GLIOBLASTOMA AND INCREASED SURVIVAL WITH LONGER CHEMOTHERAPY DURATION

BY

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Abstract

Background:

The five year survival for patients with glioblastoma (GBM) is low at approximately 4.7%. Radiotherapy plus concomitant and adjuvant temozolomide (TMZ) remain the standard of care. The optimal duration of therapy with TMZ is unknown, though treatment periods of six months, 12 months and longer have been utilized. Whether or not there is a benefit with longer treatment duration is controversial. This study sought to evaluate overall survival benefit of two years treatment.

Methods:

This was a retrospective chart review of all patients diagnosed with GBM who were treated at a regional cancer referral center. These patients were treated with TMZ for up to two years between January 1, 2002 and December 31, 2011. Survival was calculated as the time from initial surgical diagnosis until death. The Kaplan-Meier method with log-rank test was used to estimate the progression-free survival (PFS) as well as the overall survival (OS) distribution of patients after treatment. The results were compared to historical controls and data from previous clinical trials of pts treated up to one year.

Results:

Data from 56 patients were evaluated, the majority of whom had gross total resection and had external pathology review confirming the diagnosis of GBM. The OS probability was 54% (SE = 0.068) at one year, 28.3% (SE = 0.064) at two years, 17.8% (SE = 0.059) at three years and 4% (SE=0.041) at five years. The median PFS time in this study group was eight months

(95% CI = 4.0 – 9.0 mo). The probability of no progression at two years was 8.6% (SE = 0.05). Seven patients (12.5%) were treated with TMZ for two years. The median time-to-progression among these patients was 28 months (95% CI = 5.0-28.0). These patients showed an increased survival probability at three years compared to patients who did not receive the two year treatment of TMZ (log-rank test χ^2 (1, N=56) = 19.2, $p < 0.0001$).

Conclusions:

This study suggests that there may be an advantage for a longer duration of TMZ therapy among patients with GBM. In this study, treatment with TMZ for two years was associated with increased survival. While we consider the sample size to be too small for generalization, a prospective/multicenter study with a larger sample size might better evaluate the question of duration of TMZ therapy, particularly if both clinical and basic science data are paired.

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Introduction

Background and Rationale

Brain tumors account for two percent of all cancers, but their share of cancer morbidity and mortality remains disproportionate due to the little advances achieved in this disease.[1] Gliomas account for more than 80% of primary central nervous system (CNS) malignancies.[2] Malignant, high grade gliomas are grade III, which include anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytoma, and grade IV which is glioblastoma (GBM). Most malignant gliomas are GBMs.

The Central Brain Tumor Registry of the United States (CBTRUS), which is the nation's largest registry of primary brain tumors, reported 311,202 new cases of both malignant and benign brain and CNS tumors from 2005 to 2009.[2] The average annual age-adjusted incidence rates for GBM across 45 states with cancer registries that met or exceeded the North American Association of Central Cancer Registries' (NAACCR) high quality standards for 2005 through 2009 were 2.53 and 3.98 per 100,000 person-years for females and males, respectively.[2] The male to female incidence rate ratio was 1.58 whereas the white to black ratio was 2.06.[2] GBMs constituted 15.8% of all reported tumors and 54% of all gliomas. The most prevalent locations of all brain tumors were the frontal lobe (25.6%) and the temporal lobe (19.6%).[2] CBTRUS data collected between 2005 and 2009 suggested the mortality rate from malignant brain and CNS tumors was 3.48 for females and 5.23 for males per 100,000 person-years.[2] Kansas was one of six states where incidence was not reported in the CBTRUS report, but the mortality rates from malignant brain and CNS tumors were 3.93 and 6.39 per 100,000 person-years for females and males, respectively.[2]

The five-year survival rates for the most common malignant histologic subtypes — anaplastic astrocytoma and glioblastoma — are 25.9% and 4.7%, respectively.[2] For all histologic types, pediatric and young adult populations have a better survival than do older adults. For all primary malignant brain tumors combined, the five year survival rate among children younger than age 14 is 62%, compared to 5% in adults 65 years of age and older.[3]

Despite a multidisciplinary and aggressive treatment approach, GBM, the most common high grade malignant brain tumor, continues to have the lowest five-year survival rates among all human cancers.[4] The median survival time from diagnosis rarely exceeds 12 months,[5] and may even be shorter.[6] The patients who survive for more than 36 months are considered long-term survivors.[7]

Treatment of GBM is particularly challenging due to resistant tumor cells, fragility of the brain, and inability of most agents to cross the blood-brain barrier to reach the tumor. Historically, the standard therapy consists of surgical resection followed by radiotherapy. Early clinical trials of the effectiveness of radiotherapy versus radiotherapy plus concomitant chemotherapy displayed statistically insignificant survival benefit of chemotherapy.[8] However, more recent clinical trials and long-term analyses have identified a specific chemotherapeutic agent, temozolomide (TMZ), as conferring a statistically significant survival benefit when given concurrently with radiation therapy (as opposed to radiotherapy alone).[9-11] Radiation therapy plus concomitant and adjuvant TMZ is currently the standard of care for treatment of patients with GBM.[10] TMZ is a DNA alkylating agent but its way of action is still unknown. Recently, Yamaki et al concluded that TMZ induces TAp63 expression in GBM tissues which suppresses MYC transcription and inhibits GBM progression.[12]

For newly diagnosed GBM, research suggests that the application of adjuvant TMZ

chemotherapy requires a minimum of four (three-to-four week) cycles to achieve beneficial treatment.[10] For elderly patients diagnosed with GBM, research indicates that six (three-to-four week) cycles may be sufficient.[13] The clinical trials which originally established the benefit of TMZ did so utilizing a six cycle (six months) period of treatment.[9-10] More recent data suggest that a one year duration of adjuvant TMZ therapy may yield superior progression-free and overall survival without TMZ toxicity[14] and this regimen is being more evaluated in a current clinical trial (RTOG 0525). The benefit of even longer treatment periods is unknown. Given this background, the optimal duration of therapy with TMZ appears to be unknown.

Objectives

The objective of this study was to evaluate the survival benefit, if any, of a longer treatment duration, with an intent to treat of two years with TMZ, given that all the other treatment guidelines have been followed.

Methods

Study Design

The study design consisted of a chart review of patients with GBM who were treated by a clinical practitioner, at a cancer referral center in the Midwest, according to the latest guidelines with the intent to treat for two years of adjuvant therapy with TMZ. The results were compared to historical controls and data from previous clinical trials, where the patients were treated for up to one year.

Setting

The source of the study data is the electronic medical charts of one clinician's patient population at a tertiary referral center. The registry was searched using three keywords: brain neoplasm, GBM, and glioblastoma. The results were then filtered according to diagnosis date so

that only those treated between January 1, 2002 and December 31, 2011 were displayed. Pertinent study variables were then extracted for those who met inclusion criteria.

Participants

Patients were selected according to the following inclusion criteria: age 18 or older with a GBM diagnosis that received TMZ as first line chemotherapy with the intent to treat for two years. All eligible patients had surgery with the intent of gross resection, followed by imaging assessment within 24 to 48 hours from surgery and then radiation with TMZ within two to four weeks from diagnosis, depending on the need for rehabilitation.

Variables

The continuous variables that were abstracted included age, time to progression and time to death. The categorical variables collected included: Karnofsky's performance score (KPS), gender, region of Kansas, surgical intervention, external pathology report verification and the use and type of seizure medications.

Survival was calculated as the time from surgical diagnosis until death or end of the study period, whichever came first. The date of death was registered and verified through hospital records or the obituary regardless of the cause.

Date of diagnosis, date of progression, and date of death were compared to calculate time interval variables. The outcome of interest was death. Seizure medications were collected as possible effect modifiers. Potential confounders included type of surgical resection, inaccurate pathology report, and demographics.

Data Sources and Measurements

Data were obtained from the electronic medical records. This information was obtained from the patients themselves, their hospital records, and their outpatient imaging follow up results.

Multiple variables have been studied in the past to establish correlation with increased survival, some of which were at the molecular level. The only exogenous environmental exposure that has been linked to GBM has been ionizing radiation.[15] For this reason, the region of Kansas where the patients lived in the last 10 years was recorded to evaluate for possible environmental exposures.

Other important prognostic factors included age and KPS.[16] Younger patients and those who had a good performance score (scored high on the Karnofsky evaluation scale) tend to have a better survival.[9] Furthermore, Stupp et al. suggested that radiotherapy plus TMZ was associated with a significant improvement in median overall survival in nearly all subgroups of patients except in patients who underwent biopsy only and those with a poor performance status.[9] In the current study, the performance status measurement was based on Karnofsky's standardized score evaluation (Table 1). The extent of surgery was reported according to surgical reports and imaging evaluation after surgery. The population of interest in this study was adults 18 years or older.

Patients presenting with seizures needed to be started on antiepileptic therapy. Antiepileptic therapy might also be started as prophylaxis after brain surgery for about three months. While it was previously hypothesized that hepatic metabolism inducers, like first generation antiepileptic medications, interfere with chemotherapy agents' efficacy, the 2010 European Society for Medical Oncology clinical practice guidelines do not agree with this when it comes to temozolomide.[17]The data about the antiepileptic drug used were also collected for analysis.

Table 1: Karnofsky Performance Status Scale

Value	Level of Functional Capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance, but able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Bias

Patients with missing data about progression time and survival time were censored in the analysis. These missing data, had they been available, might have changed the results. To prevent any additional bias from censoring, we assumed that censoring was not related to any

adverse effect from treatment or lack of effectiveness. Misclassification bias was addressed by recording whether the pathology report was reviewed at an external laboratory.

Study Size

The initial sample size was 211 individuals after the keywords search through the registry, 66 subjects with a diagnosis of GBM that were treated with TMZ were identified for the study. Ten subjects were censored due to missing data bringing the final study size to 56 patients.

Statistical Methods

All data were collected in a Microsoft Excel (version 2007) spreadsheet and analyzed using Statistical Analytics Software (SAS) version 9.3. Analysis was conducted to establish a correlation between the duration of treatment and long-term survival of those patients with GBMs. All tests were evaluated at a 0.05 or less level of significance.

