CLINICAL STUDY – PATIENT STUDY

Improved survival time trends for glioblastoma using the SEER 17 population-based registries

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Abstract The EORTC/NCIC 22981/26981 study demonstrated an improvement in median overall survival (OS) from 12.1 to 14.6 months in patients with glioblastoma (GBM) who received temozolomide with post-operative radiotherapy (RT). The current study was performed to determine if those results translated into a survival benefit in a population-based cohort. Patients diagnosed between 2000 and 2006 with a GBM who underwent surgery and post-operative RT were selected from the Surveillance, Epidemiology and End Results database. Patients were grouped into time periods: 2000–2001, 2002–2003, 2004 and 2005–2006 (which represented those treated after the EORTC/NCIC trial presentation in 2004). Relative survival (RS) was estimated by the Kaplan–Meier method, and Cox multivariable regression modeling was used to estimate proportional hazard ratios (HR). Over time, there was improvement in the median and 2-year RS of 12 months and 15% for 2000–2001, 13 months and 19% for 2002–2003, 14 months and 24% for 2004, and 15 months and 26% for 2005–2006 ($P < 0.0001$ compared to 2000–2001 and 2002–2003; $P = 0.07$ compared to 2004). The estimated adjusted HR showed that patients diagnosed in 2005–2006 had significantly improved survival when compared to patients diagnosed in 2000–2001 (HR = 0.648, 95% CI 0.604–0.696). The median and 2 year RS of 15 months and 26% in 2005–2006 was similar to the median and 2 year OS of 14.6 months and 26% seen in the EORTC/NCIC phase III study. These results are encouraging and suggest that the current treatment of glioblastoma nationwide is now associated with an improved survival compared to previous time cohorts.

Keywords Glioblastoma · Radiation · Temozolomide · SEER

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Introduction

Glioblastoma (GBM) is associated with a poor prognosis [1–5]. Historically, treatment included surgical resection followed by post-operative radiation therapy which was associated with a small survival benefit [6].

A practice changing phase III study by the European Organisation for Research and Treatment of Cancer (EORTC) group and National Cancer Institute of Canada Clinical Trials Group (NCIC) established the current treatment regimen when it was presented in 2004 [7, 8]. This study randomized patients to post-operative radiation therapy versus post-operative radiation therapy with concurrent temozolomide followed by six cycles of adjuvant

temozolomide. Initially, it revealed a significant improvement in 2 year overall survival from 10.4% with post-operative radiotherapy alone to 26.5% with post-operative radiotherapy plus temozolomide. After a median follow up of 5 years these results persisted and the temozolomide plus post-operative radiotherapy arm was associated with a hazard ratio of 0.63 (95% CI 0.53–0.75) when compared to patients who received post-operative radiotherapy alone [9, 10].

We undertook the current study to determine if the results of the EORTC/NCIC phase III trial translated to a nationwide improvement in overall survival in patients with newly diagnosed glioblastoma. Using a large population-based cohort, we examined if patients diagnosed after the EORTC/NCIC phase III study reporting had outcomes similar to those treated on the post-operative radiation therapy plus temozolomide arm of the study.

Methods

Data and study population

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute covers 26% of the US population and collects incidence and survival data from 17 population-based cancer registries [11]. The database contains information on primary tumor site, age, gender, histology, stage at diagnosis, first course of treatment, and overall survival. Patients selected for inclusion in this study were aged 20 years and older and had a microscopically-confirmed first primary of glioblastoma (International Classification of Diseases for Oncology, Version 3 histology codes 9440–9442) diagnosed during 2000–2006. All selected patients underwent either surgical resection or biopsy followed by post-operative radiation therapy and were followed for a minimum of one year. Of 15,546 glioblastomas diagnosed in 2000–2006 in those aged 20 years and older, exclusions were performed for 2,127 second or later primaries, 86 autopsy only, 1,172 non-microscopically confirmed cases, 55 cases not included in the research database, and 13 cases alive with no survival time. In addition, 5,071 glioblastomas were excluded because they received a treatment regimen other than surgery followed by post-operative radiation therapy. One hundred three glioblastomas were excluded because the type of surgery was unknown ($n = 76$), or only local tumor destruction was performed ($n = 27$). The final sample size included 6,919 patients.

