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CLINICAL STUDY

Conditional survival of high-grade glioma in Los Angeles County during the year 1990–2000

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Abstract Survival probabilities for high-grade glioma are estimated at the time of diagnosis and provide limited information following treatment. This study determined dynamic indices to predict post-diagnosis survival for high-grade glioma patients. Survival information for 2,743 patients with high-grade glioma, diagnosed in Los Angeles County during the years 1990–2000, were used to estimate conditional survival probabilities with 95 % confidence intervals, for patients still alive at 1, 2, 3, 4, or 5 years after diagnosis. The conditional probabilities of surviving one additional year increase as the post-diagnosis survival time increases (from 43 ± 2 % conditional on surviving 1 year after diagnosis to 91 ± 2 % conditional on surviving 5 years after diagnosis). Patients diagnosed with WHO grade III gliomas have higher conditional survival probabilities than those diagnosed WHO grade IV gliomas. However, as the years after diagnosis increase, the differences in the conditional probabilities between the two groups are attenuated. At the time of diagnosis, age and tumor histology (WHO grade), tumor site, primary treatment, time of treatment start after diagnosis, as well as whether the patient was treated at a teaching hospital were significantly associated with overall survival. By 4 years post-diagnosis however, with the exception of age, variables associated with survival at baseline were no longer significantly associated with survival. Conditional survival probabilities provide clinically relevant information for understanding the prognosis for patients with high-grade gliomas.

Keywords Conditional survival · High-grade glioma · Los Angeles County

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Introduction

High-grade gliomas are the most common primary brain tumor, accounting for more than half of over 20,000 primary brain cancers diagnosed annually in the United States. These cancers are challenging to treat and are associated with relatively short survival [1]. Traditionally, estimates of survival are made at the time of diagnosis, most often utilizing median progression free and overall survival as well as 2- and 5-years survival rates. These estimates provide an overall prediction of disease outcome that are most helpful for cancer surveillance and public health intervention purposes. However, for individual survivors and physicians caring for these patients, these estimates are often not informative, or even misleading. For instance, patients who have survived a certain period of time after diagnosis (e.g. 2 years) likely have different probabilities of surviving the next 1 year from those that were estimated at the time of diagnosis. This is because a large proportion of patients will die within the first 1 or 2 years, and patients who have survived longer than 2 years likely have different survival patterns from those at the time of diagnosis. Conditional survival probabilities address this problem by calculating the survival probabilities based on the patients who have survived beyond a certain period of time, and therefore provide more accurate and dynamic estimates of survival after the initial diagnosis.

The present study, utilizing the Los Angeles County tumor registry data, was designed to answer the following question: What are the conditional survival probabilities of surviving one additional year, given that patients have already survived 1, 2, 3, 4 and 5 years after diagnosis of a high-grade glioma?

Methods

The population-based cancer registry, Cancer Surveillance Program (CSP) is both a member of the statewide population-based surveillance system, the California Cancer Registry (CCR), and part of the surveillance, epidemiology, and end results (SEER) program [2]. It extracts records of cancer patients from hospitals, institutes, clinics and medical laboratories equipped to diagnose cancer in Los Angeles County. The information collected by CSP includes demographic information, tumor characteristics, diagnostic information, extent of disease and limited treatment information, as well as the last follow-up date, vital status and cause of death.

Malignant glioma cases were identified using the International Classification of Diseases for Oncology (ICD-O-3) codes [3]. Cancer histology was characterized by the new World Health Organization (WHO) classification for brain tumors [4]. The selected glioma histology's included malignant glioma, anaplastic astrocytoma, gemistocytic astrocytoma, glioblastoma, giant cell glioblastoma and gliosarcoma. Anaplastic oligodendroglial tumors were not included. 2,983 cases of high-grade glioma diagnosed in Los Angeles County from 01/01/1990 to 12/31/2000 were retrieved. Patients who were younger than 19 years old at the time of diagnosis or who were diagnosed with malignant gliomas in the brainstem, spinal cord, optic nerve or ventricle were excluded. A total 2,743 adult patients with supratentorial high-grade gliomas, WHO grade III or IV gliomas were included in this study. Cases were followed for survival through June 2004.