The response variable, overall survival from GBM, was defined as time from surgical resection until death from all possible causes potentially attributable to GBM. Patients who were still alive or for whom no definite event status (i.e. death) was ascertainable, like those lost to follow up, were censored for the median survival calculations. For the long-term survival calculation, the patients who were still alive were accounted for.

The Kaplan-Meier method with log-rank test was used to estimate the overall survival (OS) distribution of patients after treatment. To adjust for potential confounding of overall survival by patient demographics and clinical characteristics, the Cox proportional hazards (PH) regression model was used to model the relationship between survival and those covariates. To assess model adequacy of the Cox-PH model, the proportionality assumption for this method of regression was evaluated. Covariates that have significant influence in determining survival from GBM were assessed using the stepwise method of variable selection.

Progression-free survival (PFS) was also evaluated. The event of interest in this respect was progression or recurrence of disease within two years of start of treatment. Patients who were lost to follow-up before their disease progressed were censored. The Kaplan-Meier method with log-rank test was used to estimate the progression-free survival distribution of patients after treatment.

Results

The initial search yielded 211 patients, of which 109 had GBM. Since TMZ was not first-line treatment until around 2005,[9] all patients before that period, who were treated with other agents, were excluded resulting in a total of 66 patients. Eleven of 66 patients were lost to follow up. Among these 11, time to progression was available on four of them and the date of death was obtained on two. One of those patients lost to follow up was known to have died, but the exact date of death could not be obtained.

The study population consisted of 66 patients (25 females and 41 males) with a mean age at diagnosis of 60 and a standard deviation of 12.5. A total of 56 patients were included in the analysis because of the lack of survival time data on the other 10 patients and only seven (12.5%) completed two full years of TMZ (Figure 1). The median age was 62 for the whole group and 64 for the group treated with two years of TMZ. The median Karnofsky's performance score was 80.

All the patients in the study had the intent to treat for two years, but the median survival time was 13 months (SE= 0.068) (Figure 2). The two-year survival probability was 28.3% (SE = 0.064) and the three-year survival probability was 17.8% (SE = 0.059). At five years, the computed survival probability was 4% (SE = 0.041).

Table 2: Patient Characteristics

		2 Years Treatment	Total
Age			
	20-44	2(28.6)	5(7.5)
	45-54		13(19.7)
	55-64	2(28.6)	23(34.9)
	65-74	2(28.6)	18(27.3)
	>74	1(14.2)	7(10.6)
Gender			
	Male	6 (14.6)	41 (62.1)
	Female	1 (4.0)	25 (37.9)
Kansas Region			
	Central	7 (100.0)	52 (78.8)
	Other		14 (21.2)
Tumor localization			
	Hemisphere[a]:		
	Right	5 (71.4)	37 (58.7)
	Other	2 (28.6)	26 (41.3)
	Lobe[b]:		
	Frontal	4 (57.2)	26 (39.4)
	Temporal	1 (14.2)	21 (31.8)
	Other	2 (28.6)	19 (28.8)
Treatment			
	Tumor resection :		
	Total	5 (71.4)	41 (63.1)
	Sub-total	2 (28.6)	20 (30.8)
	Biopsy		4 (6.1)
	Radiotherapy	7 (100.0)	66 (100.0)
Progression		3 (42.9)	40 (67.8)
External pathology review		5 (71.4)	32 (51.6)
Antiepileptic medications		5 (71.4)	50 (75.8)
	Enzyme inducers	3(60.0)	26 (52)
	Non enzyme inducers	2(40.0)	24 (48)

KPS=Karnofsky performance score, partly retrospectively evaluated.

[a] The data on 3 were missing.

[b] For tumors that involved more than one lobe, it was reported according to the lobe that was most affected. In addition there was one tentorial, one intraventricular, one insular, one over the corpus callosum and one with multiple masses on the left. They were all grouped with occipital and parietal masses under other.

[c] The data on 7 was missing. Patients that were lost to follow up and no evidence of death was obtained were considered to not have progressed.

[d] Data missing on 4. These were considered as not having had external pathology review.

The median time to progression was eight months (Figure 3). Patients who were treated with two years of TMZ (Figure 4) had a significant increase in the likelihood of survival after stratification (log-rank test χ^2 (1, N=56) = 19.2, p < 0.0001). Survival was significantly increased for those who had a good KPS compared to fair (log-rank test χ^2 (1, N=56) = 8.5, p = 0.0034) (Figure 5). Additionally, those who had a tumor located in the right cerebral hemisphere, compared to those with a tumor in other locations, were more likely to have increased survival (log-rank test χ^2 (1, N=56) = 5.5, p = 0.018) (Figure 6). Patients who had successful gross resection had a better survival than those who had a biopsy, but only a marginal increase in overall survival compared to those who had a sub-total resection, with statistically insignificant results (log-rank test χ^2 (2, N=56) =3.8, p = 0.15) (Figure 7). Those who progressed had decreased in survival (Figure 8). Gender (Figure 9), location (Figure 10), pathology review (Figure 11), and the use and type of anti-convulsive medications (Figures 12-13) appeared to have no effect on survival after stratification. Age stratification (age groups: 19-44, 45-54, 55-64, 65-74, and older than 74 years) showed increased survival with the youngest age groups (Figure 14), but that wasn't statistically significant, (log-rank test χ^2 (4, N=56) = 5.27, p = 0.26).

After univariate adjustment, good KPS and the location of the tumor in the right hemisphere showed significant effect on survival. When multivariable analysis adjustment is computed only the right sided brain tumors had significant increase in survival (Table 3). Having the tumor located on the left side suggests increased risk of death compared to the right side (HR=3.077, 95% CI=1.159-8.172) (Table 3). Multivariate analysis also suggests that the risk of death due to GBM is considerably reduced for persons aged 45-54 compared to those aged 75 years or older (HR= 0.161, 95% CI=0.029-0.883) (Table 3).

Table 3: Adjustment Table

	Univariate		Multivariate	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age-groups (vs. >74)				
20-44	0.301	0.060-1.521	0.407	0.038-4.366
45-54	0.566	0.190-1.683	0.161	0.029-0.883
55-64	0.853	0.330-2.206	0.573	0.123-2.676
65-74	0.788	0.290-2.136	0.529	0.099-2.822
Female (vs. male)	1.346	0.724-2.502	0.910	0.376-2.201
KPS fair (vs. good)	3.491	1.394-8.746	2.970	0.570-15.485
Central (vs. other region)	0.514	0.234-1.132	0.412	0.153-1.109
Excision: sub-total (vs. total)	1.521	0.805-2.873	1.168	0.531-2.569
Excision: biopsy (vs. total)	2.380	0.818-6.928	0.717	0.099-5.917
EIAC* (vs. non-EIAC)	0.716	0.373-1.376	0.844	0.356-2.001
Pathology review: no (vs. yes)	0.884	0.482-1.623	0.990	0.416-2.353
Left hemisphere (vs. right)	1.989	1.086-3.643	3.077	1.159-8.172
Location: frontal (vs. temporal)	1.208	0.575-2.538	1.589	0.628-4.022
Location: other (vs. temporal)	1.304	0.589-2.886	0.970	0.247-3.809

*Enzyme inducing anticonvulsant

The two years treatment group analysis did suggest persistent survival advantage even after adjustment but that was not included in the table because of a very wide confidence interval due to the small sample size.

Discussion

This study suggests an increase in overall survival for patients who successfully completed two years of TMZ therapy. Patients with a diagnosis of GBM face a particularly poor prognosis, and new therapies are needed. As previously noted, the optimal duration of therapy has not been identified. Some studies have treated patients for periods of six to 12 months.[14] In view of the fact that, for the most part, the side effects of TMZ are well tolerated, it seemed reasonable to evaluate the outcome of patients who were treated for a longer period of time.

According to population-based studies, the median age of GBM patients is 64.[2] In our sample, both, patients who completed two years of treatment and the sample as a whole had a median age above 60. Age subgroup analysis suggested survival advantage for age-group 45-54 compared to age-group older than 74, but not for the younger age-group. This is likely related to sample sizes in each subgroup. The number of individuals aged 45-54, and older than 74, may be large enough to make the analysis reasonable in these subgroups but not in the 20-44 one. Also, our patient population exhibited a high KPS, which has been associated with longer survival. In fact, all the patients who completed two years of TMZ had a good KPS score. However, multivariable adjustment suggested no effect of KPS on survival (Table 3). The results in that table were reported as confidence intervals rather than p-values because of the advantages of showing the direction of the effect studied and determining with more confidence the interval where the true value of the statistical parameter is.[18]

Table 4: List of the Long Term Survivors Studies

Review of the literature for patients with glioblastoma who survived longer than 3 years (long-term survivors)

