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Rural-Urban Disparities in Survival for Primary Malignant Brain Cancer: a SEER analysis, 2000-2008

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By

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Bachelor of Science

University of Virginia

2011

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An abstract of

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of
Master of Public Health in Epidemiology
2013

Abstract

Rural-Urban Disparities in Survival for Primary Malignant Brain Cancer: a SEER analysis, 2000-2008

By Amy Blain

Background: Previous studies have identified rural-urban differences in survival for other malignancies, but these differences have not been examined for brain cancer. This study will focus on rural-urban differences in survival for primary malignant brain tumors in adults, controlling for those factors already known to have an effect on survival. Additionally, the study will examine if poverty is a significant confounder when examining rural-urban disparities in survival in the state of Georgia.

Methods: Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program for cases of primary malignant brain cancer diagnosed from 2000 to 2008 in individuals ≥20 years of age. Unadjusted Kaplan-Meier survival curves and crude 5-year relative survival estimates were used to compare survival across the rural-urban categories. A multivariable Cox proportional hazards model was used to calculate hazard ratios for rural-urban status controlling for age at diagnosis, year of diagnosis, marital status at diagnosis, race, sex, primary tumor site, histology, stage, and treatment type.

Results: 31,713 cases comprised the final analytic dataset. Kaplan-Meier survival curves and 5-year relative survival estimates showed better survival in large metropolitan counties, decreasing across the rural-urban continuum, with the worst survival in rural non-metropolitan counties. Multivariable analysis showed a significant increased risk of death from brain cancer for small metropolitan counties, urban non-metropolitan counties, and rural non-metropolitan counties compared to large metropolitan counties, with the largest risk in rural non-metropolitan counties (HR =1.17; 95% CI: 1.04–1.32). Poverty was not a significant predictor of survival in Georgia, and only small metropolitan and rural non-metropolitan counties had a significant increased risk of death compared to large metropolitan counties.

Conclusion: Brain cancer cases living in small metropolitan counties, urban non-metropolitan counties, and rural non-metropolitan counties are all at a significant increased risk of death from brain cancer compared to cases living large metropolitan counties at the time of diagnosis. Further research is needed to explore the underlying reasons for these differences.

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Acknowledgements

I would like to thank my advisor, Dr. Kevin Ward, for his guidance and encouragement throughout this process. I would also like to thank my family and friends for their continuing support throughout both this project and my entire education.

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Background

Introduction

Though primary malignant brain tumors are rare, they have a median survival less than 2 years making them one of the most lethal cancers [1-3]. In adults, most tumors occur in the frontal, temporal, or parietal lobes, and the majority are gliomas, including astrocytomas, glioblastomas, oligodendrogliomas, and gliomas not otherwise specified (NOS) [4]. Brain cancer in adults and children differ with respect to incidence, survival, histology, primary site, etiology, and treatment [5-7]. Brain cancer is the second most common cancer in children, with a lower incidence and higher survival rate than in adults [6]. Because of these differences, analyses of brain cancers are generally conducted independently for adults and children. This research will focus on the adult population.

Based on cases diagnosed from 2005-2009 in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, the age-adjusted incidence rate for cancer of the brain and other central nervous system (CNS) was 6.5 per 100,000 per year [8]. Differences in incidence are seen by both sex and race [8,9]. The incidence rate for men was 7.7 per 100,000 compared to 5.4 per 100,000 for women. Among men, the incidence rate for whites was 8.4 per 100,000 compared to 4.7 per 100,000 for blacks while among women, the incidence rate for whites was 5.9 compared to 3.6 per 100,000 for blacks [8].

The age-adjusted death rate for cases that died from 2005 to 2009 was 4.3 per 100,000 per year. Similar patterns are seen in mortality rates by sex and race, with rates being higher in men (5.2 per 100,000) than women (3.5 per 100,000), and higher in whites than blacks among men (5.6 per 100,000 and 3.1 per 100,000) and women (3.8 per 100,000 and 2.1 per 100,000). The lifetime risk of brain or other CNS cancer is 0.62%,

which equates to 1 in 161 people developing cancer in their lifetime [8]. Survival is strongly correlated with age at diagnosis and histological type but has increased over the past three decades. The overall five-year relative survival rate for cases diagnosed from 1975 to 1977 was 22% and has increased to 35% for cases diagnosed from 2001 to 2007 [1].

