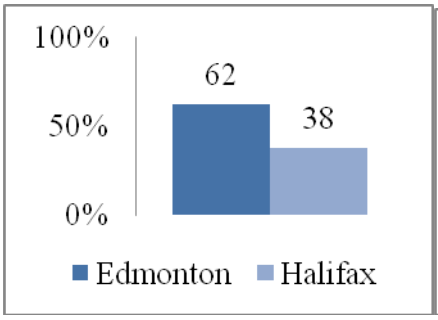
N.B: Numbers between brackets indicate percentages and all are rounded.

* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

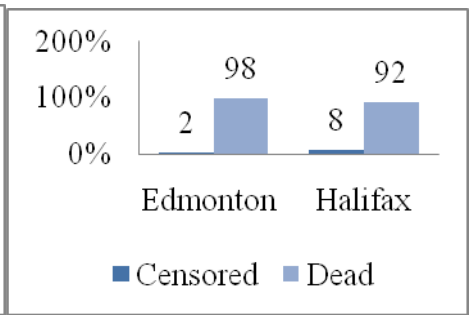
†RT: radiation therapy. TMZ: temozolomide.

Figure5.1: Distribution of outcome by patients' characteristics.

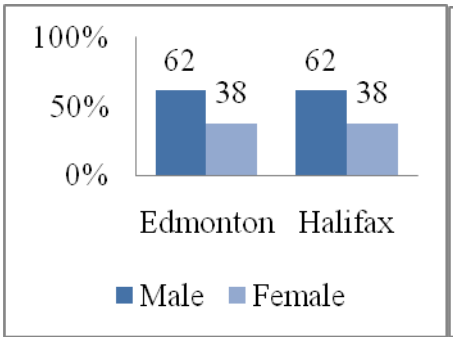
A) Total patients



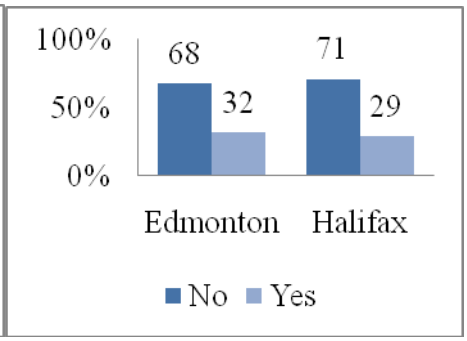
B) outcome by center



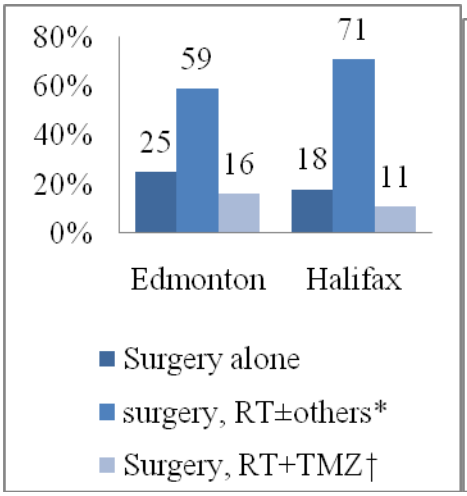
B) by gender



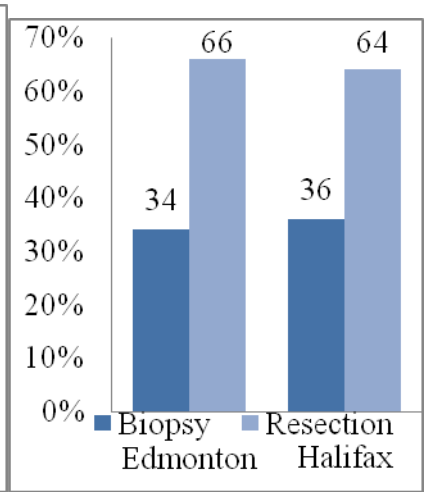
D) by presence of seizure



E) By management type



F) by surgery type



* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

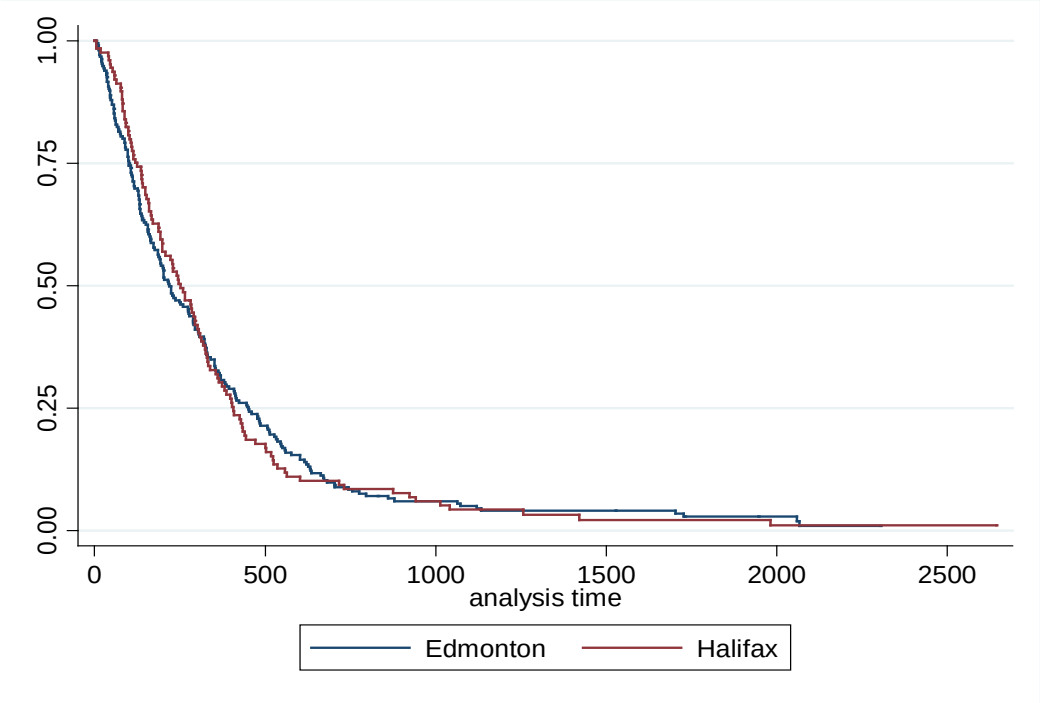


Figure 5.2: Kaplan Meir estimates of survival by center. (p-value=0.94)

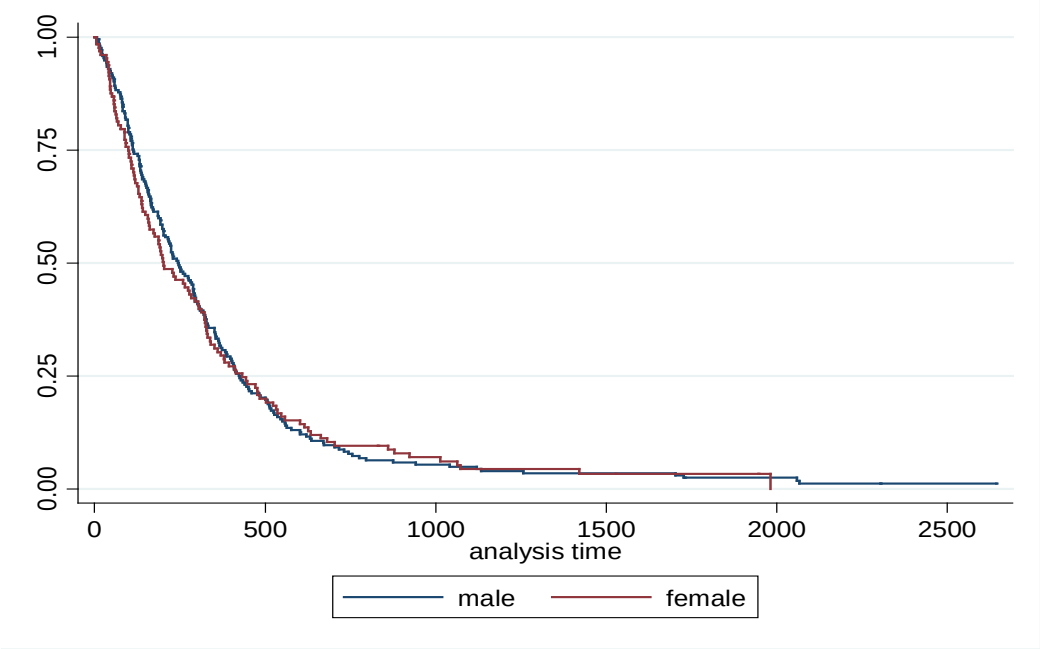


Figure 5.3: Kaplan Meir survival estimates of survival by gender. (p-value=0.79)