Patients were grouped into time periods for comparison: 2000–2001, 2002–2003, 2004, and 2005–2006 (which represented the group treated after the EORTC/NCIC trial initial presentation in the middle of 2004). Survival time

was defined as the time from diagnosis to the date of death from any cause or the date of last known follow-up. The extent of surgery was determined from the operative note and, for these analyses; this variable was grouped into subtotal resection, which included patients who underwent a biopsy, or gross total resection. Covariates in the statistical analysis included extent of surgery, age group at diagnosis (20–34, 35–44, 45–54, 55–64, 65–74, 75+ yr), sex, race (white, black, other), Hispanic ethnicity, and SEER registry. Information regarding the utilization of chemotherapy, local control, performance status, and specific radiation therapy technique (including dose, fractionation, beam energy) is not available on the SEER research database.

Statistical analysis

Estimates of relative survival (RS), the ratio of observed survival to the expected survival rate were calculated using the Kaplan–Meier method. All statistical tests were two-sided, and significance was defined as $P < 0.05$. The log rank test was used to estimate whether there were differences in RS based on the year diagnosed. To further examine the association between post-operative radiation therapy and survival, hazard ratios (HR) and the corresponding 95% confidence limits (CL) were estimated using Cox proportional hazards regression models including multivariable models for all estimates adjusted for all covariates [12]. Kaplan–Meier survival analyses were conducted using SEER*Stat version 7.0.4 [13]. Proportional hazards regression analyses were performed using PASW Statistics 18, Release Version 18.0.0 (SPSS Inc., 2009, Chicago, IL, www.spss.com).

Results

Patient characteristics are summarized in Table 1. Among the 6,919 patients, 25.7% were diagnosed during 2001–2001, 28.3% were diagnosed during 2002–2003, 15.8% were diagnosed in 2004, and 30.3% were diagnosed during 2005–2006. The median follow-up was 12 months. The median age of patients diagnosed in the study was 59 years. Approximately 80% of patients were recorded as having undergone a gross total resection.

The median and two year RS for the entire cohort was 13 months and 20%, respectively. Over the time periods studied, there was a significant improvement in the median and 2 year RS of 12 months and 15% for 2000–2001, 13 months and 19% for 2002–2003, 14 months and 24% for 2004, and 15 months and 26% for 2005–2006 ($P < 0.0001$ compared to 2000–2001 and 2002–2003; $P = 0.07$ compared to 2004) (Fig. 1). When restricted to those aged 20–69 years, the same patterns with slightly better survival

Table 1 Characteristics for patients ages 20 years and older with first primary histologically confirmed glioblastoma undergoing surgical resection and post-operative radiation diagnosed in 2000–2006; SEER 17-Registries Research Data

	N	%
Total	6,919	100.0
Gender		
Male	4,186	60.5
Female	2,733	39.5
Race		
White	6,307	91.2
Black	306	4.4
Other	302	4.4
Ethnicity		
Hispanic	638	9.2
Non-hispanic	6,281	90.8
Age group at diagnosis (years)		
20–34	258	3.7
35–44	663	9.6
45–54	1,567	22.6
55–64	1,983	28.7
65–74	1,616	23.4
75+	832	12.0
Extent of surgery (determined by operative note)		
Biopsy/subtotal resection	1,350	19.5
Gross total resection	5,569	80.5
Year of diagnosis		
2000–2001	1,775	25.7
2002–2003	1,955	28.3
2004	1,095	15.8
2005–2006	2,094	30.3
Vital status		
Deceased	6,008	86.8
Alive	911	13.2

* Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2009 Sub (1973–2007 varying)—Linked To County Attributes—Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission

Fig. 1 Overall relative survival of cohort stratified by diagnosis year groups

multivariate analysis. Registry location was significant on multivariate analysis. As expected, increasing age was associated with an increasing hazard ratio.

Discussion

This large review of patients with glioblastoma treated with surgery and post-operative radiation therapy demonstrated that patients diagnosed in 2005–2006 after the EORTC/NCIC trial was presented were associated with an improved survival compared to patients diagnosed in earlier time periods. The strength of these results is that they represent a population-based cohort from a variety of different medical centers across the nation.