In addition, a 2003 study by Barnholtz-Sloan et al. showed differences in survival by race for primary malignant brain tumors. This study of SEER brain cancer cases diagnosed from 1973 to 1997 showed a 13% increased risk of death due to any cause for black cases compared to white cases when controlling for age, sex, surgery type, histology, primary tumor site, and SEER registry site. Previous studies had shown a decreased risk of death for black cases, but these studies did not control for these other covariates known to affect survival [10].

Risk Factors

Many of the commonly studied risk factors for other cancers have not been evaluated in relation to brain cancers, and those that have been evaluated have produced little or no evidence for an association. The only well established environmental risk factor for developing brain cancer is exposure to high doses of ionizing radiation [11]. Genetic syndromes, including tuberous sclerosis, neurofibromatosis types 1 and 2, nevoid basal cell carcinoma syndrome, and syndromes involving adenomatous polyps are known to account for 1% to 4% of brain cancers [4,11], with less than 1% attributable to known genes [11].

No associations have been found with tobacco or alcohol, and there is no consistent evidence for an association with dietary factors, cellular phones, low frequency

electromagnetic fields, chemical agents, occupational exposures, or head injury or trauma [4,11]. Small risks have been seen for people working in the petroleum or oil industry, and there are a few links to *in utero* infection with influenza and chicken pox, but there is also no strong, consistent evidence for these associations. The only possible protective association that has been identified is with atopic conditions like asthma, eczema, and allergies, where patients with gliomas have fewer atopic symptoms compared to controls. Though several independent studies have suggested this effect, it has not been definitively proven [4].

Rural-Urban Disparities

Studies on other types of malignancies have shown rural-urban patterns in both incidence and survival [12-14]. A 2011 study using county-level mortality data from the national mortality database found higher mortality in rural areas for all cancers combined, lung, colorectal, prostate, breast, and cervical cancers, with the highest impact of rural residence seen in colorectal, prostate, and cervical cancers. Additionally, this study found that the impact of rural-urban status on cancer mortality is not only seen in rural areas alone, but is graded across the range of the rural-urban continuum [12]. Another similar study in 2012 focused specifically on cervical cancer and analyzed cases diagnosed from 1950-2007. Higher mortality rates were seen for women living in rural areas, with a 22% higher rate in 2007 for cases in non-metropolitan areas compared to metropolitan areas [13]. A 2001 study using data from the Mississippi State Department of Health Central Cancer Registry used a binary classification for rural-urban status, in contrast to the rural-urban continuum variable used in the previous two studies. This study found higher mortality rates for lung cancer among black women in rural counties compared to urban

counties and higher mortality for prostate cancer in rural white males compared to urban white males. For most of the analyses, no difference in mortality was seen between rural and urban residents, but a significant difference in stage at diagnosis was seen [14]. These rural-urban patterns in survival may be due to lack of access to care in rural areas, lack of screening in rural areas, a poorer quality of care in rural areas, or socioeconomic factors that differ between residents of rural counties and urban counties.

Rural-urban differences in incidence and/or survival have not been examined for brain cancer. A 2004 study analyzed county-level mortality data for brain cancer deaths from 1986 through 1995 to detect clusters of elevated mortality rates, finding several statistically significant clusters of both elevated and reduced mortality rates [15]. None of these areas had rates that were extremely different from the overall mortality rate for the nation and the study did not examine the rural-urban location of any of these clusters.

This study will focus on rural-urban differences in survival for primary malignant brain tumors in adults, controlling for those factors already known to have an effect on survival. Additionally, we will examine if poverty contributes to any rural-urban disparities that are seen in the state of Georgia.

Methods

38,287 cases of primary malignant brain cancers were identified using SEER data in individuals aged ≥20 years for the diagnoses years 2000 through 2008, with follow-up through December 31, 2009 [16]. The SEER registry contains data representing approximately 28% of the US population. Data from 18 SEER registries were included in the analysis: Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Joes-Monterey, Rural Georgia, the Alaska Native Tumor registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia.