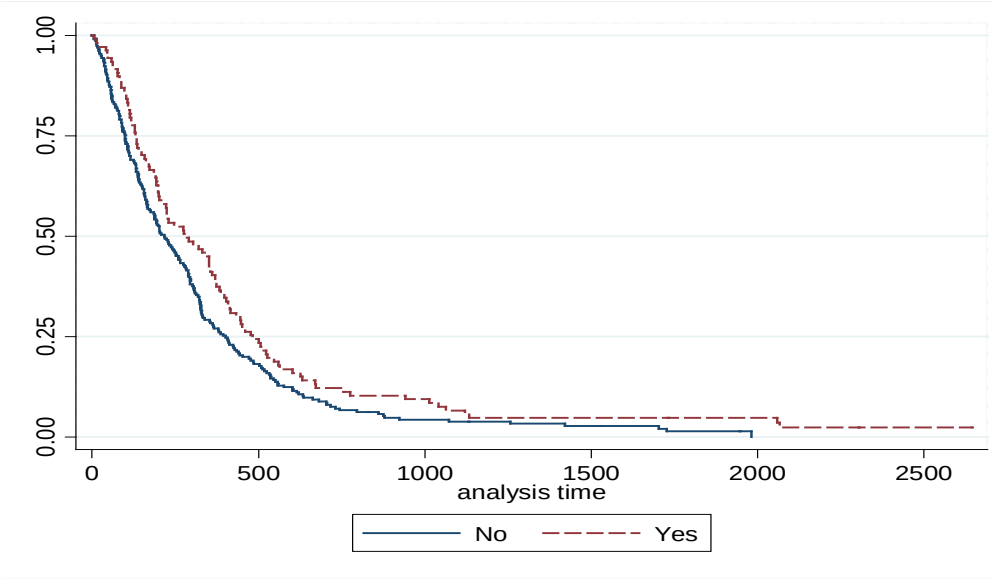


Figure 5.4: Kaplan Meir survival estimates of survival by presence of seizure. (p-value=0.03).

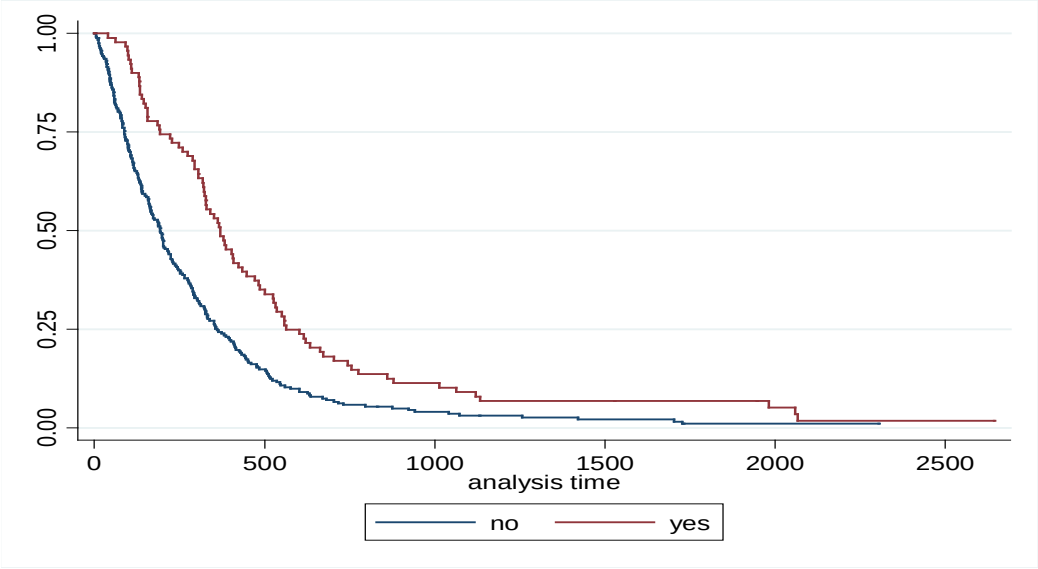


Figure 5.5: Kaplan Meir estimates of survival by participation in trials. (p-value <0.0001).

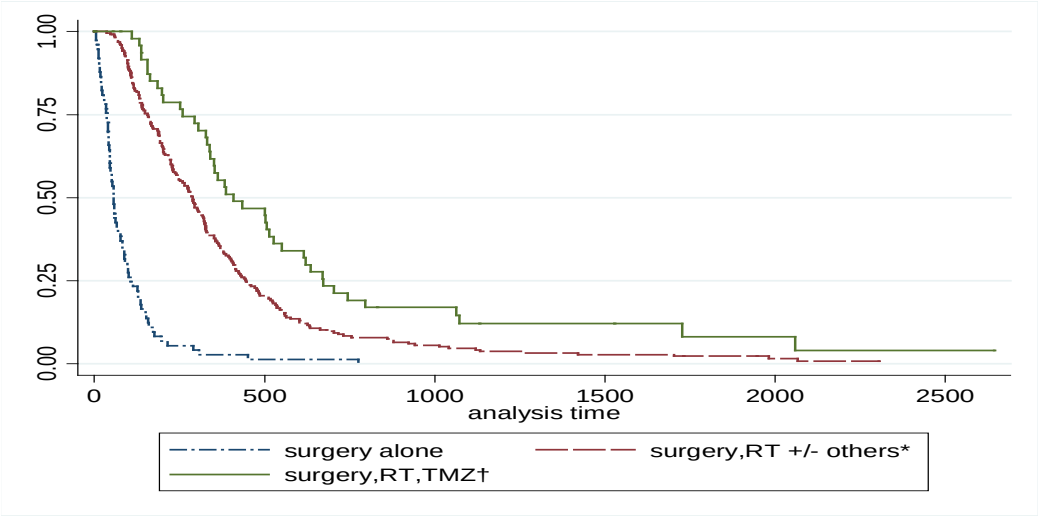


Figure 5.6: Kaplan Meir estimates of survival by type of management. When RT +/- others is the reference, (p- value for surgery alone <0.0001; p- value for surgery, RT and TMZ =0.002).

* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

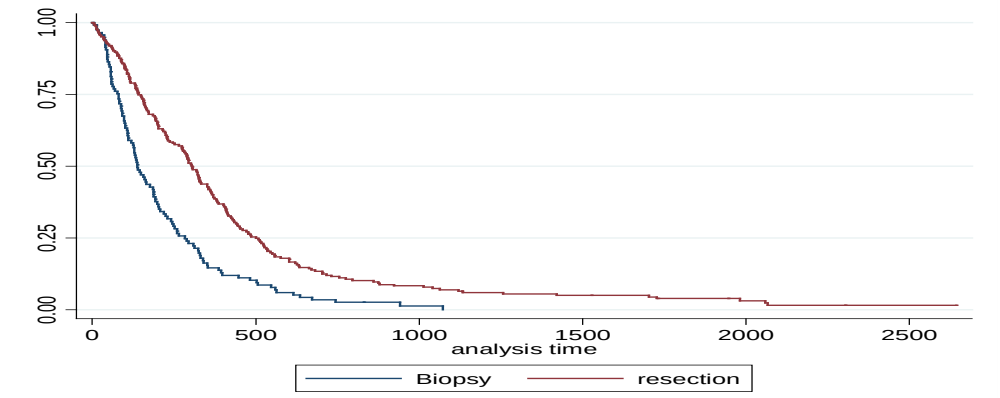


Figure 5.7: Kaplan Meir estimates of survival by type of surgery. (p- value <0.0001).