The SEER research data showed that patients with glioblastoma diagnosed in 2005–2006 who underwent surgical resection and post-operative radiation had a median survival of 15 months and a 2 year relative survival of 26%, which was a significant improvement compared to earlier time periods and compares favorably with the outcomes reported in the EORTC/NCIC phase III study (median survival of 14.6 months and a 2 year overall survival of 26.5%) (Fig. 2) [7]. After controlling for known patient characteristics our study revealed being diagnosed in 2005–2006 was associated with a significant hazard ratio of 0.648. This also compares favorably to the adjusted hazard ratio for death in the radiotherapy plus temozolomide group as compared to the radiotherapy group of the EORTC/NCIC study of 0.62 (95% CI 0.51–0.75). The similar survival seen between the two cohorts are encouraging and suggest that the results of the EORTC/NCIC phase III were rapidly implemented into clinical practice across the United States. This quickly translated into a survival benefit for patients with newly diagnosed glioblastoma. As a comparison, glioblastomas in the SEER

were found with 2 year RS of 18% for 2000–2001, 22% for 2002–2003, 28% for 2004, and 30% for 2005–2006 (P < 0.0001 compared to 2000–2001 and 2002–2003; P = 0.18 compared to 2004).

After adjusting for known patient characteristics, the estimated adjusted hazard ratio showed that patients diagnosed in 2005–2006 had significantly improved survival when compared to patients diagnosed in earlier time periods (HR = 0.648, 95% CI 0.604–0.696) (Table 2). Race, ethnicity, and extent of resection were not significant on
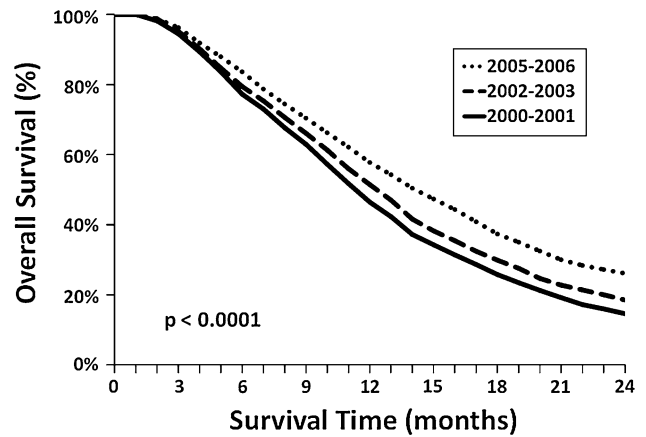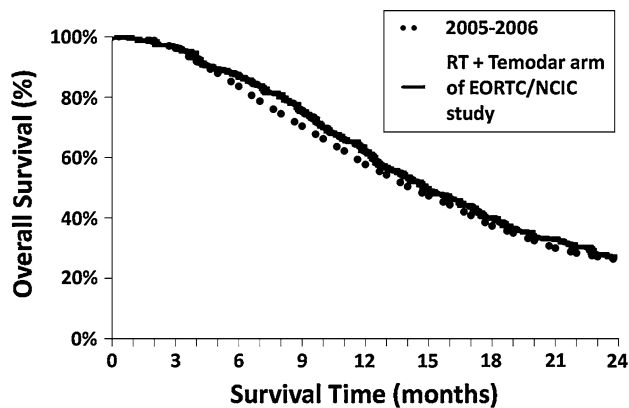
Fig. 2 Overlay of Kaplan–Meier survival curves of patients with glioblastoma diagnosed from 2005–2006 from the SEER Registry and patients enrolled on the EORTC/NCIC trial treated with post-operative radiation and temozolomide

Table 2 Multivariate analysis of overall survival risk factors

	Hazard ratio	95.0% CI for hazard ratio		P value
		Lower	Upper	
Age at diagnosis group (years)				
20–34				<0.001
35–44	1.315	1.103	1.569	0.002
45–54	1.859	1.580	2.187	<0.001
55–64	2.371	2.019	2.785	<0.001
65–74	3.489	2.974	4.114	<0.001
75+	4.923	4.156	5.831	<0.001
Gender				
Male vs. female	0.931	0.884	0.981	0.008
Race group				
White				0.361
Black	1.067	0.943	1.207	0.303
Other	0.941	0.828	1.069	0.349
Ethnicity				
Hispanic vs non-hispanic	0.992	0.906	1.087	0.870
Extent of surgery				
Gross total vs. subtotal	0.999	0.995	1.002	0.363
Year of diagnosis group				
2000–2001				<0.001
2002–2003	0.865	0.809	0.924	<0.001
2004	0.735	0.678	0.796	<0.001
2005–2006	0.648	0.604	0.696	<0.001