The outcome of interest was survival time, which was defined as the time in months from diagnosis until death from brain cancer or the earlier of the date the case was last known to be alive, the end of the follow-up period (December 31, 2009), or a maximum of 5 years. Survival was censored for cases that died of other causes, cases that were lost to follow-up, and at a maximum of 5 years.

Rural-urban status of cases, the primary predictor variable of interest, was assessed using the Rural-Urban Continuum code in the SEER data. This variable is based on the county of residence at the time of diagnosis and has 9 categories based on the size of the county and its proximity to a metropolitan area: (1) counties in metropolitan areas with ≥1 million people; (2) counties in metropolitan areas with 250,000 to 1 million people; (3) counties in metropolitan areas with less then 250,000 people; (4) counties in non-metropolitan areas with an urban population of ≥ 20,000 people adjacent to a metropolitan area; (5) counties in non-metropolitan areas with an urban population of ≥ 20,000 people not adjacent to a metropolitan area; (6) counties in non-metropolitan areas

with an urban population of 2,500 to 19,999 people adjacent to a metropolitan area; (7) counties in non-metropolitan areas with an urban population of 2,500 to 19,999 people not adjacent to a metropolitan area; (8) completely rural counties with an urban population less than 2,500 adjacent to a metropolitan area; (9) completely rural counties with an urban population less than 2,500 not adjacent to a metropolitan area. For analysis, these were combined into 5 groups: large metropolitan counties (1), medium metropolitan counties (2), small metropolitan counties (3), urban non-metropolitan counties (4-7), and rural non-metropolitan counties (8-9) [12]. Cases with unknown rural-urban status were excluded from the analysis.

Age at diagnosis, year of diagnosis, marital status at diagnosis, race, sex, primary tumor site, histology, stage, and treatment type were also controlled for in the analysis. Age at diagnosis was categorized in 10-year intervals from 20 years of age to 79 years of age, and a final category for 80 years of age and older. Marital status was categorized in to 3 groups: married; unmarried, including single, separated, divorced, and widowed; and unknown. Race was categorized into 3 groups: white, black, and other, which includes American Indian/Alaska Native, Asian/Pacific Islander, and other unspecified race. Primary tumor site was classified into 10 groups: cerebrum, frontal lobe, temporal lobe, parietal lobe, occipital love, ventricle NOS, cerebellum NOS, brain stem, overlapping lesion of the brain, and brain NOS. Histology was classified based on the histology brain groupings in the SEER database and limited to the following groups: glioblastoma, astrocytoma NOS, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, oligodendroglioma, anaplastic oligodendroglioma, ependymoma, mixed glioma, neoplasm, medulloblastoma, glioma NOS. Stage was categorized as localized,

regional/distant, and unknown or unstaged. Treatment was categorized into 4 groups: radiation and surgery, radiation alone, surgery alone, and no documented surgery or radiation.

Statistical Analysis

Unadjusted Kaplan-Meier survival curves and 5-year relative survival estimates were used to compare survival across the rural-urban categories. Multivariable analysis was then conducted, controlling for possible confounding factors to calculate adjusted hazard ratios and 95% confidence intervals (CIs). The proportional hazards assumption was assessed for all variables included in the model using the graphical method comparing log-log survival curves, the goodness of fit test, and using an extended Cox model with time-dependent variables. Interactions between rural-urban status and the other confounders and collinearity were also assessed for the model.

For cases from the state of Georgia, an additional census tract level poverty variable was included to assess the role poverty plays in explaining any rural-urban disparities that might exist in survival. This variable is based on the residential address of the cancer patient at the time of diagnosis, which is used to obtain the census tract in which the patient resided. It is divided into four categories based on the proportion of the population in that census tract below the federal poverty level: <5% below, 5 to <10% below, 10 to <20% below, and 20-100% below. Cases with unknown values for this poverty variable were excluded from the analysis. This variable was only available for cases from Georgia and was not available at the national level.