	Number of cases	Mean age	male	female	Mean KPS score	GTR	RT	Chemotherapy
Netsky *et al.*, 1950	8	na	na	na	na	na	na	na
Roth and Elvidge, 1960	20	na	na	na	na	na	na	na
Ley *et al.*, 1962	6	na	na	na	na	na	6	na
Taveras *et al.*, 1962	13	na	na	na	na	na	na	na
Elvidge and Barone, 1965	2	24.5	1	1	na	2	1	0
Gullotta and Bettag, 1967	1	45	1	na	na	1	1	0
Jelsma and Bucy, 1967	6	na	na	na	na	6	na	na
Dara *et al.*, 1980	3	na	na	na	na	na	na	3
Johnson 1981	1	32	na	1	na	1	0	0
Hatanaka *et al.*, 1984	1	50	1	na	100	0	1	0
Bucy *et al.*, 1985	1	30	1	na	na	1	1	0
Salford *et al.*, 1988	2	14.5	1	1	na	1	2	0
Akslen *et al.*, 1989	2	41.5	1	1	na	2	2	1
Ishikura *et al.*, 1989	1	8	na	1	na	1	0	0
Margetts and Kalyan-Raman, 1989	3	41.3	2	1	90[a]	3	3	3
Imperato *et al.*, 1990	5	42.6	3	2	na	5	5	4
Shibamoto *et al.*, 1990	1	51	1	na	na	1	1	0
Rutz *et al.*, 1991	1	21	1	na	na	1	1	0
Vertosick, Jr. and Selker, 1992	13	40.9	7	6	86[a]	na	13	13
Hiesiger *et al.*, 1993	10	47	na	na	81	1	10	10
Chandler *et al.*, 1993	22	39.2	10	12	80	2	22	18
Phuphanich *et al.*, 1993	7	37	5	2	na	na	7	6
Archibald *et al.*, 1994	7	37.7	2	5	na	2	7	7
Wester *et al.*, 1994	1	45	na	1	na	1	1	0
Morita *et al.*, 1996	10	39.2	7	3	na	10	na	na
New *et al.*, 1997	1	34	na	1	100	1	1	1
Pollak *et al.*, 1997	2	20	1	1	na	2	2	0
Klein *et al.*, 1998	1	11	na	1	na	1	1	1
Cervoni *et al.*, 1998	1	13	na	1	80	1	1	1
Salvati *et al.*, 1998	11	39	5	6	80	11	11	11
Puzzilli *et al.*, 1998	1	50	1	na	90	0	1	0
Scott *et al.*, 1999	15	43.5	9	6	90	na	na	na
Yoshida *et al.*, 2000	2	40	1	1	na	1	2	2
Sabel *et al.*, 2001	1	69	1	na	na	1	0	0
Burton *et al.*, 2002*a*[b]	41	39	16	25	90	na	na	na
Valery *et al.*, 2002	1	42	na	1	na	1	1	1
Floeth *et al.*, 2003	1	37	1	na	100	1	1	1
Ho *et al.*, 2003	6	na	na	na	na	na	na	na
McLendon and Halperin 2003	17	40.2	11	6	na	na	na	na
Schmidinger *et al.*, 2003	5	47	3	2	na	na	na	na
Jagannathan *et al.*, 2004	4	46.3	2	2	na	na	4	na
Rainov and Heidecke 2004	1	27	1	na	90	na	na	na
Shinojima *et al.*, 2004	6	44.2	na	6	85	4	6	6
Deb *et al.*, 2005	6	27	3	3	na	na	na	na
Yamanaka *et al.*, 2006	1	42	1	na	90	1	1	na
Steinbach *et al.*, 2006	10	42	4	6	90	9	10	9
Total	281	36.9	104	105	89	75	126	98

Data from a recent review for glioblastoma patiens living longer than 5 years (Shinojima *et al.*, 2004) are included.
[a]Calculated on the basis of data that were provided in the concerning paper.
[b]The study population is also published in another paper by Burton *et al.*, 2002*b*.
na = not available, Data were not provided in the paper.
KPS = Karnofsky Performance score; GTR = gross total resection; RT = radiotherapy.

Table 4 lists the reported long term survivors accounted for in the medical literature until 2006. While some of the numbers seem intriguing, we found that a number of important features, primarily details regarding pathology review and treatment regimen, are missing. Inadvertent inclusion of patients with lower grade gliomas could skew the results toward a more favorable outcome. In our series, all the patients except four had evidence of additional confirmation of the GBM diagnosis and more than half had the results externally reviewed at another center.

This study is consistent with the CBTRUS data regarding male to female ratio (1.64 vs 1.58, respectively), median age, and the most prevalent locations being frontal and then temporal lobes. However, contrary to the previously published data, the current study suggested that good KPS, and total resection were not associated with improvement over fair KPS and sub-total resection, after multivariate adjustment. This may be accounted for by the small sample size and the low percentage of patients with subtotal resection and fair KPS in our patient population. In our series, we also observed a longer survival for those patients diagnosed with right-sided GBMs than those located on the left side. Whether or not this is simply a peculiar finding in a small study is unknown. Another potential explanation could be that the left hemisphere is the dominant hemisphere and where the language center is located most of the time, causing patients with left sided GBM to do worse because of loss of essential functions. To our knowledge, this is the first study that examined treatment duration of two years with temozolomide.

Limitations:

Several limitations exist in this study analysis. First, the sample size is too small to allow any generalization. However, most of the studies involving GBM and TMZ also have relatively small sample sizes. A prospective, multicenter study with a larger sample size might better evaluate the question of duration of TMZ therapy, particularly if both clinical and basic science

data are paired. Second, this study was a retrospective chart review with some missing data that may have introduced bias to the results.

We did note that one long term survivor (81 months) in the successfully treated group had no external pathology review. Although a pathology review may have also confirmed the GBM diagnosis, there are isolated case reports about very long term survival with verified GBM with one patient still alive after 21 years.[19]

Several genes have been implicated in GBM long term survival, mainly the MGMT promoter gene hypermethylation.[20] More recently, over-expression of Deltrex-1 (DTX1) gene was correlated with increased cell migration and invasion,[21] while over-expression of SLC7A7 predicts poor PFS and OS in patients with GBM.[22]DNA molecular data for the patients in this study at the time of data collection were not available, and retrospective analysis was not possible because of HIPAA rules and the requirement to destroy the samples after death.

Research suggests that human cytomegalovirus (HCMV) infection plays a role in survival.[23] Patients with GBM who had low grade HCMV infection had increased survival and time to progression compared to moderate and high grade infection. This data was also not available in this study.

Additionally, newer studies about surgical resection and survival in GBM have evaluated a new technology consistent of fluorescence guided resection. Research suggests that complete surgical resection of the enhancing tumor on early MRI and no fluorescent residual tissue can have longer OS compared to those with residual fluorescent tissue,[24] but this technology was not available for our sample to be evaluated.

Conclusions

This study suggests that there may be an advantage for a longer duration of TMZ therapy in patients with GBM. In this review, treatment with TMZ for two years was associated with an increased survival benefit, regardless of age, a higher KPS score or a total initial resection. Furthermore, a right sided brain GBM may have a survival advantage over a left sided brain GBM. Despite the lack of basic science data, the results of this study seem to be worthy of further evaluation with a prospective large sample study.