research data in those aged 20 years and older who did not undergo the treatment regimen of surgery followed by post-operative radiation therapy had median survival of 5 months or less and much poorer 2 year RS (4% for 2000–2001, 6% for 2002–2003, 7% for 2004, and 7% for 2005–2006 ($P < 0.0001$ compared to 2000–2001,

$P = 0.001$ compared to 2002–2003, $P = 0.14$ compared to 2004)). The improvements in 2-year relative survival seen in all glioblastomas, regardless of treatment, appear to be primarily driven by those who received surgery followed by post-operative radiation therapy.

Besides the introduction of temozolomide during the time period studied there were other significant systemic therapeutic advancements in the treatment of glioblastoma including the use of carmustine wafers (polifeprosan 20 with carmustine implant, Gliadel®) and utilization of bevacizumab for recurrent disease [14, 15]. Advances in surgical resection included utilizing awake craniotomies, frameless computer guided stereotaxis, and intra-operative imaging to facilitate aggressive resection and minimize post-operative neurologic complications [16, 17]. Furthermore, there were improvements in the delivery of radiation therapy in the adjuvant and recurrent setting during the time period studied, including using intensity modulation, stereotactic radiosurgery, and brachytherapy [18–22]. All of these advancements may have also contributed towards the improvement in survival that we observed among this cohort, however, individually none of these advances can account for the improved survival seen.

Approximately 80% of the cohort was coded as having undergone a gross total resection which is higher than most published series [7, 23]. A large retrospective series from MD Anderson revealed that 47% of patients were able to undergo a resection removing more than 98% of the tumor based on the post-operative MRI. Patients who underwent removal of greater than 98% of the tumor had a statistically significant improvement in their overall survival. The high percentage of patients in our cohort who underwent gross total resection is likely due to the coding of this variable being based on the operative note per the SEER manual, and not based on residual disease seen on post-operative imaging. A previously published study found that the operative note only correlated with the post-operative MRI findings 30% of the time [24, 25]. The lack of survival benefit based on extent of resection on multivariate analysis is likely a result of this discrepancy in coding. Increasing age was also noted to be associated with a worse hazard ratio which is consistent with other series [26–31]. Despite these potential problems with reporting, the percentage of gross total resection was controlled for when determining the hazard ratio.

This study was limited primarily because of the extent of information available in the SEER research database [32]. No information on radiotherapy technique (total dose, fraction size, radiation volume) was available. Furthermore, we cannot comment on whether chemotherapy was administered, or types of salvage therapy. In spite of this, between 2004 and 2005 the only major development in the treatment of glioblastoma was the presentation of the

EORTC/NCIC phase III trial. We hypothesize that the majority of patients diagnosed in 2005–2006 were treated with temozolomide plus post-operative radiation therapy which led to the survival benefit when compared to earlier time periods. Furthermore, the survival benefit and reduction in hazard ratio associated with the time period 2005–2006 was almost in exact concordance with the results of the temozolomide plus post-operative radiation therapy arm of the EORTC/NCIC trial, lending further support to our hypothesis. Finally, we cannot rule out the contribution that changing patterns of care independent from the EORTC/NCIC regimen to improving survival [33]. Recent advances include improved imaging, anti-thrombotic care, and FDA approved second line anti-angiogenic therapy. However, due to the widespread and increasing use of temozolomide over this time period it appears likely to have been a significant contributor to the improved survival we identified.

Conclusion

This large study of patients undergoing post-operative radiation therapy for glioblastoma revealed that patients diagnosed in 2005–2006 had a median and 2 year RS of 15 months and 26% in 2005–2006 similar to the median and 2 year overall survival of 14.6 months and 26% seen in the EORTC/NCIC phase III study. These results are encouraging and suggest that the current treatment of glioblastoma nationwide is now associated with an improved survival compared to previous time cohorts.

Conflict of interest No author indicated a conflict of interest.

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