All analyses were performed with SEER*Stat Version 8.0.2 and SAS Version 9.3 (National Cancer Institute and SAS Institute, Cary, NC). The study was approved by the Emory University institutional review board.

Results

After excluding cases where the brain cancer was not the first and only primary cancer (5,332), cases reported only from autopsy or a death certificate (750), cases with unknown or missing rural urban status (25), cases with unknown race (93), and limiting to cases with one of the histological tumor types of interest, 31,713 cases remained for analysis. Among these cases, 19,037 (60.0%) lived in large metropolitan counties, 5,971 (18.8%) in medium metropolitan counties, 2,883 (9.1%) in small metropolitan counties, 3,338 (10.5%) in urban non-metropolitan counties, and 484 (1.5%) in rural non-metropolitan counties. Sex was not significantly different across these categories, but marital status, race, and age at diagnosis were significantly different (Table 1). The largest proportion of unmarried cases was seen in the large metropolitan counties while the largest proportion of married cases was seen in the urban non-metropolitan counties. Larger proportions of black cases and cases of other races lived in large metropolitan counties. Primary tumor site, histology, stage, and treatment type also differed significantly across the rural-urban status categories (Table 2). Cases in large metropolitan counties were more likely to receive both surgery and radiation than any other area, and a slightly larger proportion of cases in urban non-metropolitan counties and rural non-metropolitan counties received no treatment compared to the metropolitan counties.

Kaplan-Meier survival curves differed significantly by rural-urban status (Log-Rank 84.12; $p<.0001$) (Figure 1). The curves showed similar survival for large and medium metropolitan counties and similar survival in small metropolitan counties and urban non-metropolitan counties. Rural non-metropolitan counties consistently had the

lowest survival. Crude 5-year relative survival estimates also showed the highest survival in large metropolitan counties (23.8%), decreasing across the spectrum, with the lowest survival in rural non-metropolitan counties (14.6%) (Table 3).

Age, sex, histology, primary site, stage, and treatment type did not satisfy the proportional hazards assumption, so the multivariable cox regression model stratified on these covariates and controlled for rural urban status, year of diagnosis, marital status, and race. No interaction was seen between rural-urban status and the other covariates.

Multivariable analysis showed a significant increased risk of death from brain cancer for small metropolitan counties, urban non-metropolitan counties, and rural non-metropolitan counties compared to large metropolitan counties (Table 4). Rural non-metropolitan counties had the largest increased risk of death at 17% (HR =1.17; 95% CI: 1.04–1.32).

For every year after 2000 that a case was diagnosed there was a 4% decreased risk of death from brain cancer compared to cases diagnosed in 2000 (HR =0.96; 95% CI: 0.95–0.96). Unmarried cases had a 9% increased risk of death compared to married cases (HR =1.09; 95% CI: 1.05–1.12). There was not a significant increased risk of death from brain cancer for black cases compared to white cases, or other race cases compared to whites (HR =0.99; 95% CI: 0.93–1.06 and HR =0.93; 95% CI: 0.86–1.01, respectively).

When the analysis was limited to cases in Georgia, age was combined into fewer categories (20-39 years, 40-69 years, and 70+ years), treatment was recategorized into a binary treated or not treated variable, and race was limited to white and black due to the small number of cases of other race groups. A total of 3029 cases were available for analysis. The census level poverty indicator was not significant in the multivariable cox

regression model when controlling for rural urban status, age, year of diagnosis, marital status, race, sex, primary tumor site, histology, stage, and treatment type (p=.5559). Without poverty in the model, small metropolitan counties and rural non-metropolitan counties were the only rural-urban categories with a significant effect on survival, and the effects were larger than seen in the SEER-wide analysis (HR= 1.14; 95% CI: 1.00–1.30 and HR= 1.33; 95% CI: 1.05–1.67, respectively).

Discussion

The results of this study suggest that cases living in small metropolitan counties, urban non-metropolitan counties, and rural non-metropolitan counties are all at an increased risk of death from brain cancer compared to cases living in large metropolitan counties at the time of diagnosis, with the highest risk increase in rural non-metropolitan counties. This is consistent with the graded increase in risk across the range of the rural-urban continuum identified for several other types of cancer [12].