Figure 1: Flow Diagram of the Study Sample

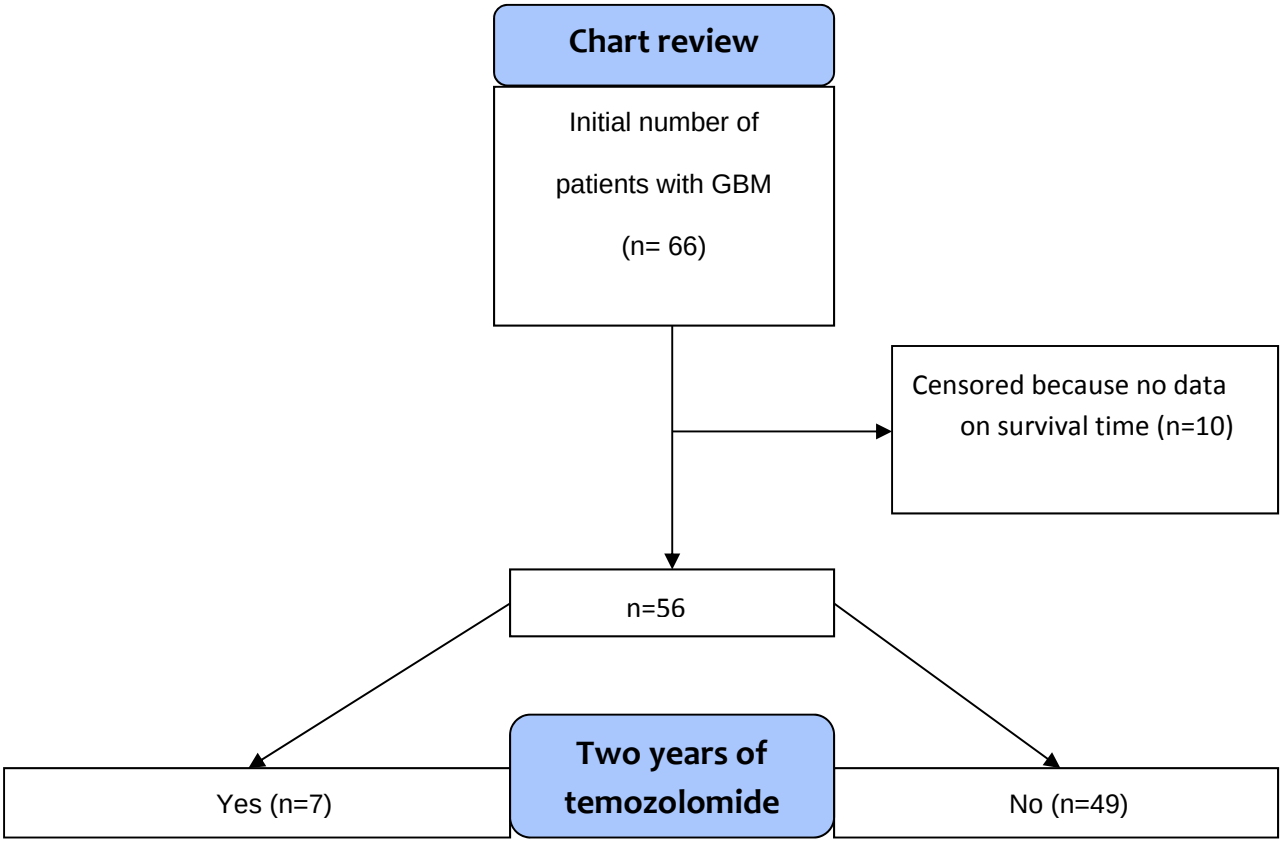


Figure 2: Overall Survival

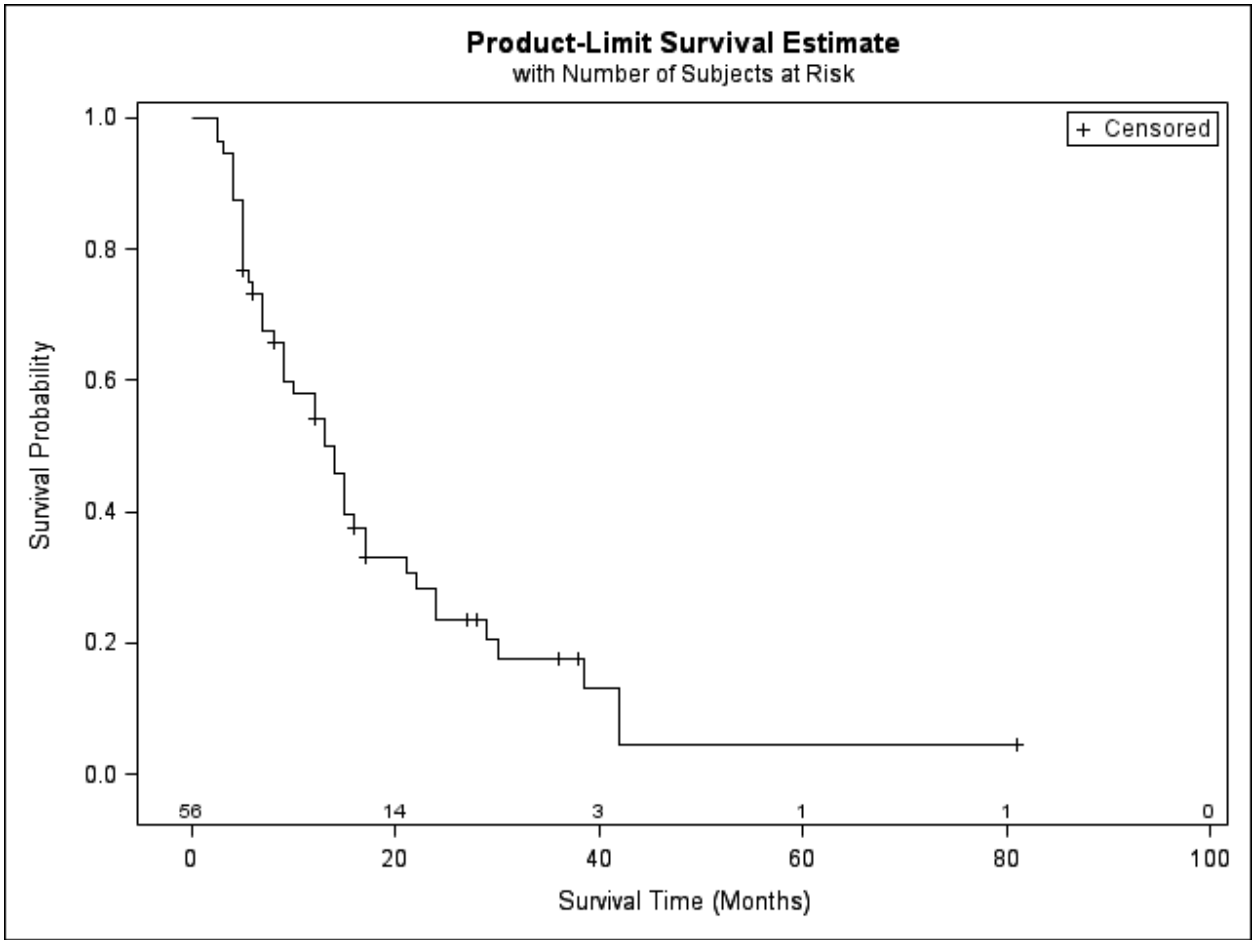


Figure 3: Progression-Free Survival

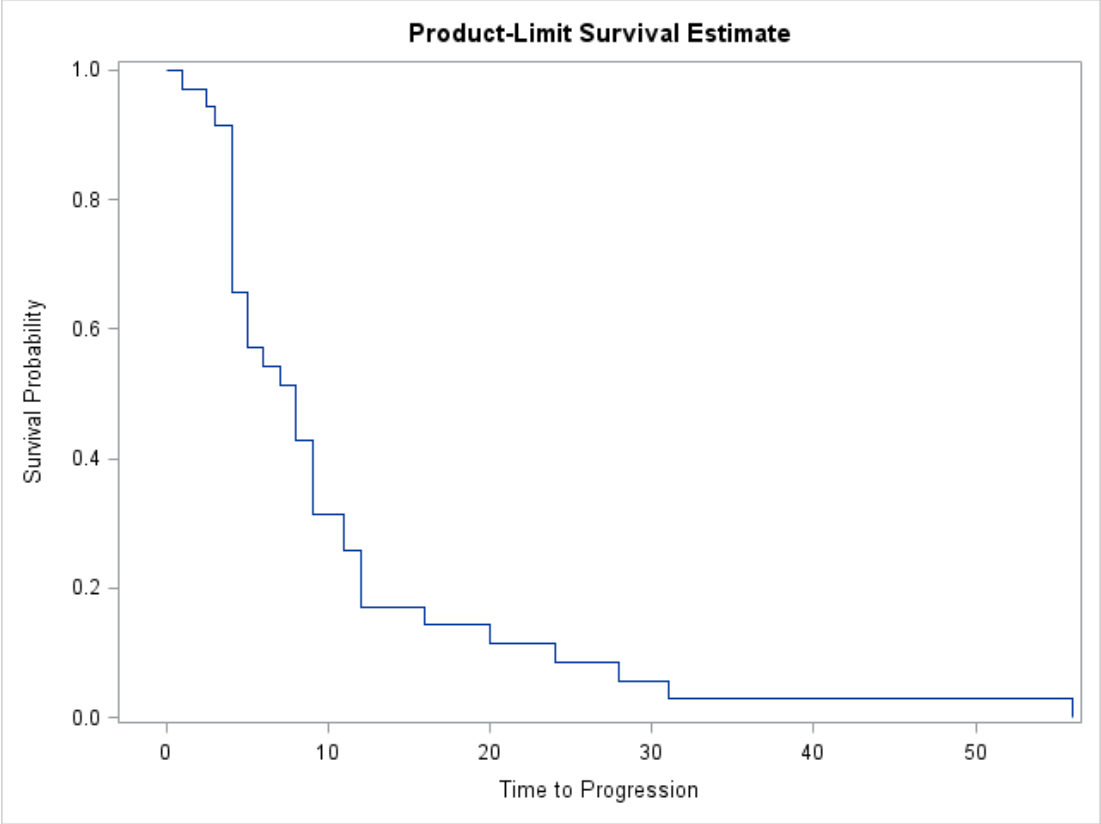


Figure 4: Overall Survival by Treatment Duration

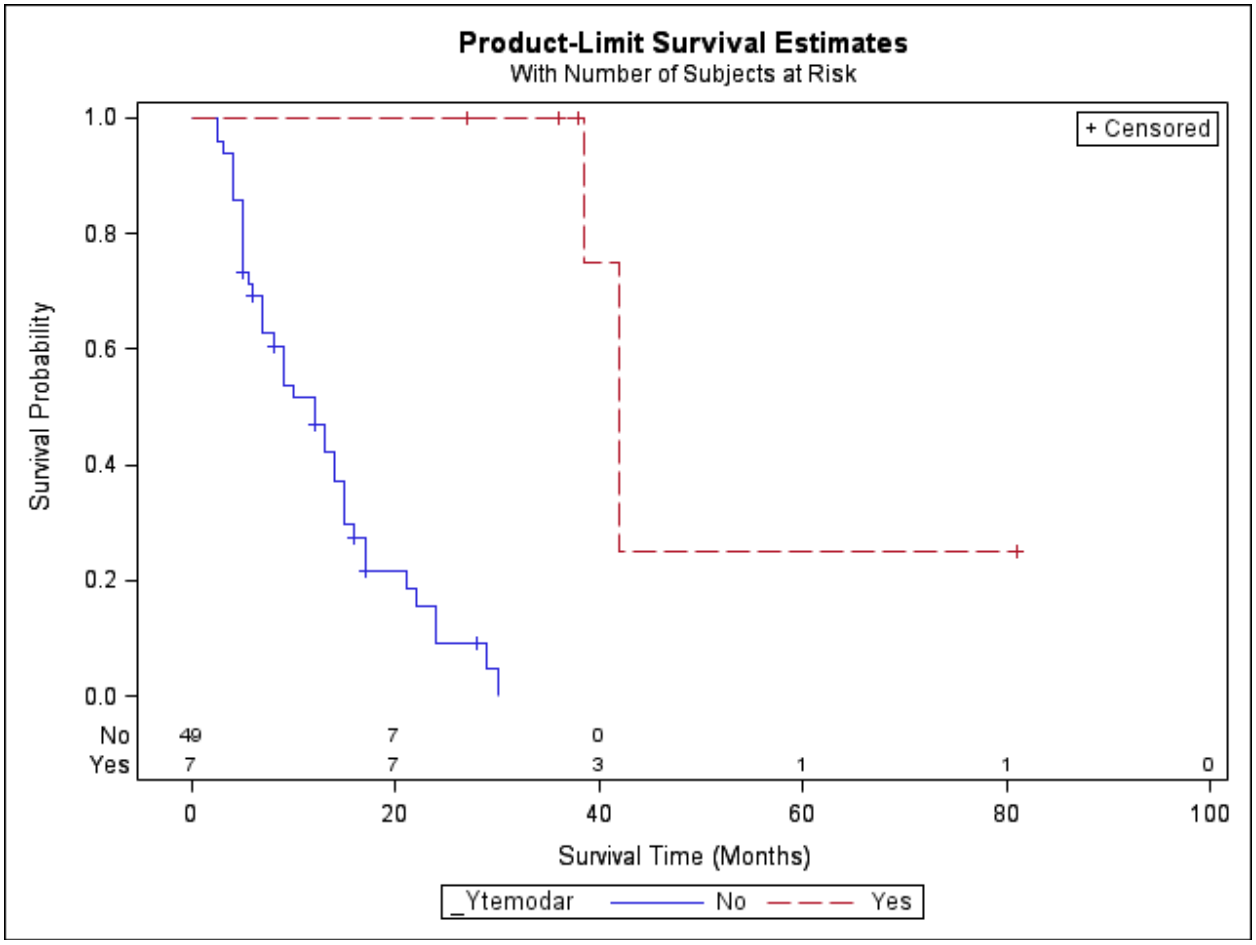


Figure 5: Overall Survival by Karnofsky's Performance Score

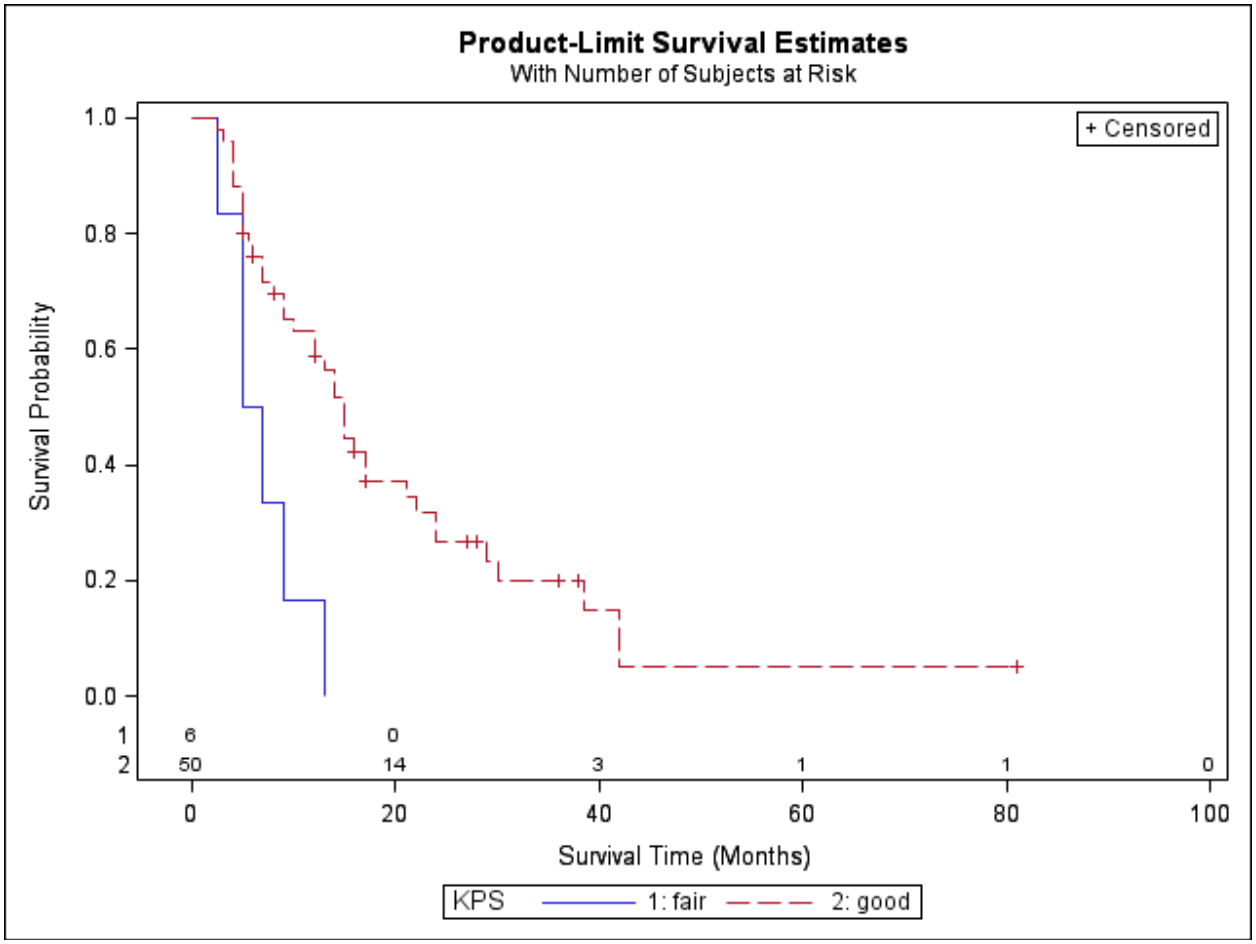


Figure 6: Overall Survival by Brain Hemisphere Location of the Tumor

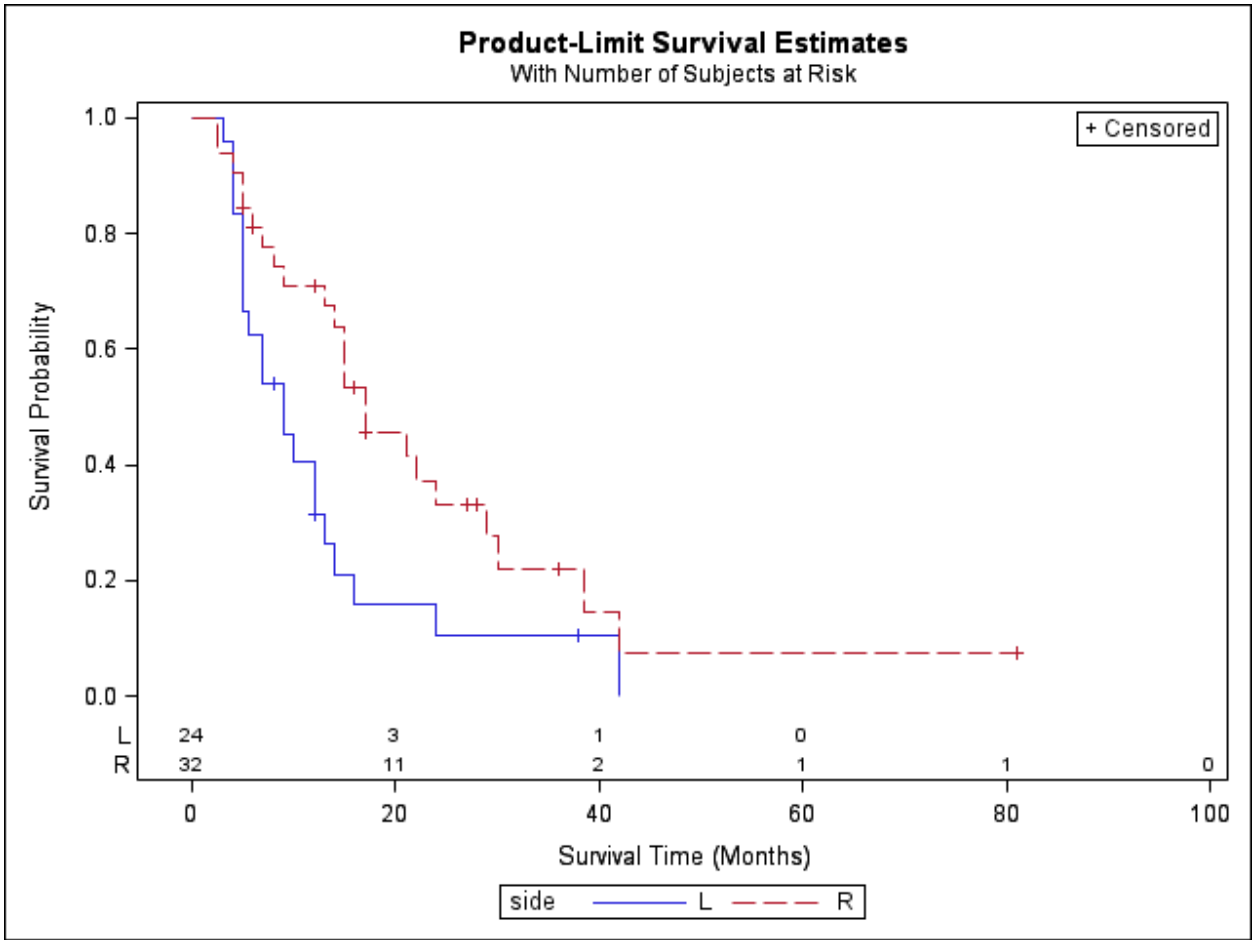


Figure 7: Overall Survival by Surgical Resection