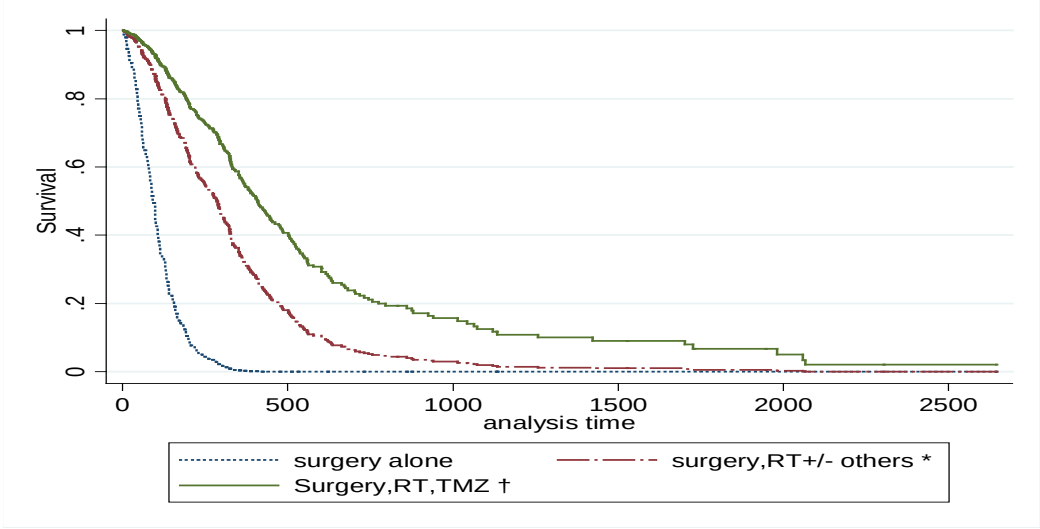
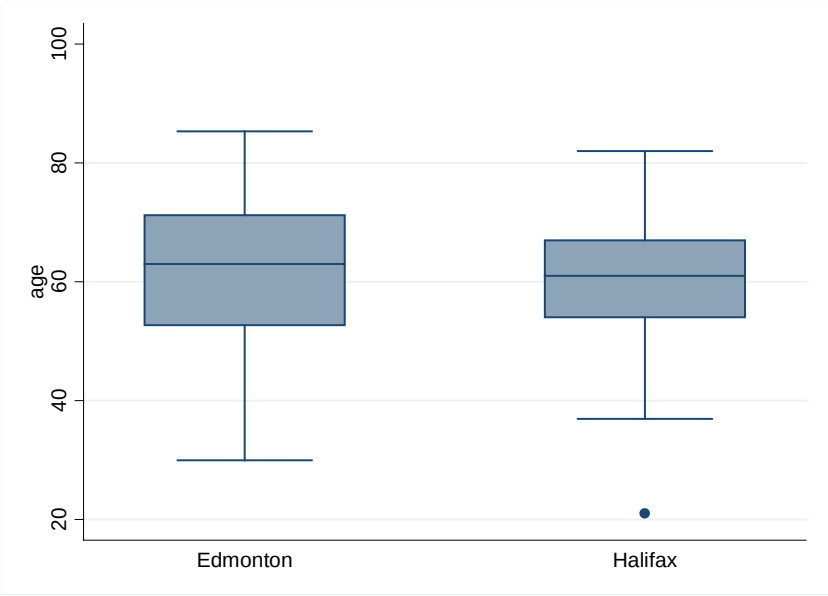


Figure 5.8: Adjusted estimates of survival from Cox's proportional hazards regression of the overall study patients. (p- value <0.0001 for Surgery alone vs. +/- others <0.0001; p-value <0.0001 for Surgery, RT, TMZ vs. RT +/- others)

* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

A)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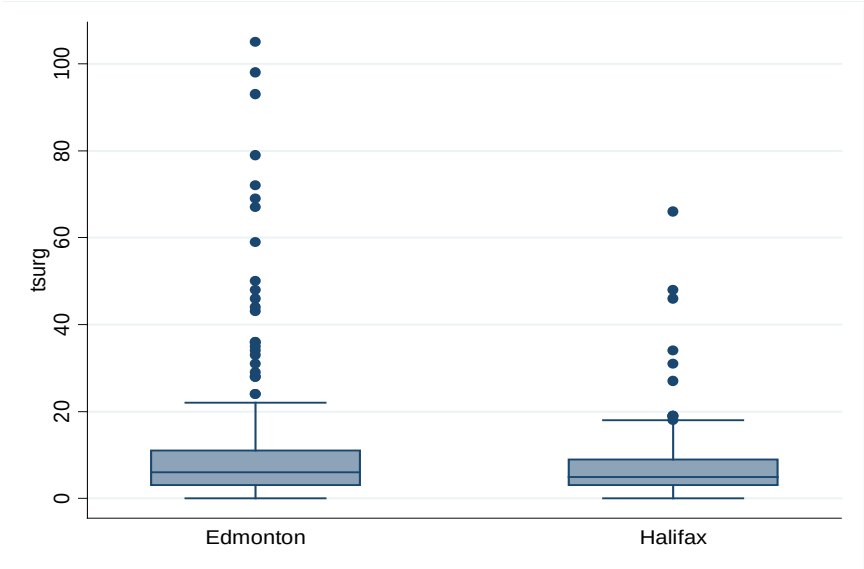
B)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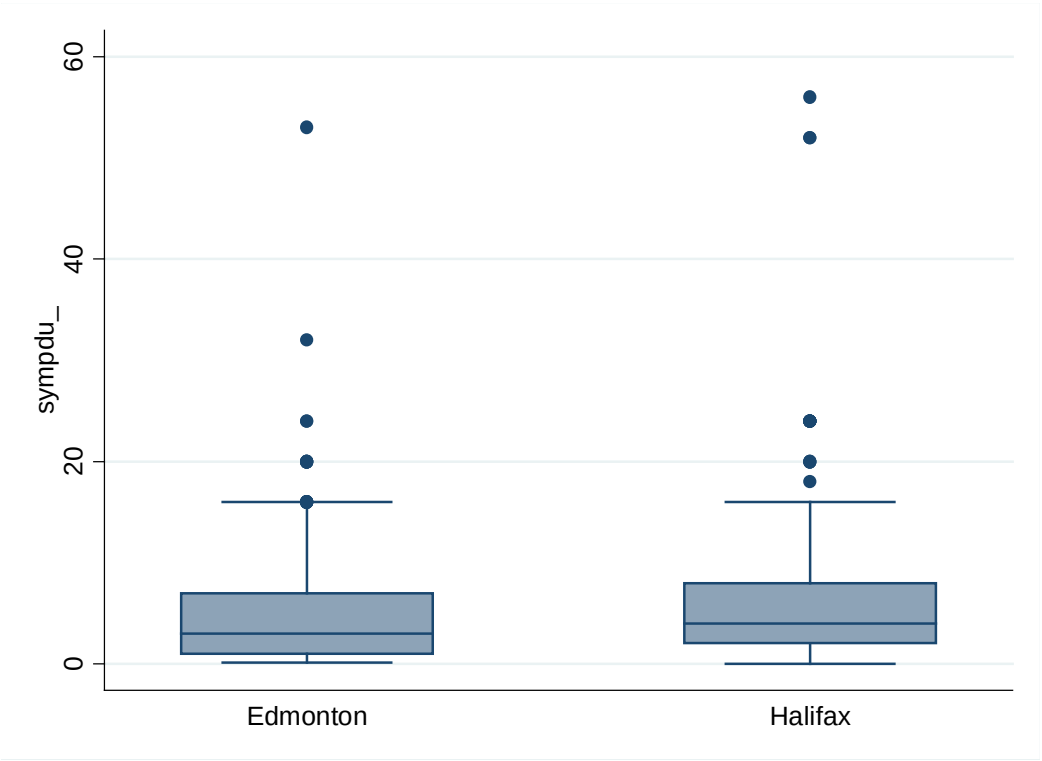


Figure 5.9: Box and whisker plots for age (A), time to surgery (B) and symptoms duration (weeks) (C).

Table 5.4: Significant predictors of survival from the multivariate analysis.