Treatment differs based on the primary site of the brain tumor and the histology, but most types of brain cancer are treated with surgery and/or radiation. Chemotherapy is an additional option for some histologies [5]. The volume of cases treated at a hospital has been shown to be an indicator of quality of care for brain tumor surgery, with better short-term outcomes in higher volume hospitals [17]. This may play a role in explaining the survival differences observed across the rural urban spectrum as areas outside of large metropolitan counties are likely to have lower volume hospitals.

A lack of access to care in rural areas may also explain the observed survival differences. As a result of limited access to care, rural patients may present with a later stage at diagnosis or receive less favorable treatment [12]. Socioeconomic factors that differ between residents of rural counties and urban counties are another possible contributing factor. Further research is needed to explore the underlying reasons for these survival differences.

The 2003 Barnholtz-Sloan study that identified an increased risk of death for black cases was not a cause-specific survival analysis [9]. In this cause-specific survival analysis, focusing on deaths from brain cancer, there was no significant increased risk of

death for black cases or cases in the other race category, which includes American Indian/Alaska Native, Asian/Pacific Islander, and other unspecified race. The decreased risk of death associated with year of diagnosis is consistent with the previously mentioned improved survival over time [1].

Poverty was not found to be a significant predictor of survival in Georgia, suggesting that the 33% increased risk of death due to brain cancer seen for cases residing in rural non-metropolitan counties in Georgia might not be related to poverty levels in that census tract. This may also be an issue of sample size.

Strengths and Limitations

To our knowledge, this study is the first to examine rural-urban disparities in survival for brain cancer. Another major strength of this study is the utilization of SEER data. The SEER registry contains data with both high quality and completeness and is population based, allowing a large sample size for analysis of a rare cancer like brain cancer. However, SEER data is criticized for not being a random sample of the country and not being entirely representative of the underlying demographics of the US population. For example, SEER data over-represent urban areas within the US. The rural areas covered by SEER may not be representative of the rural areas throughout the US and therefore the results found in this study may not be generalizable to the nation as a whole. The study was also limited by the variables available in the SEER database, and was unable to control for potentially important factors like chemotherapy treatment or socioeconomic status at the national level.

In summary, the effect of rural-urban county of residence on survival for brain cancer is consistent with what has previously been seen for other malignancies. There is a

graded increase in risk across the rural-urban continuum, suggesting all cases residing outside of large metropolitan counties at the time of diagnosis have an increased risk of death from brain cancer.

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Figure 1: Kaplan-Meier Survival Curve by rural-urban status for cases of primary malignant brain cancer, Adults aged ≥20 years, SEER Registry, 2000-2008