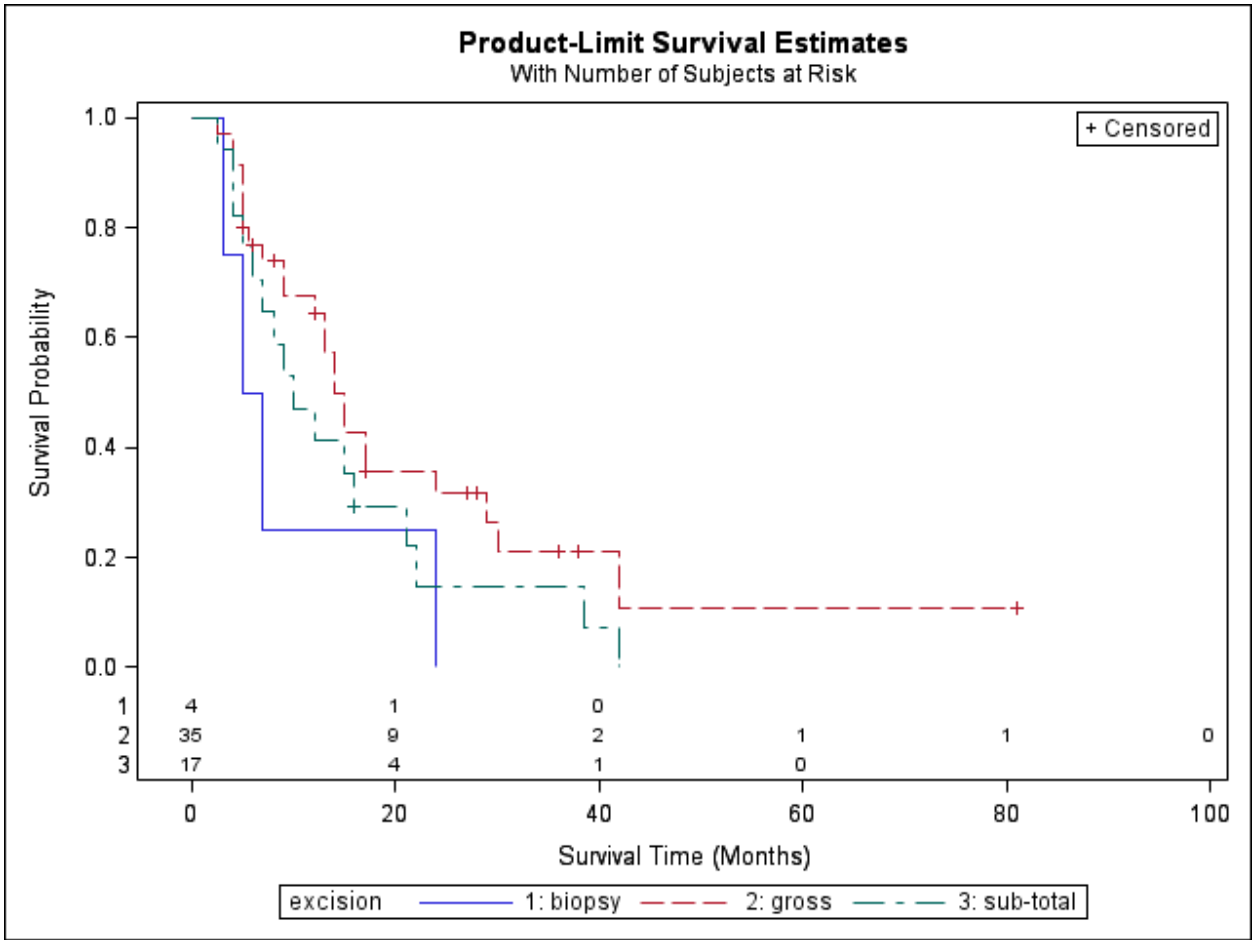


Figure 8: Overall Survival by Progression of Tumor

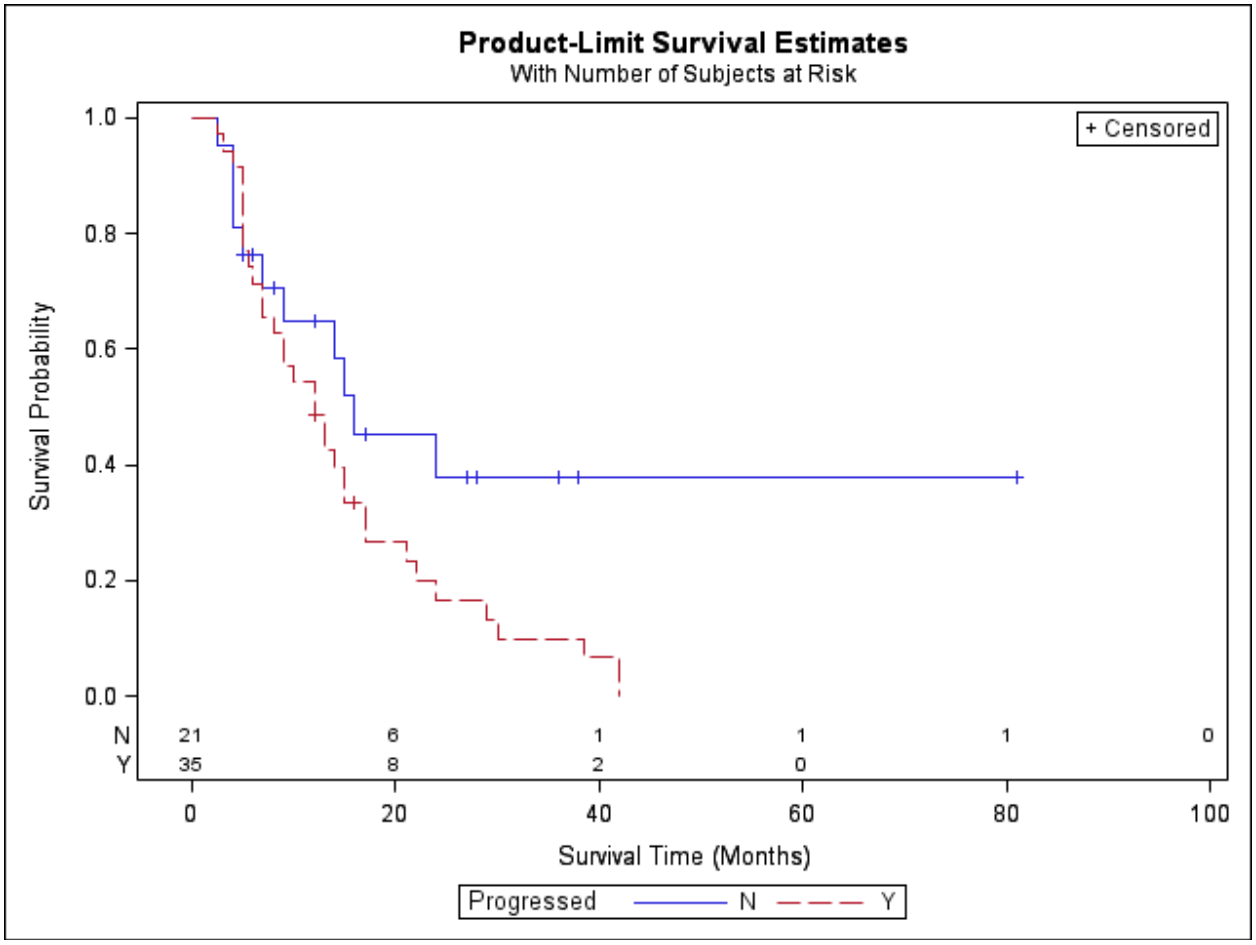


Figure 9: Overall Survival by Gender

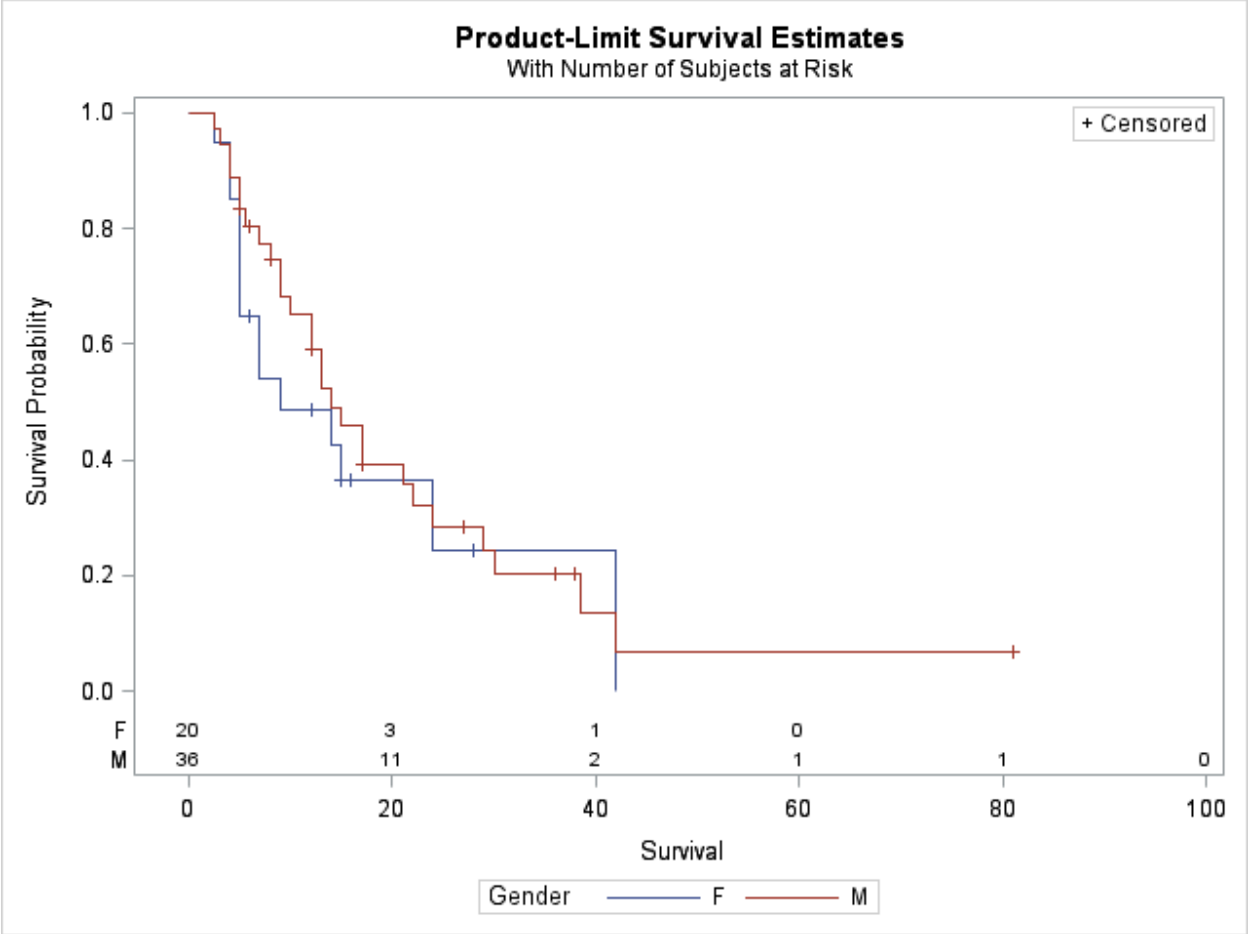


Figure 10: Overall Survival by Lobar Location of the Tumor

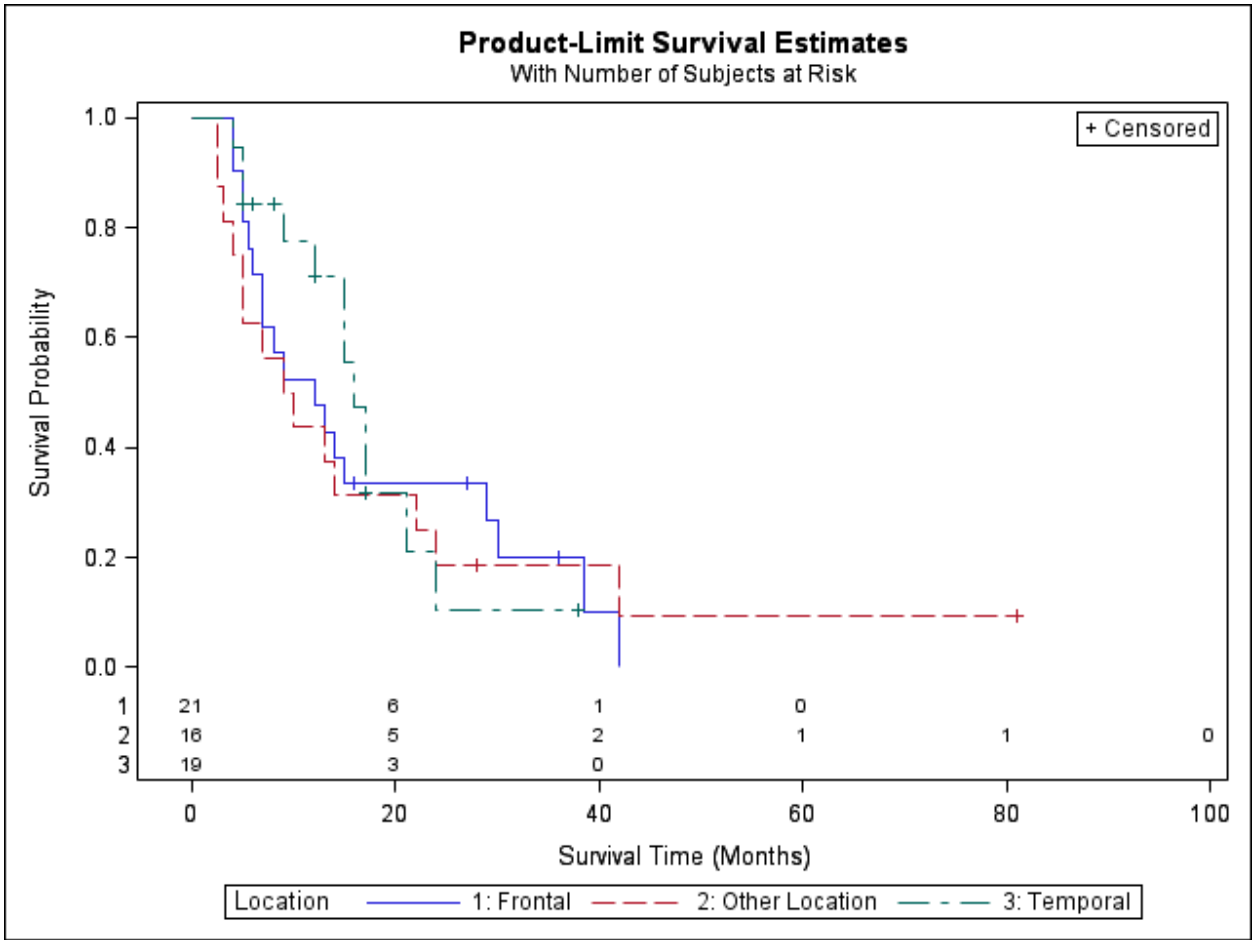


Figure 11: Overall Survival by Pathology Review

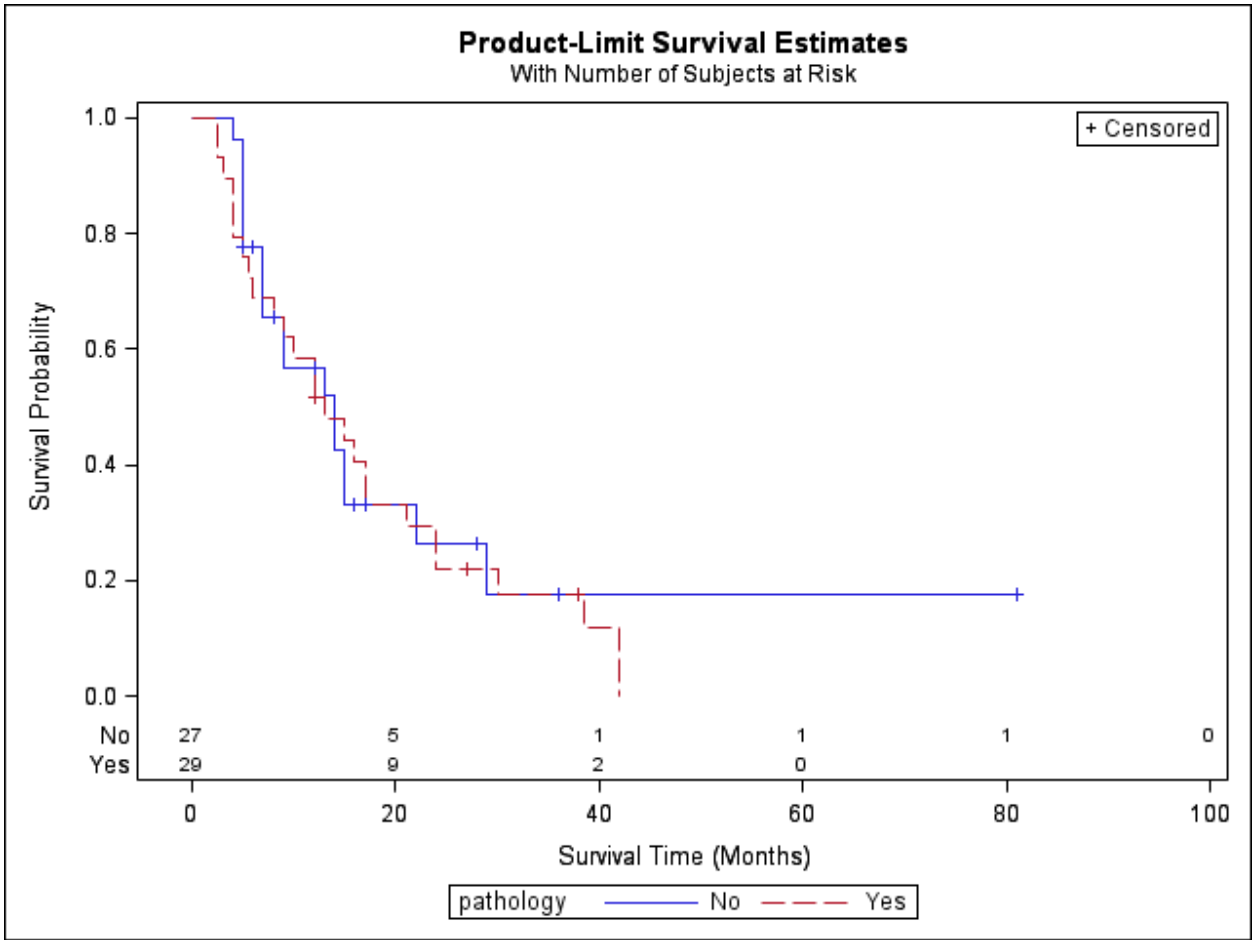


Figure 12: Overall Survival by Anti-Convulsive Treatment

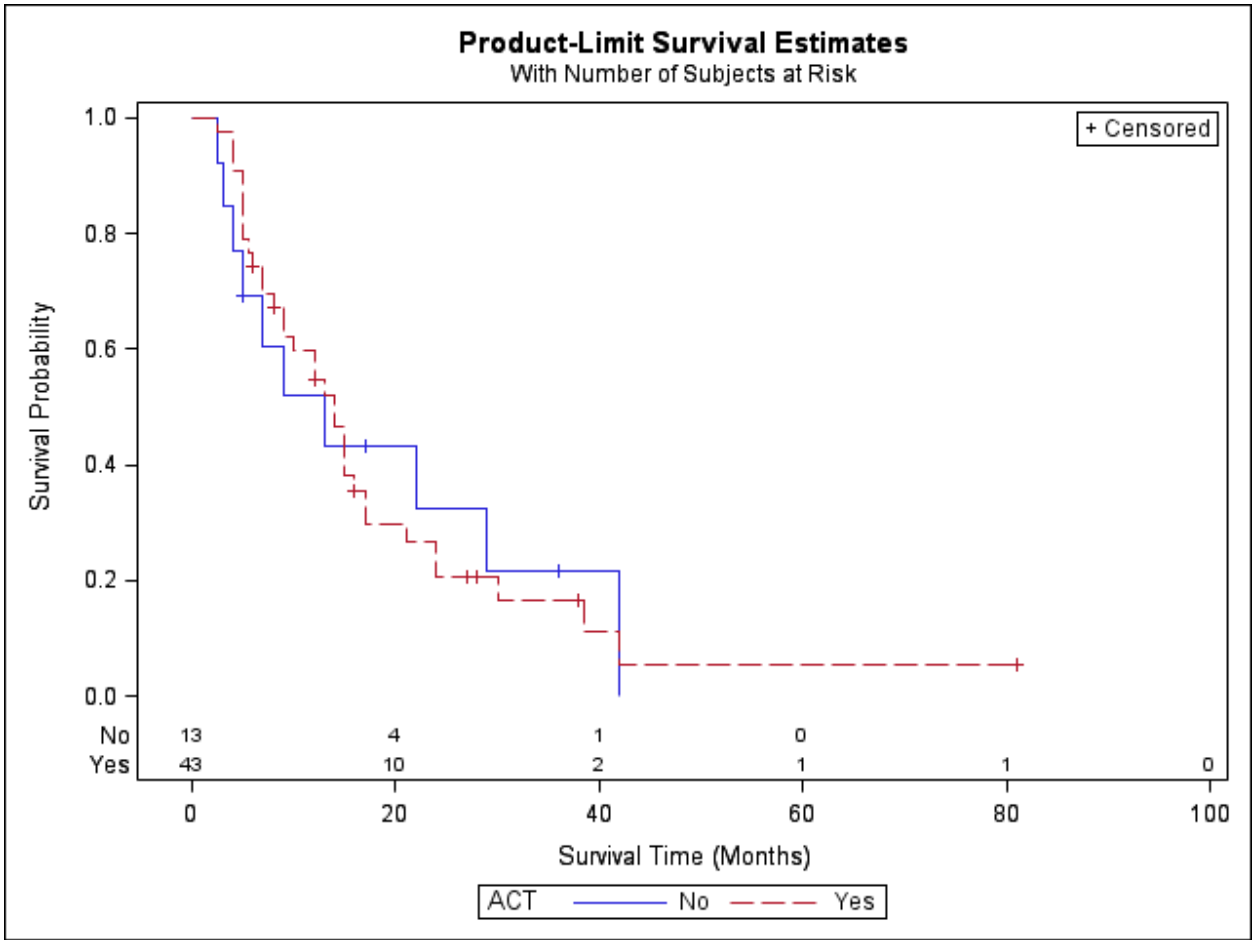


Figure 13: Overall Survival by Type of Anti-Convulsive Treatment Used