Covariate	**Hazard Ratio and Percentage (%)**	**95% CI**	**P.value**
Age	1.02 (-)	1.00-1.023	0.01
Seizure Reference group NO	0.88 (31)	0.55-0.89	0.004
Surgery type Reference group Biopsy	0.50 (65)	0.39-0.64	<0.0001
Type of management*			
-Surgery alone	5.2 (22)	3.85-7.06	<0.0001
-Surgery, RT, TMZ†	0.52 (14)	0.37-0.74	<0.0001
Trials Reference group NO	0.74 (27)	0.57-0.96	0.02

* Reference group was the group received RT with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide

†RT: radiation therapy. TMZ: temozolomide

Chapter 6

Time to Radiation (Sub group analysis)

Introduction

In this chapter, a subgroup analysis in conducted for those patients who received radiation as part of their treatment. Of the total number of patients (n = 346), there were 267 patients who received radiation therapy. The main objective of the subgroup analysis is to compare those patients who received radiation therapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide with those patients who received the standard therapy of concomitant and adjuvant temozolomide.

Results

In this subgroup analysis, there were 267 patients, 161 (60 %) patients were from Edmonton, and 106 (40 %) patients from Halifax (Figure 6.1A). Out of this total number, 253 (98 %) patients died and 6 (2 %) patients were censored and based on site 155 (96%) patients died in Edmonton and 6 censored (4 %) where in Halifax 98 (93%) patients died and 7 (7%) patients censored (Figure 6.1B).

The age of the patients is higher in Edmonton compared to Halifax. The mean age in Edmonton is 61, with a median age of 63; SD was 11 and IQR of 17. In Halifax the mean age is 58, with a median age of 59, SD was 11 and IQR of 14. It also seemed that patients are presenting later to hospital in Halifax compared to Edmonton. The mean of symptom duration in Halifax is 8 weeks with a median of

4 weeks ,SD was 10 and IQR of 7, where in Edmonton the mean of symptom duration is 5 weeks with a median of 3 weeks , SD was 6 and IQR of 5 (Table 6.1).

There was some male predominance in both sites. There were 103 (64%) males in Edmonton and 58 (36%) female patients. In Halifax there were 70 (66%) males and 36 (34%) female patients (Figure 6.1C).

A total of 104 (65%) patients in Edmonton presented with no seizures, and a total of 75 (71%) patients presented with no seizures or seizure symptoms in Halifax. A total of 57 (35%) patients presented with seizures in Edmonton, and 31 (29%) patients in Halifax presented with seizures (Figure 6.1D).

In Edmonton, 126 (78%) patients were offered radiotherapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide, whereas in Halifax, 92 (87%) patients were offered this. For the gold standard treatment, 35 (22%) patients received it in Edmonton, but in Halifax only 14 (13%) patients received the gold standard treatment (Figure 6.1E).

. There were 47 (29%) patients in Edmonton that were offered biopsy and 114 (71%) patients were offered GBM resection (Figure 6.8). Similar results were found in Halifax with 34 (32%) patients offered biopsy and 72 (68%) patients offered resection (Figure 6.1F)

A larger portion of patients in Edmonton were involved in trials with 68 (42%) patients involved in trials (diagnostic or therapeutic) while in Halifax there

was only 19 (18%) patients who were involved in trials. On the basis of initiating temozolomide as the standard treatment and considering the year 2004 as a cut off point between the 2 groups regarding the time factor, there we 76 (72%) patients whom were treated before 2004 in Halifax and 30 (29%) patients who received treatment after 2004. In Edmonton there were 100 (62%) patients that were treated before 2004 and 61 (38%) patients that were treated after 2004.

The time to surgery is shorter in Halifax, where the patients were operated on in a mean time of 7 days with a median of 5 days. In Edmonton the time to surgery is 12 days with a median of 7 days. However, in Edmonton the time to radiotherapy was shorter with a mean time of 52 days with a median of 48 days. In Halifax, the time for patients to be started on radiotherapy is longer with a mean of 68 days and a median of 44 days (Table 6.1). Further description of the data by type of management is illustrated in (Table 6.2 and Table 6.3).

The univariate analysis again showed no significant difference between the two centers and the gender as well (Figure 6.2, 6.3). However, the following variables showed a significant relationship with the patient survival in the univariate analysis: age (HR 1.02, 95% CI: 1.01-1.03), involvement in trials (HR 0.68, 95% CI: 0.52-0.89) (Figure 6.4) type of management (gold standard treatment (HR 0.58, 95% CI: 0.41-0.81) (Figure 6.5) and the type of surgery, surgical resection (HR 0.53, 95% CI: 0.40-0.70, compared to the biopsy group (Figure 6.6).

In the multivariate analysis, we included all the variables with $p \leq 0.2$. There were a total of eight variables and we kept the center and the time factor variables always in the model to see if they will affect the significance of the other variables. The variables were: age, symptom duration, and the presence of seizures, the type of surgery, the type of treatment, patient involvement in trials, the time to surgery, and the time to radiation therapy. The final model showed that four variables were statistically significant in contributing to the survival of GBM: age (HR 1.02, 95% CI: 1.01-1.03), the type of surgery ;resection group (HR 0.50, 95% CI: 0.37-0.66) in comparison to biopsy group), the type of management received ;gold standard (HR 0.53, 95% CI 0.38-0.75) in comparison to radiation therapy with or without any chemotherapeutic agent other than concomitant and adjuvant temozolomide) and the time to radiation therapy (HR 0.95, 95%CI 0.91-0.99).

Table 6.1: Distribution of age, symptoms duration and time to surgery by centre.

covariate	Mean	Median	Standard Deviation
Age (years)			
Edmonton	61	63	11
Halifax	58	59	11
Symptoms duration(weeks)			
Edmonton	4	3	6
Halifax	8	4	10
Time to Surgery (days)			
Edmonton	12	5	18
Halifax	7	5	9

Table 6.2: Median of covariates by the type of management for patients received radiotherapy.

covariate	Surgery, RT+/- others *	Surgery, RT, TMZ†
Age (years)	63	56
Symptoms duration (weeks)	4	4
Time to surgery (days)	5	4
Time to radiation therapy	45	49

* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide.

Table 6.3: Characteristics of patients by treatment groups. *

covariate	Surgery Only	Surgery, RT+/- others†	Surgery, RT, TMZ‡
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)

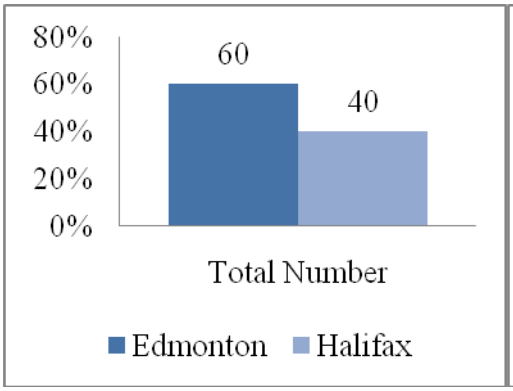
*N.B: Rounded percentages are indicated in parenthesis.

† RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

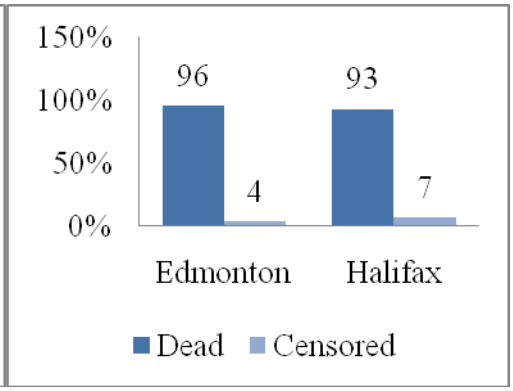
‡RT: radiation therapy. TMZ: temozolomide.

Figure 6.1: Distribution of outcome by patients' characteristics.