Overall survival was calculated as the time from the date of diagnosis (first surgery and pathological diagnosis) to the date of death for any reason, or the date the patient was last known to be alive. In contrast, the conditional survival was calculated as the time from the date of a landmark (e.g. 1 year anniversary post-diagnosis) to the date of death or the date the patient was last known to be alive, conditional on the patient surviving beyond the landmark date. Thus the conditional survival probabilities excluded patients who did not survive beyond the landmark date; stated differently, conditional survival analysis includes only those patients who are known to be alive and therefore still "at risk" of surviving or dying after the landmark date.

Numbers and percentages were used to summarize the study data. In univariate analysis, the log-rank test was used to test the association of overall survival with demographics, marital status, socioeconomic status, tumor characteristics at diagnosis, primary treatment, treatment start time, and type of treating hospital. The relative risk of death as well as associated 95 % confidence intervals were calculated based on the Pike estimate [5], using the observed and expected number of events from log-rank test statistic. Those factors significantly associated with overall survival in the univariate analysis were included in a multivariable analysis using the Cox proportional hazards model.

Kaplan–Meier plots were used to estimate and illustrate the probabilities of overall and conditional survival [6]. Bar charts were used to show the estimated probability of surviving 5 years from the time of diagnosis and conditional on having already survived for 1, or 2 or 3 years by age ($\leq$55 years, 56–70 years and >70 years) and WHO status.

Results

A total of 2,743 malignant glioma patients meeting the inclusion criteria were identified in the CSP database. Baseline demographics and disease characteristics are summarized in Table 1. The median age at diagnosis was 64 years old; slightly more patients were male (55 %) than female (45 %). More patients were diagnosed with WHO grade IV gliomas (76 %) than with WHO grade III gliomas (24 %). After diagnosis, 83 % of patients underwent some form of treatment (i.e. surgery, radiation or chemotherapy). The associations of overall survival with demographics and disease baseline characteristics are shown in Table 2. Age at diagnosis, tumor site, WHO grade, primary treatment, time to start of treatment, as well as whether the patient was treated at a teaching hospital were statistically significantly associated with overall survival in univariate analysis (Table 2) and in multivariable analysis (Table 3, unconditional portion). Overall median survival and its 95 % confidence interval were 6.6 (6.2, 6.9) months with median follow-up of 8.6 years.

Trend of survival

The probability of overall survival (unconditional) at 1 year after diagnosis was 0.31 $\pm$ 0.01 and probability of surviving 2, 3, 4, and 5 years from diagnosis was 0.13 $\pm$ 0.01, 0.10 $\pm$ 0.01, 0.08 $\pm$ 0.01, and 0.06 $\pm$ 0.01, respectively (Fig. 1). In the conditional survival analysis, as patients remained alive longer (e.g. 1 and 2 years after diagnosis), the (conditional) probability of surviving additional years increased (Fig. 2a–d). The probabilities of survival at