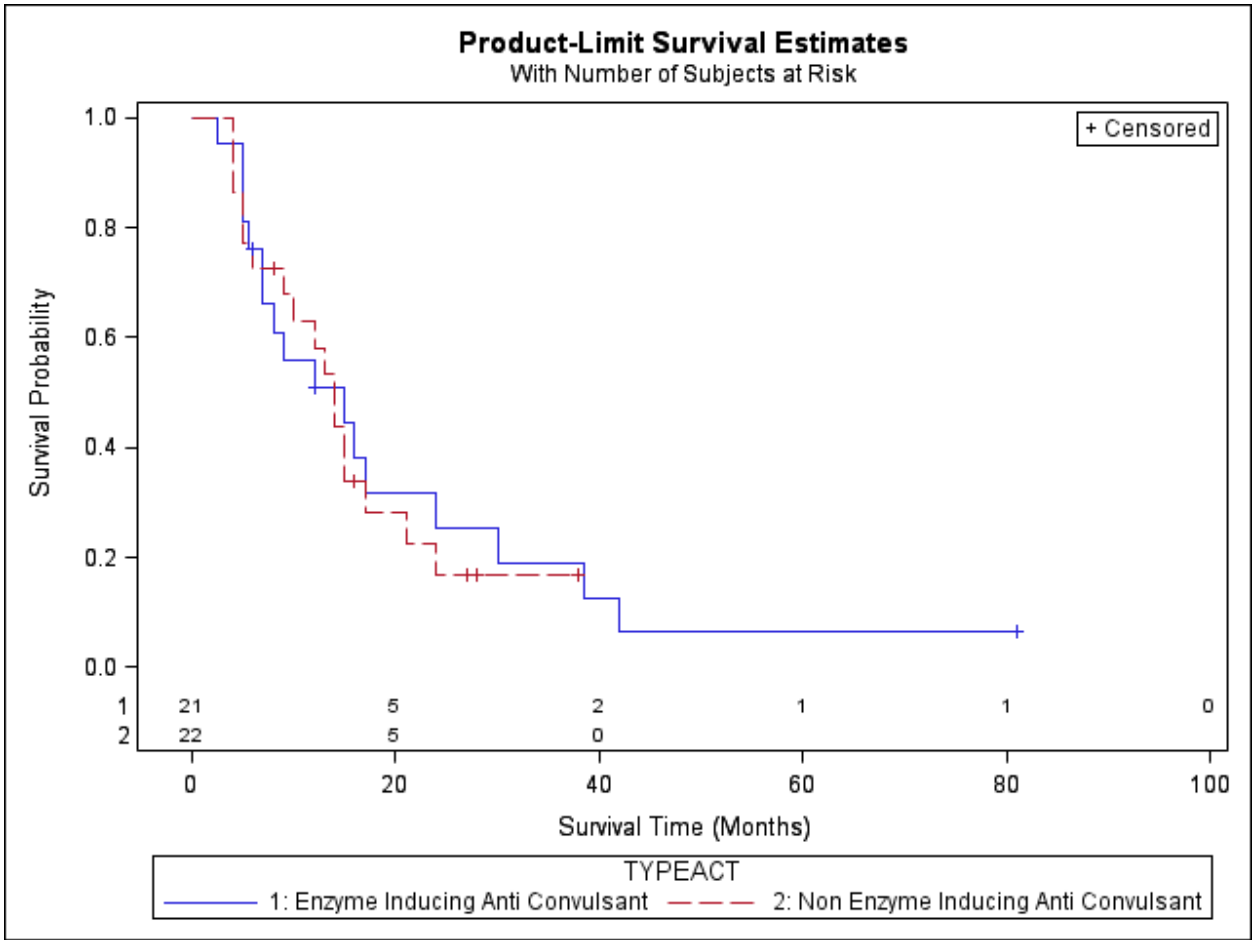
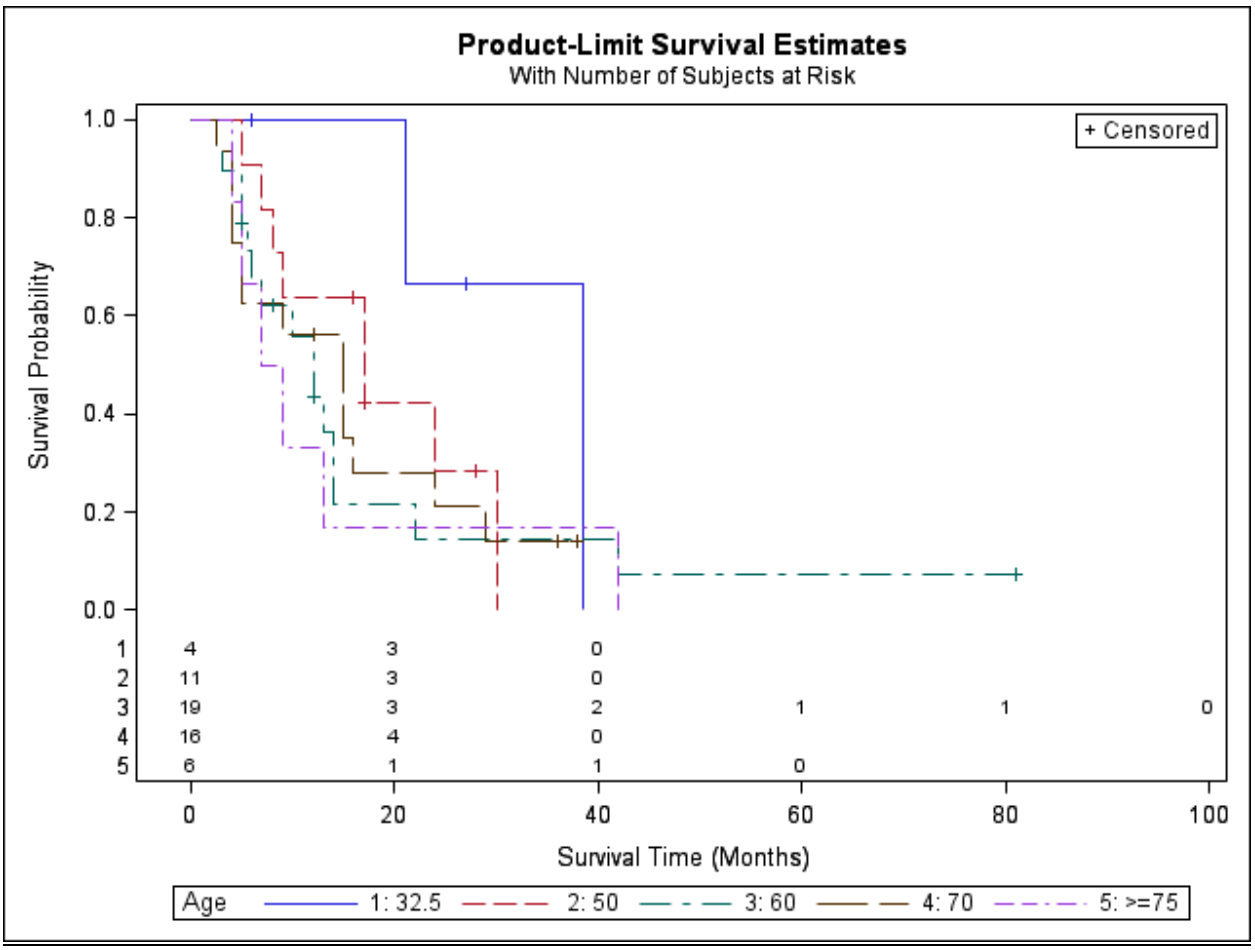


Figure 14: Overall Survival by Age-group



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Appendix

KU SCHOOL OF MEDICINE WICHITA
The University of Kansas

February 7, 2012

HSC Number:	**220121479**
Primary Investigator:	**Ablah, Elizabeth PhD, MPH**
Title:	**Glibolastoma and Increased Survival with Longer Chemotherapy Duration**
Protocol:	**Version 2; February 2, 2012**
Sponsor:	**N/A**
Study Action:	**Amendment Request**
Type of Review:	**Expedited Review under §46.110**
Approval Date:	**HSC2 Approved 2/7/2012**
Meeting Date:	**2/20/2012**
Expiration Date:	**01/26/2013**

Dear Investigator:
Your amendment request, detailed below, was reviewed and **APPROVED** by the Human Subjects Committee 2. Therefore, you are approved to incorporate the revisions listed below. Any subsequent revisions must be reported to, and approved by, the HSC2 prior to implementation.

Protocol Revision
Revisions to data being collected, subject selection, and total number of subjects needed to complete the study. Data collection sheets have been revised to reflect changes in the protocol.

If applicable to this amendment, a new copy of the stamped consent form that supersedes any previously approved consent form is enclosed. **Use this most current HSC2 approved stamped consent to consent subjects** and retain a copy with all research documentation.

If you have any questions or need assistance, please contact me at (316) 293-2610 or jrush@kumc.edu

Sincerely,

Jason M. Rush, BS, CIP
Research Compliance Coordinator

Office of Compliance
1010 N. Kansas | Wichita, KS 67214-3199 | (316) 293-2600 | Fax (316) 293-2628