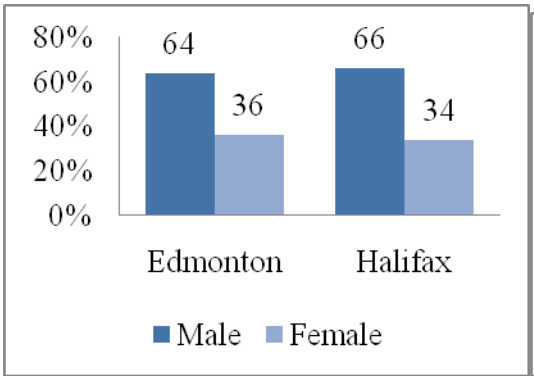
Total patients



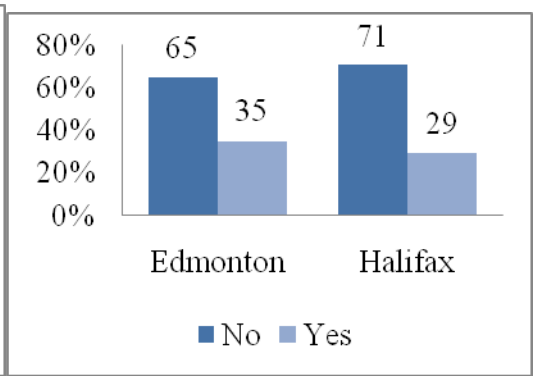
B) by center



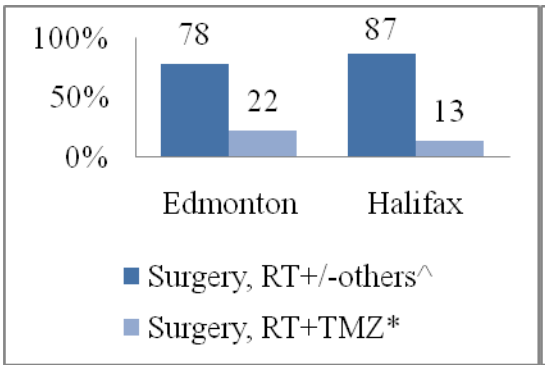
C) By gender



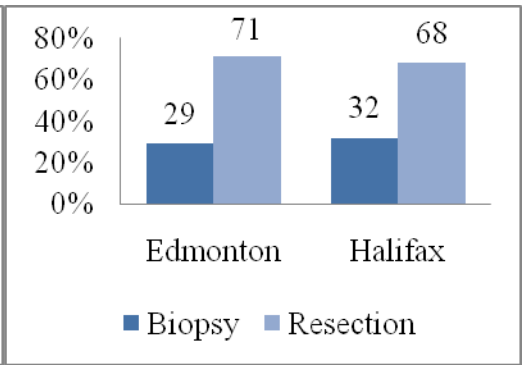
D) By presence of seizure



E) By management type



F) by surgery type



* RT +/- others: radiation therapy with or without chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

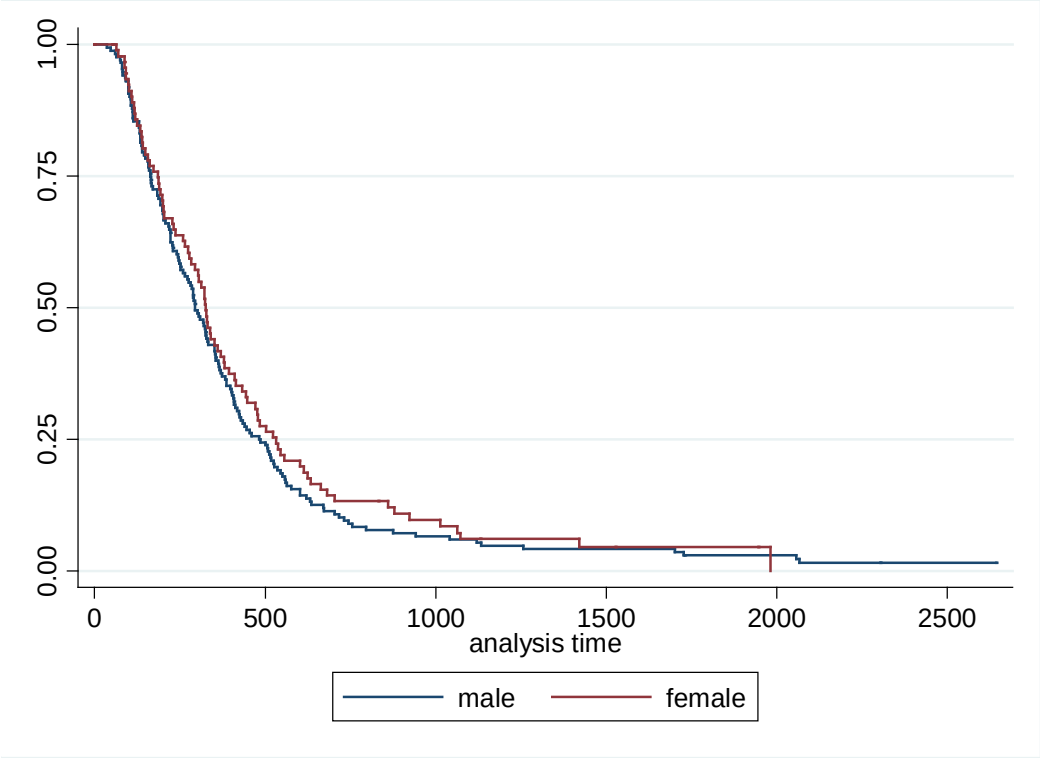


Figure 6.2: Kaplan Meir estimates of survival by gender. (p- value=0.42)

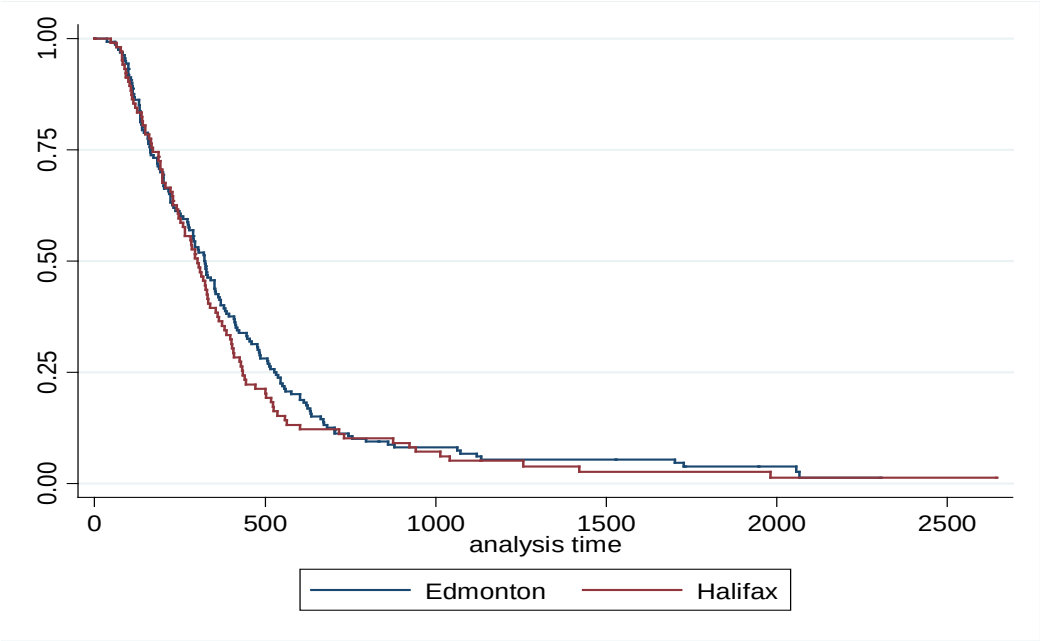


Figure 6.3: Kaplan Meir estimates of survival by center. (p- value=0.35).

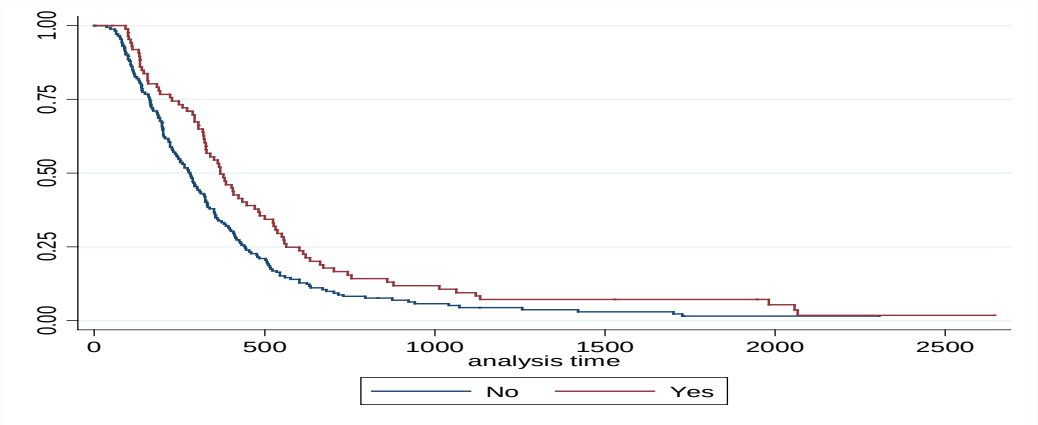


Figure 6.4: Kaplan Meir estimates of survival by participation in trials. (p- value =0.005).