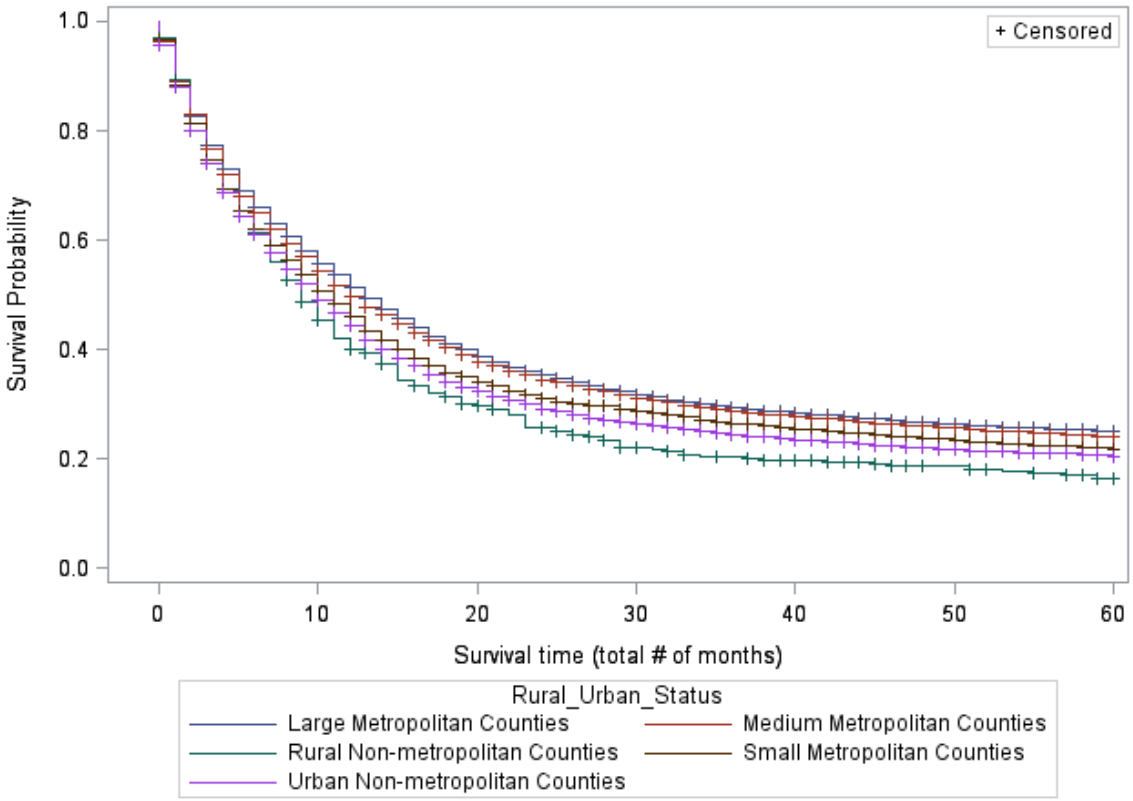

Table 1. Demographic characteristics by rural-urban status for cases of primary malignant brain cancer, Adults aged ≥20 years, SEER Registry, 2000-2008

Demographic Characteristic	Large Metro (n=19037) n	%	Medium Metro (n=5971) n	%	Small Metro (n=2883) n	%	Urban Non-metro (n=3338) n	%	Rural Non-metro (n=484) n	%	p-value
Sex											.8973
Male	10688	56.1	3386	56.7	1637	56.8	1873	56.1	268	55.4	
Female	8349	43.9	2585	43.3	1246	43.2	1465	43.9	216	44.6	
Race											<.0001
White	16694	87.7	5424	90.8	2672	92.7	3095	92.7	467	96.5	
Black	1215	6.4	286	4.8	152	5.3	165	4.9	16	3.3	
Other	1128	5.9	261	4.4	59	2.1	78	2.3	1	0.2	
Age											<.0001
20-29 years	1296	6.8	445	7.5	213	7.4	191	5.7	21	4.3	
30-39 years	1981	10.4	582	9.8	256	8.9	264	7.9	34	7.0	
40-49 years	2978	15.6	932	15.6	424	14.7	463	13.9	65	13.4	
50-59 years	3969	20.9	1245	20.9	593	20.6	699	20.9	97	20.0	
60-69 years	3570	18.8	1142	19.1	591	20.5	721	21.6	123	25.4	
70-79 years	3357	17.6	1011	16.9	513	17.8	680	20.4	95	19.6	
80+ years	1886	9.9	614	10.3	293	10.2	320	9.6	49	10.1	
Marital Status											
Married	11324	59.5	3648	61.1	1777	61.6	2117	63.4	292	60.3	<.0001
Unmarried	7110	37.4	2161	36.2	1009	35.0	1047	31.4	162	33.5	
Unknown	603	3.2	162	2.7	97	3.4	174	5.2	30	6.2	

Table 2. Clinical characteristics by rural-urban status for cases of primary malignant brain cancer, Adults aged ≥20 years, SEER Registry, 2000-2008