Table 1 Baseline characteristics

Factors	Number of patients	Percent (%)
Total patients	2,743	100
Age at diagnosis		
≤55	932	34
56–70	933	34
>70	878	32
Median (range)	64.2 (19.1–100.9)	
Gender		
Male	1,515	55
Female	1,228	45
Marital status		
Married	1,698	63
Single	978	37
Socioeconomic status		
High–high class	738	27
Middle–high class	584	21
Middle class	520	19
Middle–low class	431	16
Low–low class	288	11
Missing	182	7
Year of diagnosis		
1990–1992	775	28
1993–1995	721	26
1996–1998	751	27
1999–2000	496	18
Tumor site		
Front of lobe	652	24
Occipital lobe	80	3
Parietal lobe	430	16
Temporal lobe	495	18
Overlapping lesion of brain	715	26
Brain, NOS	189	7
Cerebellum, NOS	159	6
Ventricle, NOS	20	1
Overlapping lesion of brain and CNS	2	<1
Nervous system, NOS	1	<1
WHO tumor grade		
WHO grade III	662	24
Malignant glioma	191	29
Anaplastic astrocytoma	382	58
Gemistocytic astrocytoma	89	13
WHO grade IV	2,081	76
Glioblastoma, NOS	2,024	97
Giant cell glioblastoma	22	1
Gliosarcoma	35	2
Treatment of primary		
No treatment received	473	17
Surgery only	423	15
Radiotherapy only	446	16
Chemotherapy only	16	1
Combination therapy	1,385	50
Treatment started after diagnosis		
No treatment received	473	17
≤30 days	2,056	75
>30 days	206	8
Median (range and quartiles[a])	3 (0–1,476) Q1 = 0 & Q3 = 12	
Missing	8	
Treating hospitals		
Teaching hospitals	979	36
Non-teaching hospitals	1,764	64

[a] Q1 = lower quartile (25th percentile) and Q3 = upper quartile (75th percentile)

1 year after diagnosis, and for one additional year conditional on having already survived 1, 2, 3, 4, and 5 post-diagnosis years are listed in Table 4. This increase was greatest during the first 2 post-diagnosis years, from 0.43 ± 0.02 conditional on surviving 1 year post diagnosis, to 0.72 ± 0.02 conditional on surviving 2 years after diagnosis, and leveled out as patients survived longer, i.e., 0.80 ± 0.03, 0.84 ± 0.03 and 0.91 ± 0.02 conditional on surviving 3, 4, and 5 years after diagnosis respectively.

The prognosis for patients with WHO grade III tumors was better than those with WHO IV gliomas, estimated by both unconditional and conditional survival probabilities—however, this difference, which was both substantial and statistically significant at the time of diagnosis and conditional on surviving 1 and 2 years, was no longer substantial or statistically significant once patients had survived 4 or 5 years; absolute differences in the probability of surviving one additional year were 0.47–0.26 = 0.21, 0.40, and 0.30 conditional on surviving 0, 1, and 2 years, but were 0.05, and 0.08, conditional on surviving 4 and 5 years, respectively. In both groups of patients, the conditional probability of one additional year of survival increased as patients survived longer (Table 4, Figs. 1, 2a–d). This trend was also seen in the probability of surviving 5 additional years survival conditioned on having survived for 1, 2, or 3 years (Fig. 3a).

A similar pattern was seen when patients were grouped by age: (1) younger patients manifested better one-year survival probabilities, (2) the conditional probabilities of one additional year of survival increased each year post-diagnosis, and (3) the differences among the age groups decreased as the time post-diagnosis increases (Fig. 3b).

Table 2 Association of baseline characteristics with overall survival—univariate analysis