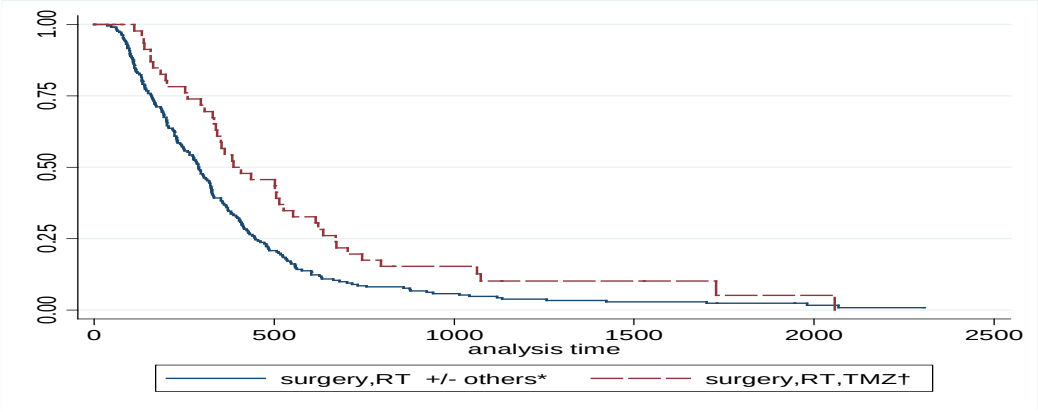


Figure 6.5: Kaplan Meir estimates of survival by type of management. (p- value =0.001.)

* RT +/- others: radiation therapy plus or minus chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide

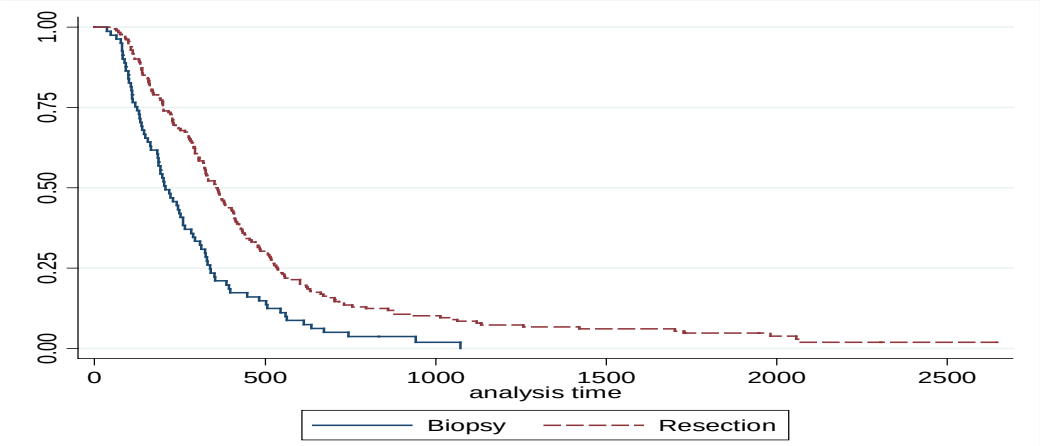


Figure 6.6: Kaplan Meir estimates of survival by type of surgery.(p-value<0.0001).

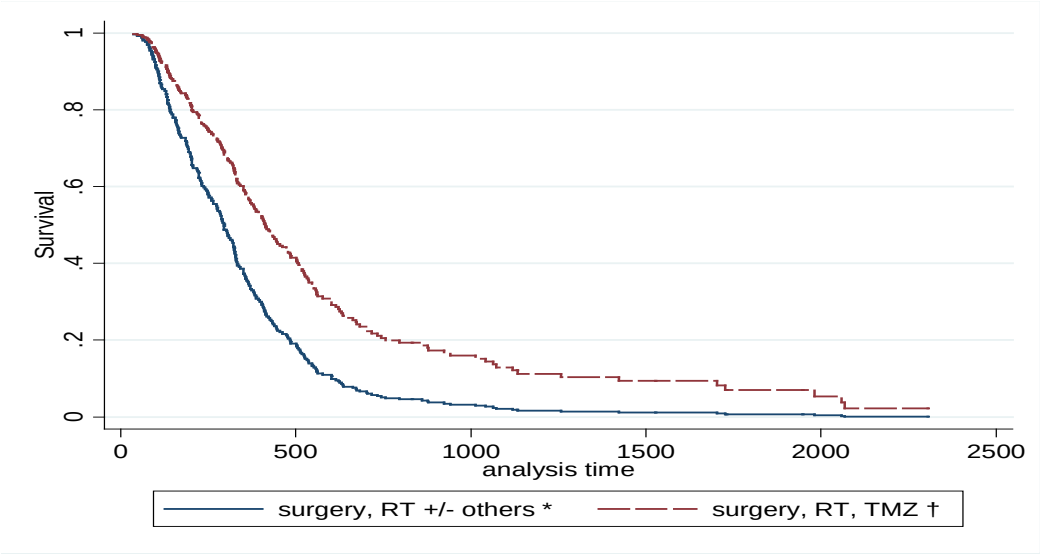
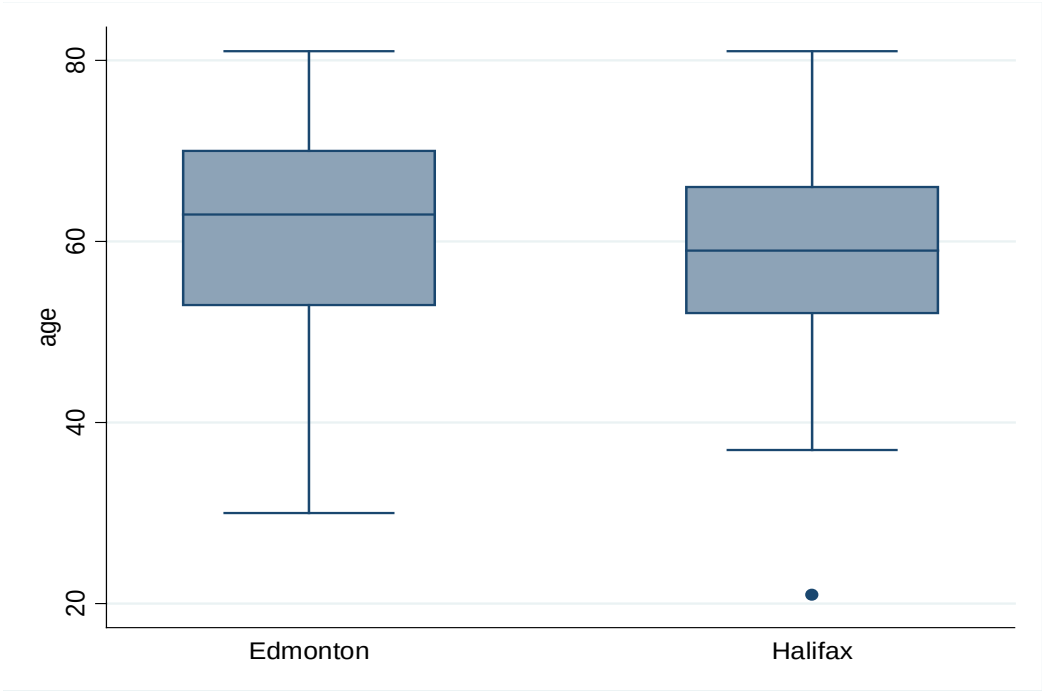


Figure 6.7: Adjusted estimates of survival from Cox's proportional hazards regression of the subgroup patients. (p-value =.0.001).

* RT +/- others: radiation therapy plus or minus chemotherapeutic agent other than concomitant and adjuvant temozolomide.

†RT: radiation therapy. TMZ: temozolomide.