Clinical Characteristic	Large Metro (n=19037) n	%	Medium Metro (n=5971) n	%	Small Metro (n=2883) n	%	Urban Non-metro (n=3338) n	%	Rural Non-metro (n=484) n	%	p-value
Primary Site											<.0001
Cerebrum	834	4.4	280	4.7	116	4.0	1831	5.5	26	5.4	
Frontal lobe	5388	28.3	1667	27.9	788	27.3	895	26.8	127	26.2	
Temporal lobe	3958	20.8	1195	20.0	593	20.6	713	21.4	103	21.3	
Parietal lobe	2491	13.1	900	15.1	418	14.5	505	15.1	83	17.2	
Occipital lobe	631	3.3	186	3.1	107	3.7	121	3.6	23	4.8	
Ventricle	186	1.0	81	1.4	32	1.1	38	1.1	6	1.2	
Cerebellum	500	2.6	151	2.5	71	2.5	88	2.6	9	1.9	
Brain stem	472	2.5	160	2.7	69	2.4	74	2.2	4	0.5	
Overlapping	3035	15.9	908	15.2	477	16.6	444	13.3	67	13.8	
Brain, NOS	1542	8.1	443	7.4	212	7.4	277	8.3	36	7.4	
Histology											<.0001
Glioblastoma	11050	58.0	3460	58.0	1704	59.1	1999	59.9	314	64.9	
Astrocytoma	1408	7.4	464	7.8	223	7.7	254	7.6	44	9.1	
Pilocytic astrocytoma	325	1.7	103	1.7	50	1.7	58	1.7	6	1.2	
Diffuse astrocytoma	240	1.3	91	1.5	52	1.8	93	2.8	7	1.5	
Anaplastic astrocytoma	1406	7.4	463	7.8	230	8.0	218	6.5	31	6.4	
Oligodendro-glioma	1116	5.9	356	6.0	153	5.3	154	4.6	27	5.6	
Anaplastic oligodendro-glioma	479	2.5	160	2.7	59	2.1	93	2.8	11	2.3	
Ependymoma	287	1.5	88	1.5	30	1.0	46	1.4	5	1.0	
Mixed glioma	721	3.8	205	3.4	84	2.9	90	2.7	7	1.5	
Neoplasm	756	4.0	210	3.5	109	3.8	136	4.1	18	3.7	
Medulloblastoma	260	1.4	68	1.1	46	1.6	24	0.7	1	0.2	
Glioma, NOS	989	5.2	303	5.1	143	5.0	173	5.2	13	2.7	
Stage											.0013
Localized	14086	74.0	4536	76.0	2150	74.6	2442	73.2	367	75.8	
Regional/Distant	3500	18.4	1020	17.1	533	18.5	597	17.9	72	14.9	
Unknown	1451	7.6	415	7.0	200	6.9	299	9.0	45	9.3	
Treatment											.0043
None*	3608	19.0	1096	18.4	545	18.9	676	20.3	94	19.4	
Surgery	3970	20.9	1305	21.9	591	20.5	747	22.4	104	21.5	
Radiation	2711	14.2	904	15.1	442	15.3	509	15.3	86	17.8	
Both	8748	46.0	2666	44.7	1305	45.3	1406	42.1	200	41.3	

*No documented surgery or radiation

Table 3. Unadjusted 5-year relative survival by rural-urban status for cases of primary malignant brain cancer, Adults aged ≥20 years, SEER Registry, 2000-2008

Rural Urban Status	5-year Relative Survival	95% CI	
Large Metropolitan county	23.8%	23.2%	24.5%
Medium Metropolitan county	22.8%	21.7%	24.1%
Small Metropolitan county	21.1%	19.4%	22.8%
Urban Non-metropolitan county	19.5%	18.1%	21.1%
Rural Non-metropolitan county	14.6%	11.3%	18.4%

Table 4. Adjusted* hazard ratios from Cox multivariable 5-year survival analysis for cases of primary malignant brain cancer, Adults aged ≥20 years, SEER Registry, 2000-2008

Rural Urban Status	Hazard Ratio	95% CI	
Large Metropolitan county	1.000	Reference	
Medium Metropolitan county	1.026	.987	1.068
Small Metropolitan county	1.085	1.029	1.144
Urban Non-metropolitan county	1.117	1.064	1.174
Rural Non-metropolitan county	1.168	1.038	1.315

*Adjusting for year of diagnosis, marital status, and race and stratified on age, sex, histology, primary site, stage, and treatment type