	N	Relative Risk[1] (95 % Confidence interval (CI))	Median survival (95 % CI) (months)	*p*-Value[2]
All Patients				
Overall survival	2,743		6.6 (6.2, 6.9)	
Age at diagnosis				<0.001
≤55	932	1.00	14.0 (13.1, 15.1)	
56–70	933	2.15 (1.95, 2.37)	5.9 (5.5, 6.4)	
>70	878	3.23 (2.91, 3.57)	3.5 (3.3, 3.8)	
Gender				0.26
Male	1,515	1.00	7.0 (6.4, 7.5)	
Female	1,228	1.05 (0.97, 1.13)	6.1 (5.5, 6.6)	
Marital status				0.25
Married	1,698	1.00	7.2 (6.6, 7.7)	
Single	978	1.05 (0.97, 1.14)	5.5 (5.0, 6.3)	
Socioeconomic status				0.56
High–high class	738	1.00	7.7 (6.8, 8.5)	
Middle–high class	584	1.07 (0.96, 1.20)	5.8 (5.1, 6.5)	
Middle class	520	1.02 (0.91, 1.15)	6.5 (5.8, 7.4)	
Middle–low class	431	1.07 (0.95, 1.21)	5.8 (5.0, 6.6)	
Low–low class	288	0.97 (0.84, 1.12)	6.9 (5.3, 8.2)	
Missing	182			
Tumor site				<0.001
Frontal/occipital/parietal/temporal lobes	1,657	1.00	7.7 (7.0, 8.2)	
Cerebellum/ventricle/brain NOS/ multilobar	1,086	1.27 (1.18, 1.38)	5.1 (4.6, 5.7)	
WHO tumor grade				<0.001
WHO grade III	662	1.00	10.1 (8.5, 11.8)	
WHO grade IV	2,081	1.83 (1.67, 2.02)	6.1 (5.6, 6.4)	
Treatment of primary				<0.001
Combined therapy	1,385	1.00	10.8 (10.1, 11.3)	
Single treatment	885	1.79 (1.64, 1.95)	4.3 (4.0, 4.6)	
No treatment received	473	2.89 (2.59, 3.22)	1.9 (1.6, 2.1)	
Treatment started after diagnosis				<0.001
>30 days	206	1.00	11.4 (10.3, 13.3)	
≤30 days	2,056	1.42 (1.22, 1.64)	7.7 (7.3, 8.3)	
No treatment received	473	3.26 (2.75, 3.87)	1.9 (1.6, 2.1)	
Missing	8			
Teaching hospital				<0.001
Yes	979	1.00	11.2 (10.1, 11.8)	
No	1764	1.75 (1.62, 1.90)	4.9 (4.5, 5.1)	

[1] Relative risk can be thought as the average increase chance of dying at any point in time for patients in the second or third group compared to those in the first group

[2] Based on logrank test

Discussion

High-grade glioma is a relatively rare cancer with very poor survival. According to the Central Brain Tumor Registry in the United States during the years of 1998 to 2002, the estimated age-adjusted incidence of high-grade gliomas is 6.7 and 4.6 patients per 100,000 persons per year, for WHO grade III and grade IV gliomas respectively (Central Brain Tumor Registry in the United States, 2006). Gliomas account for 1.4 % of all new cancer cases and 2.3 % of all cancer deaths in the United States [2]. In general, non-Hispanic whites have the highest incidence of glioma and mortality rates from glioma among all the ethnic groups [2]. Among all the newly diagnosed cases of primary brain cancer in the United States, approximately 50 % are histologically classified as glioma and 50 % of all gliomas are glioblastoma (WHO grade IV) [7].

Table 3 Association of baseline characteristics with survival—multivariable analysis

	Unconditional			Conditioned on having survived 3 years		
	N	Relative risk[1] (95 % CI[2])	*p*-Value[3]	N	Relative risk[1](95 % CI)	*p*-Value[3]
Age at diagnosis			<0.001			0.038
≤55	932	1.00		214	1.00	
56–70	933	1.97 (1.78, 2.17)		25	1.85 (1.03, 3.32)	
>70	878	2.50 (2.24, 2.79)		10	2.30 (0.88, 6.01)	
Tumor site			0.002			0.44
Frontal/occipital/parietal/temporal lobes	1,657	1.00		176	1.00	
Cerebellum/ventricle/brain NOS/multilobar	1,086	1.14 (1.05, 1.23)		73	1.18 (0.78, 1.78)	
WHO tumor grade			<0.001			0.041
WHO grade III	662	1.00		168	1.00	
WHO grade IV	2,081	1.91 (1.72, 2.11)		81	1.53 (1.02, 2.29)	
Treatment of primary			<0.001			0.20
Combined therapy	1,385	1.00		175	1.00	
Single treatment	885	1.74 (1.59, 1.91)		53	0.76 (0.47, 1.24)	
No treatment received	473	2.65 (2.35, 2.99)		21	0.54 (0.25, 1.18)	
Time to treatment start after diagnosis			0.003			0.14
No treatment or ≤30 days	2,529	1.00		206	1.00	
>30 days	206	0.79 (0.68, 0.93)		42	1.40 (0.90, 2.19)	
Missing	8			1		
Teaching hospital			<0.001			0.96
Yes	979	1.00		145	1.00	
No	1,764	1.31 (1.20, 1.43)		104	1.01 (0.69, 1.47)	