A)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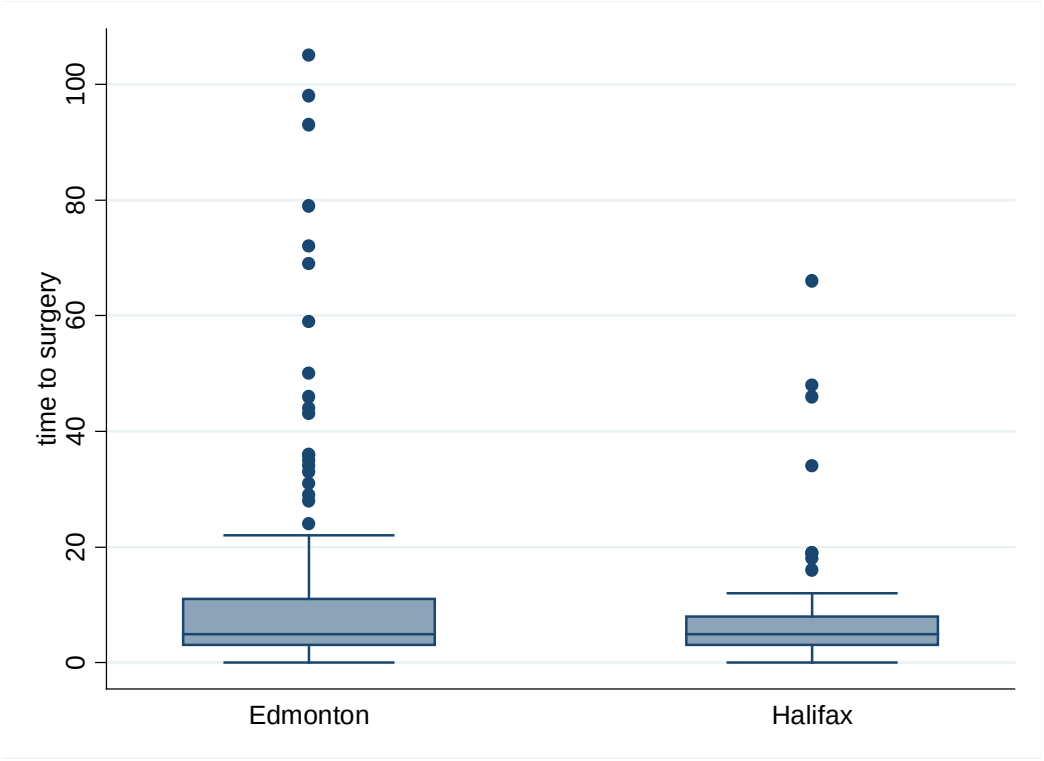
time to surgery
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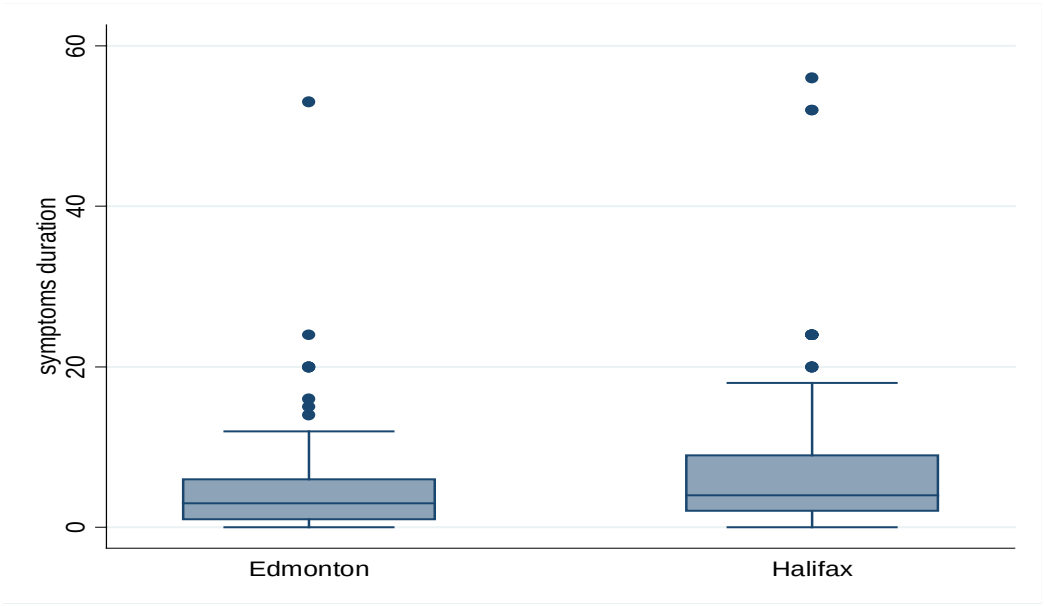
C)



D)

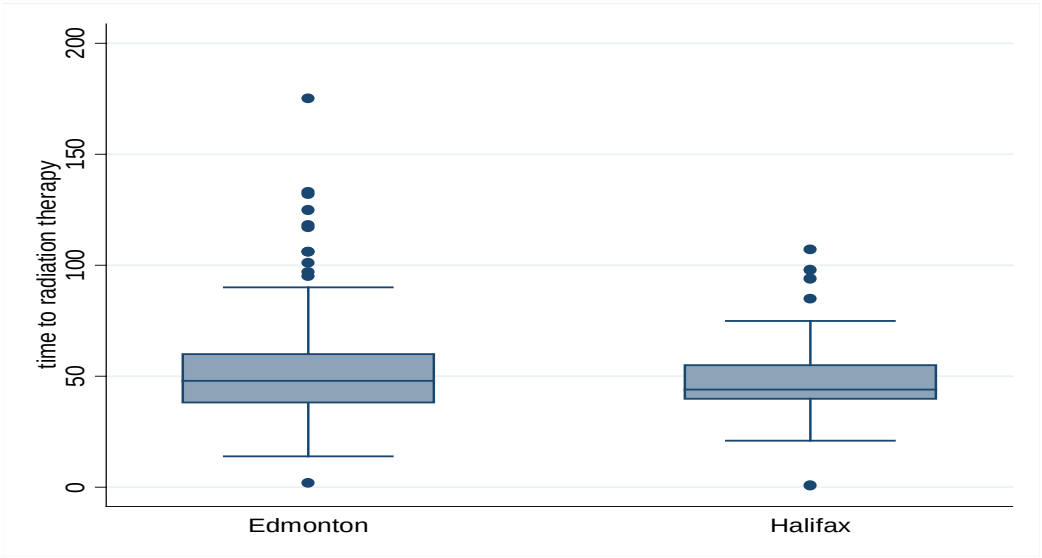


Figure 6.8: Box and whisker plots for age (A), time to surgery (B), symptoms duration (weeks) (C), and time to radiation therapy (days) (D).

Table 6.4: Significant predictors of survival from the multivariate analysis.

Covariate	**Hazard Ratio and Percentage (%)**	**95% CI**	**P.value**
Age	1.02 (-)	1.01-1.03	<0.0001
Surgery type Reference group: Biopsy	0.50 (70)	0.37-0.67	<0.0001
Type of management *	0.53 (18)	0.38-0.75	<0.0001
Time to radiation(weeks)	0.95 (-)	0.91-0.99	0.048

*reference group is standard treatment group received surgery, radiation therapy and temozolomide.

Chapter7

Discussion

There are a few randomized controlled trials in GBM literature that showed a clinical and statistical significance in the improvement patient survival. It is no doubt that the study conducted by Stupp et al is considered as a landmark paper in the history of GBM literature. Since the publication of Stupp et al's results, between 2002 and 2004, many centers around the world started to change their practice in the treatment of GBM to include surgery, radiation therapy and concomitant and adjuvant temozolomide therapy.

In our retrospective cohort study, multiple factors were found to affect and assist in predicting the overall survival of GBM patients. The overall results in both centers showed that age is a significant factor in the prediction of survival with each unit increase in age (one year) there is a 2% increase in the hazard ratio. This has been reported in many observational studies in the literature. The presence of seizures at the time of presentation, being the only symptom at presentation or part of the overall patient's presentation, showed a protective mechanism where it reduced the hazard ratio by 12% compared to those patients who did not have seizures as their presentation or part of their presentation. 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.

The type of surgery, which was dichotomized in our study to biopsy versus resection, showed a protective mechanism by a 50% reduction in the hazard ratio for patients who had resection compared to the patients that underwent biopsy only. The resection group in our study combined both groups of patients who either had a subtotal or a total resection. Despite that, the significance of this factor of predicting survival was very high ($p<0.0001$).