[1] Relative risk can be thought as the average increase chance of dying at any point in time for patients in the second or third group compared to those in the first group

[2] 95 % CI = 95 % confidence interval

[3] Based on Cox proportional hazards model, adjusted for other variables in the model

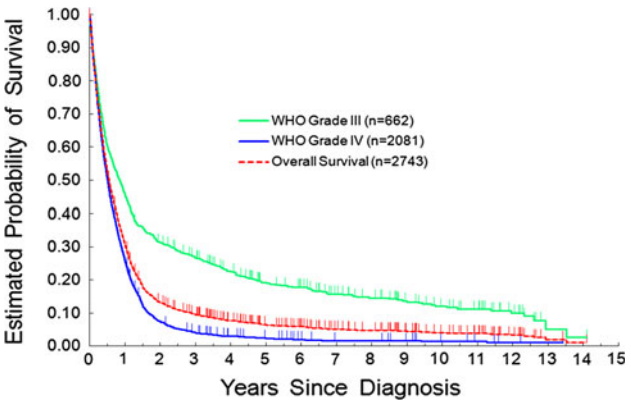

Fig. 1 Kaplan-Meier plots of overall (unconditional) survival from diagnosis of all patients with malignant gliomas (*dashed red line*) and by WHO grade: grade III (*solid green line*) and grade IV (*solid blue line*)

In the present study, data were analyzed from a large cohort of 2,743 adult patients with supratentorial high-grade glioma diagnosed in Los Angeles County between the years of 1990 and 2000, the largest reported study of conditional survival analyses in patients with high-grade glioma. In this study conditional probabilities to predict patients' survival were used. The study showed that as patients survived longer after initial diagnosis, their probability of subsequent survival markedly increased.

The traditional estimates of survival are the survival rates which vary greatly depending upon prognostic characteristics and thus are challenging to apply for individual patients [8–11]. Conditional survival probabilities are estimated among a specific cohort of patients by excluding those who did not survive to the start of the landmark or time point of interest. Therefore, this conditioned cohort study represents a subpopulation of patients, in contrast to the analysis beginning at the time of diagnosis when all patients were included. In the present study, the estimated chance of 5-year survival after diagnosis is 6 % (136 out of 2,743 of patients survived 5 years after diagnosis—Fig. 1), a figure often cited in the literature and based on university brain tumor treatment centers [12–14]. However, when analyzed by

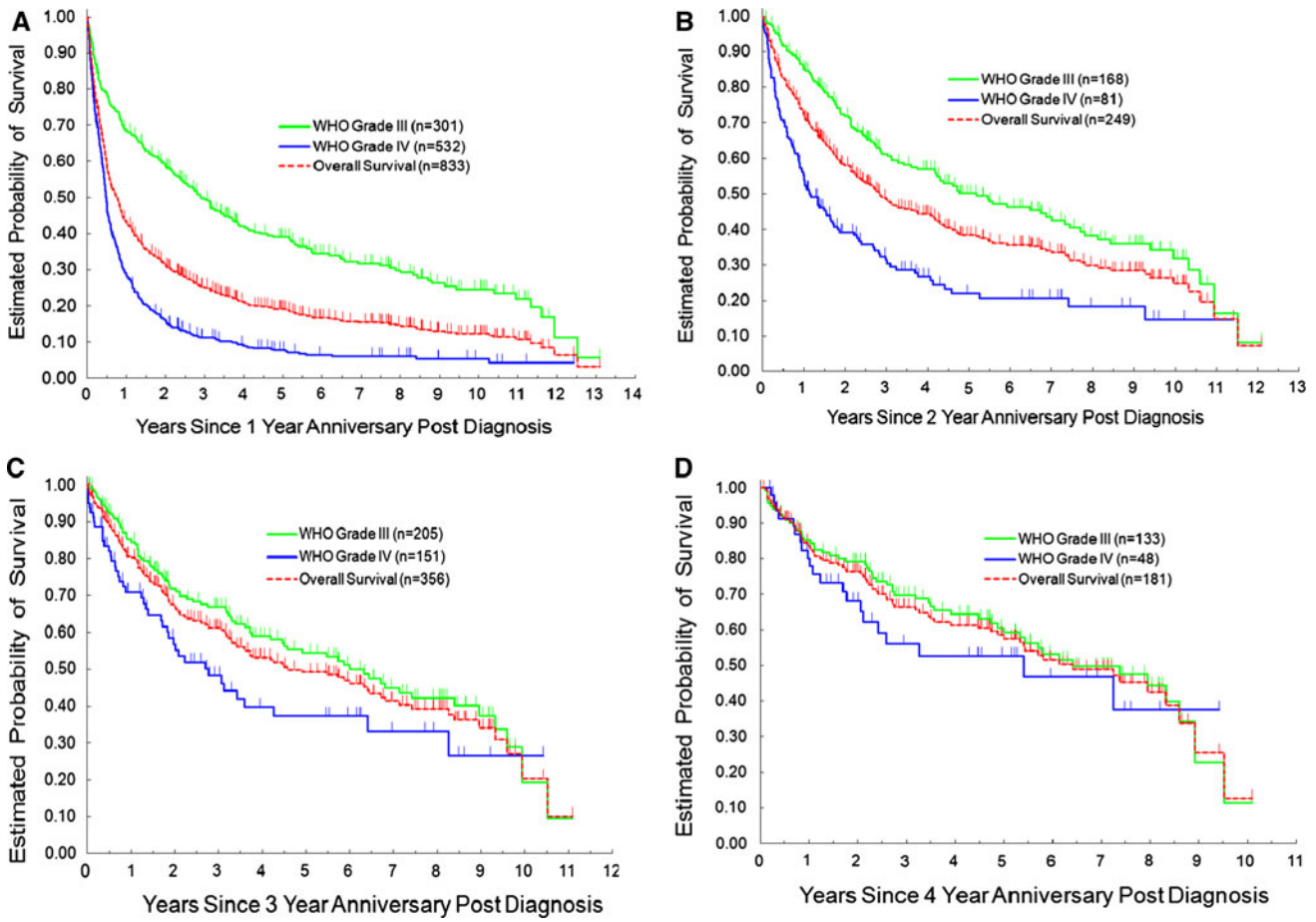

Fig. 2 Kaplan-Meier plots of conditional survival of patients with malignant gliomas (all patients: *dashed red line*) and by WHO Grade (Grade III: solid green line. Grade IV: solid blue line). **a** Survival conditional on having survived one year post diagnosis. **b** Survival conditional on having survived 2 years post diagnosis. c Survival conditional on having survived three years post diagnosis. **d**: Survival conditional on having survived 4 years post diagnosis

conditional survival probabilities and conditional median survival times, the data demonstrate that as patients survive longer after diagnosis, their probabilities of surviving an additional one year increases (ranging from 43 % conditioned on 1-year survival to 91 % conditioned on 5-year survival) (Table 4), irrespective of original glioma grade.

The survival rate among the study population dropped steeply after diagnosis and overall median survival is approximately 6.6 months (Fig. 1). The very short median survival, nearly 40 % of that reported in clinical trials in patients with glioblastoma (median survival 14.6 months), reflects perhaps more accurately survival in a large urban community treating all patients without the restrictions imposed by trial inclusion or exclusion criteria [15] and in a wide variety of hospitals. Polley et al. [16] recently reported the overall and conditional probabilities of survival on 498 patients treated on 6 Phase II trials between 1975 and 2002; although 128 of these 498 received temozolomide, their outcome was not significantly different from patients on the pre-temozolomide protocols. Overall in the Polley series, the 4 year survival was 7 % (95 % CI: 5, 10 %); this was doubled what was observed in the group of WHO grade IV patients in this manuscript which was 3 % (95 % CI: 2, 4 %). As with the series reported in this manuscript, the conditional probabilities increased as the time post diagnosis increased (Fig. 4). Interestingly however, the (unconditional) survival during the first year was nearly doubled in the Polley series (58 % (95 % CI: 54, 63 %) vs. 26 % (95 % CI: 24 %, 28 %)). Selecting patients by way of entry into clinical trials, usually by specifying independence in activities of daily living (i.e. a Karnofsky performance status >60) and age (<71 years), results in what might be expected as optimal survival rates based on contemporary treatment paradigms. Rarely reported are trials designed for elderly patients with high-grade gliomas or for patients with compromised neurological performance. Los Angeles County, the site of the present study, is a large ethnically diverse community with a significant proportion of socioeconomically challenged patients that negatively impacts survival in essentially all cancer diagnoses.