The involvement of patients in trials is a debatable factor in the current literature. There are many studies that show that patient involvement in trials is a positive prognostic factor where patients feel well supported and perceive a heightened degree of medical care. On the other hand, there are other studies in the literature that argues against this finding and reports that patient involvement in trials was not associated in any improvement with survival. Our study supports that patient involvement in trials was associated with a protective mechanism by reducing the hazard ratio by 26% in patients who were involved in trials compared to those patients who were not. Therefore, our study supports the first opinion that patient involvement in trials is beneficial to patient survival, as we did include both diagnostic and therapeutic trials in our study.

The option of going for surgery alone without pursuing other types of treatments showed the same results that have been reported over the last four to five decades, that surgery alone is associated with very short survival of GBM patients. The group of patients that received radiation therapy with or without any chemotherapeutic agents other than concomitant and adjuvant temozolomide

showed a significant difference compared to the group that received surgery alone ($p<0.0001$). The 6 months of addition survival that was noticed for the group of patients who received radiation therapy with concomitant and adjuvant temozolomide after surgery is well supported by the literature.

Gender, the duration of symptoms, and the time to surgery factors were not significant in the prediction of survival. We believe that the duration of symptoms was not a significant factor because of the presence of recall bias that distorts the accuracy of the data that the patients are providing to the treatment team. In regards to the insignificance of the time to surgery factor, this might be related to the short time between the diagnoses of GBM on CT or MRI to the time of being operated on.

Regarding the subgroup analysis (Chapter 6), most of the factors remained significant in the final model except for the presence of seizures and the patient involvement in trials.

The time to radiation therapy was significant in this subgroup analysis. Unfortunately there are no studies that looked specifically at the timing of radiation therapy and evaluated its importance in the prediction of survival. Some trials have included the time to radiation as a variable, but this factor was not defined appropriately as there was no specific definition for this time interval. In our study, the time to radiation therapy was calculated from the time of diagnosis from CT or MRI to the day of starting radiation therapy. In some of the randomized controlled trials they reported the mean time to radiation therapy as

being 5 weeks from the time of diagnosis. However, these studies did not clarify whether the time of diagnosis began from a diagnosis of GBM based on CT or MRI, or from the time of the final pathology report to the day of starting radiation therapy. Regardless, this factor gives the treating team an additional ability in improving the survival of patients in addition to the use of concomitant and adjuvant temozolomide.

In looking at each center alone, they were not far from the overall results. The only factor that was significant in the prediction of survival in the patients in Edmonton that was not significant in the prediction of survival in the patients in Halifax was age. We think that this is related to the younger age group of patients in Halifax who received concomitant and adjuvant temozolomide. The rest of the factors remained significant in the prediction of survival with a close hazard ration (surgery type, type of management, involvement in trials).

The time to receiving the final pathology report was thought to be an important factor in the prediction of survival because the radiation therapy cannot be started until the final pathology report is released. Unfortunately, the findings in the literature regarding this are lacking. In our study there were no collinearity between the time to radiation therapy and the time to the release of the final pathology report i.e. they were independent factors. Time to receiving final pathology report did not prove to be significant in the prediction of survival in GBM patients.

Strengths of the Study

This study is evaluating the efficiency of the Stupp et. al trial from the real life perspective. As mentioned above, it is always argued that patients in trials are always doing better for a variety of reasons.(40) Some of the discrepancy can be related to the fact that patients enrolled in trials are subject to extra care with their health concerns being immediately addressed and investigated when they are raised by the patients.(41) This difference may also be related to the psychological effect of patients experience based on the expectation that they are being looked after and assessed more carefully. (8)

The number of the patients in most of the GBM studies found in the literature is in the range from 100 to 300 patients.(42, 43) (44)However, randomized controlled trials have a higher number of patients included in their study, with the number of the patients reaching about 500 or more in most of the trials for GBM.(3, 45) Therefore, our total patient population of 346 is considered a relatively large sample size. Also having the study based on two Canadian tertiary care centers is bringing us closer to the idea of being able to generalize the findings to the entire Canadian population. Even though it is difficult to conclude that our findings are generalizable solely based on two cities, we hope to encourage the other Canadian centers to publish their experience with concomitant and adjuvant temozolomide treatment in GBM patients.

Limitations

The first limitation of study is the retrospective nature of it. The retrospective approach is known to be inferior to the prospective studies. The second limitation encountered is the lack of having complete data. We faced this issue in both the prospectively and retrospectively collected data. This issue has made some limitations in including some of the variables or excluding them from the study based on the availability of the data. The third limitation was the unavailability of the Karnofsky score in the charts. The Karnofsky score is known to be an important functional evaluation of the patients. Unfortunately it was not documented in the charts.

Forth; as the study is retrospective in nature, selection bias is present as well. It is present in many aspects, starting from the neurosurgeon that sees the patient and decides what type of surgical intervention is warranted (biopsy or resection). It is also present in the decision of the radiation oncologist on deciding if the patient requires radiotherapy as an intervention, and if so, what kind of radiotherapy implemented is affected as well (curative vs. palliative). From the neuro-oncologist's point of view, the decision to offer or not to offer chemotherapeutic agents is affected as well. Fifth is the recall bias which present in two variables: presence of seizure and the duration of symptoms prior to the presentation. The last limitation is the double nature of the data that was collected, as the data from Halifax was prospectively collected while the data from Edmonton was retrospectively collected.

Chapter 8

Conclusion

This retrospective cohort study showed that there are a few factors that the treating team can work on in trying to achieve longer survival for GBM patients. Surgical resection whenever possible, radiation therapy with concomitant and adjuvant temozolomide and shortening the time between diagnosis on CT or MRI and the time to initiation of radiation therapy are all important factors in improving the survival of GBM patients. The time to the release of the final pathology report still needs to be worked on and we hope that other centers either in Canada or abroad can report their results in this regards as this would aid the care centers in knowing the number of neuropathologists that are needed in each center based on the number of cases that are done.

Our results cannot be generalizable to the entire Canadian population, but we hope that this study will be followed by other studies that will involve more centers and compare the results of those centers to one another or for every center to publish their own experience in treating GBM patients with concomitant and adjuvant temozolomide in order to gain the real life perspective of such treatment.

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Appendices

Table 1: Significant predictors of survival from the multivariate analysis for Edmonton patients only.			
Covariate	**Hazard Ratio**	**95% CI**	**P.value**
Age	1.01	1.00-1.023	0.01
Seizure Reference group NO	0.88	0.55-0.89	0.004
Surgery type Reference group Biopsy	0.50	0.39-0.64	<0.0001
Type of management*			
-Surgery alone	5.2	3.85-7.06	<0.0001
-Surgery, RT, TMZ †	0.52	0.37-0.74	<0.0001
Trials Reference group:	0.74	0.57-0.96	0.02

* Reference group was the group received RT plus or minus chemotherapeutic agent other than concomitant and adjuvant temozolomide

† RT: radiation therapy. TMZ: temozolomide

Table 2: Significant predictors of survival from the multivariate analysis for Halifax patients only.

Covariate	Hazard Ratio	95% CI	P.value
Surgery type Reference group Biopsy	0.47	0.31-0.70	<0.0001
Type of management*			
-Surgery alone	6.9	3.85-12.42	<0.0001
-Surgery, RT, TMZ†	0.50	0.25-1.01	0.05
Trials Reference group: No	0.50	0.28-0.88	0.01

* Reference group was the group received RT plus or minus chemotherapeutic agent other than concomitant and adjuvant temozolomide

†RT: radiation therapy.TMZ: temozolomide

Table 3: Significant predictors of survival from the multivariate analysis including time to pathology report covariate.

Covariate	Hazard Ratio	95% CI	P.value
Age	1.02	1.00-1.03	0.003
Seizure Reference group: No	0.67	0.48-0.95	0.02
Surgery type Reference group Biopsy	0.50	0.34-0.73	<0.0001
Type of management*			
-Surgery, RT, TMZ†	0.46	0.30-1.01	0.71
Time to final pathology	0.98	0.96-1.00	0.09

* Reference group was the group received RT plus or minus chemotherapeutic agent other than concomitant and adjuvant temozolomide

†RT: radiation therapy. TMZ: temozolomide.