Table 4 Comparing unconditional probability of survival at 1 year with conditional probabilities of surviving one additional year

	Unconditional survival at 1 year		Conditional probability of surviving one additional year after surviving 1, 2, 3, 4 or 5 years post diagnosis[1]									
			1 year		2 years		3 years		4 years		5 years	
	N	Prob. ±SE[2]	*N*	Prob. ±SE[2]	*N*	Prob. ±SE[2]	*N*	Prob. ±SE[2]	*N*	Prob. ±SE[2]	*N*	Prob. ±SE[2]
Overall	2,743	0.31 ± 0.01	833	0.43 ± 0.02	356	0.72 ± 0.02	249	0.80 ± 0.03	181	0.84 ± 0.03	136	0.91 ± 0.02
WHO grade												
III	662	0.47 ± 0.02	301	0.69 ± 0.03	205	0.85 ± 0.03	168	0.85 ± 0.03	133	0.85 ± 0.03	101	0.93 ± 0.03
IV	2,081	0.26 ± 0.01	532	0.29 ± 0.02	151	0.55 ± 0.04	81	0.71 ± 0.05	48	0.80 ± 0.06	35	0.85 ± 0.06
p-Value[3]		<0.001		<0.001		<0.001		0.041		0.48		0.55
Age at diagnosis												
≤55	932	0.56 ± 0.02	523	0.55 ± 0.02	285	0.78 ± 0.02	214	0.83 ± 0.03	161	0.83 ± 0.03	123	0.91 ± 0.03
56–70	933	0.24 ± 0.01	226	0.22 ± 0.03	50	0.52 ± 0.07	25	0.63 ± 0.10	15	1.00 ± 0.00	11	0.91 ± 0.09
>70	878	0.10 ± 0.01	84	0.25 ± 0.05	21	0.48 ± 0.11	10	0.67 ± 0.16	5	0.50 ± 0.25	2	1.00 ± 0.00
p-Value[3]		<0.001		<0.001		<0.001		0.038		0.51		0.52

[1] Conditional probability of surviving additional 1 year, given that the patient has survived 1, 2, 3, 4, or 5 years after diagnosis

[2] Probabilities of surviving 1 year ± Greenwood standard error

[3] *p*-Value based on Cox proportional hazards model, adjusted for other variables in the model which include age at diagnosis, tumor grade, tumor site, primary treatment, time to start treatment, and type of treating hospital (see Table 3)

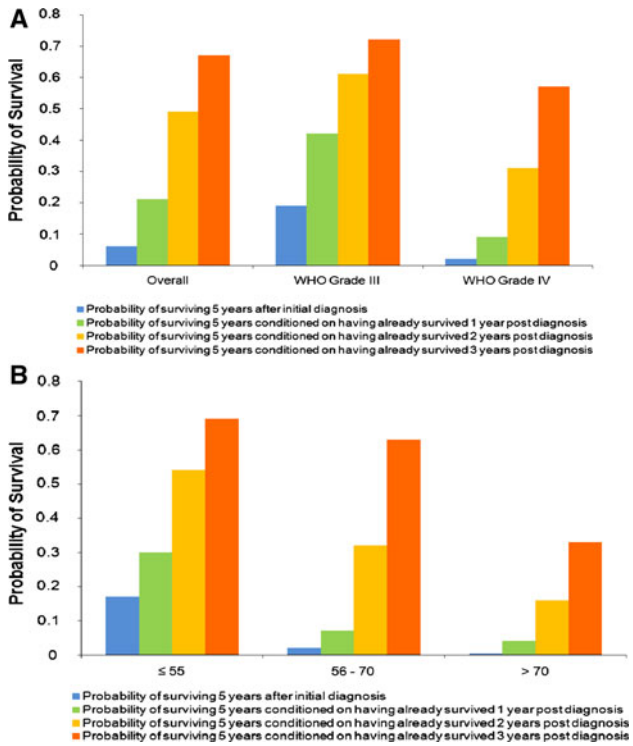

Fig. 3 Unconditional and conditional probabilities of surviving 5 additional years according to age (**a**) and WHO grade (**b**). *Blue bars* represent (unconditional) probability of surviving 5 years after diagnosis. *Green*, *yellow*, and *red bars* represent the probability of surviving an additional 5 years, conditional on already having survived 1, 2 or 3 years post diagnosis, respectively

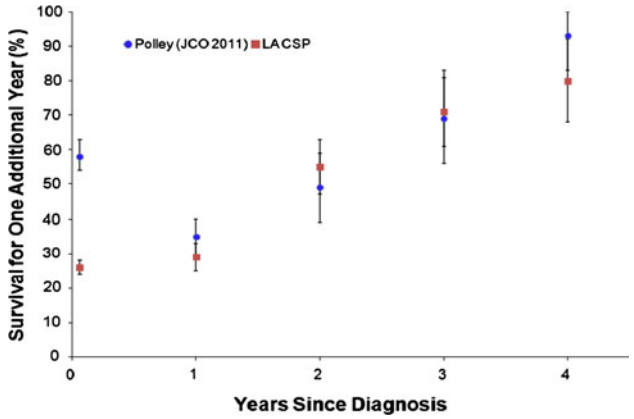

Fig. 4 One year survival probabilities (represented as percents) and 95 % confidence intervals for glioblastoma (WHO grade IV). Patients in the Los Angeles County CSP cancer registry series (in *red squares*) are compared to patients enrolled on 6 Phase II clinical trials reported by Polley et al. [16] (in *blue circles*). Unconditional probabilities are represented at 0 years after diagnosis—i.e. Survival since diagnosis; conditional probabilities are provided for having survived 1, 2, 3 and 4 years post

Age is a well recognized negative prognostic factor for high-grade glioma and this study recapitulates its prognostic significance (Fig. 3b) [17–19]. However, the study data also suggests that when a high-grade glioma was diagnosed in the older age cohort, defined as patient's ≥56 years of age, the probabilities of surviving one additional year increase substantially as patients survive longer (Table 4).

In conclusion, the present study examines the outcome of 2,743 patients with high-grade glioma, all identified in a population-based database, making it an ideal platform for performing conditional survival analyses. Although the CSP, the source where the data in this study was retrieved,

is a California based cancer registry, the results are generalizable to patients with high-grade glioma in the United States. However, as a population-based cancer registry, CSP description of disease treatment is not exact. For example, it does not differentiate chemotherapy regimen, extent of surgery resection, types of salvage therapy, baseline performance status, etc. In addition, the data collection in the present study involves patients diagnosed between 1990 and 2000; the vast majority of these patients received all of their therapy prior to 2004 (when the data were abstracted). This is before temozolomide (Temodar [TMZ], Merck Pharmaceutical, Whitehouse Station, NJ), together with concurrent radiotherapy, became the standard of care for patients with newly diagnosed glioblastoma [7]. Therefore, this study does not reflect the impact of newer treatment, similar to other large comprehensive datasets [20]. This study suggests that conditional survival probability may be helpful to predict prognosis for patients with not only high-grade glioma, but other diseases with changing hazards over time. In summary, estimated by conditional survival method, patients diagnosed with high-grade glioma appear to have a large gain in their conditional survival probability over time.

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