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Glioblastoma multiforme: Geographic variations in tumor size, treatment options, and survival rate

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This is to certify that the doctoral dissertation by

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Abstract

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MSN, Georgetown University, 1993

BSN, Columbia Union College, 1988

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

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Abstract

Glioblastoma multiforme (GBM) is a destructive brain cancer that results in death 12 to 15 months after diagnosis. The purpose of this retrospective study was to determine if variations in tumor size at diagnosis, treatment options, and survival rate occur in GBM patients living in urban and rural areas of the United States. Using the behavior model of health services as the theoretical framework, this study used secondary data sets of GBM cases reported from 1988 to 2011 from the Surveillance, Epidemiology, and End Results program. Tumor size was measured in millimeters; treatment was evaluated by ascertaining the number of GBM patients who had surgical resection of their tumors, radiation, and chemotherapy; and survival rate was evaluated using Cox Regression analysis. With a sample size of 33,202 cases, data were examined using descriptive and multivariable analyses with SPSS. Results showed statistically significant differences in tumor size at diagnosis in rural patients compared to urban patients ($p = 0.0085$; $p = 0.018$), more urban patients were treated with radiation compared to rural patients ($p < 0.001$), and rural patients had poorer survival rates than urban patients ($p < 0.001$). Finally, when controlling for region, race, age, gender, education, and income, longer survival time was associated with urban status, female cases, and higher family income ($p < 0.0001$), and greater age was associated with reduced survival time ($p < 0.0001$). Study results could promote positive social change by identifying predictive variables associated with health outcomes of GBM patients. It may also educate providers on the risk of rurality of patients diagnosed with GBM, and inform lawmakers responsible for the creation of healthcare policy and the equitable allocation of healthcare resources.

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Dedication

This dissertation is dedicated to two very special people in my life: my sister, Doll, and my husband, Jim. My sister, Doll, courageously and tenaciously fought to beat the dismal odds of Glioblastoma Multiforme. Although she eventually succumbed to this disease in October 2011, she left a lasting legacy of hope and inspiration to her family and friends who loved her. This dissertation would not have been possible without the love and support from my husband, Jim (affectionately known as Dude). He wholeheartedly supported my dream of earning a PhD; in fact, my dream became his dream. He took over all responsibilities of running a household, kept the home fires burning, and spent many evenings and weekends alone. All I had to do was worry about work during the day and course work at night and on weekends. Dude, you are my best friend, my confidante, and the most special love of my life.

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Chapter 1: Introduction to the Study

Glioblastoma multiforme (GBM) is a malignant brain neoplasm known for its destructive ability to invade healthy brain tissue at an accelerated rate, resulting in death 12 to 15 months after diagnosis (Holland, 2000). For this reason, Holland (2000) has referred to GBM as "the terminator" (p. 6242). Once diagnosed, patients typically undergo surgery for tumor removal followed by radiation and chemotherapy (Jelsma & Bucy, 1967). Despite these treatment modalities, there are few long term GBM survivors. Research has focused on finding effective and novel therapies aimed at prolonging life such as immunotherapy, gene therapy, and viral therapy (Holland, 2000). Immunotherapy research has focused on whether or not the body's immune system responds to the presence of a GBM tumor, referred to as a glioblastoma-specific immune response (Haque, Nagarkatti, Nagarkatti, Banik, & Ray, 2010). Gene therapy research has focused on switching out the defective portion of a gene causing GBM for a functional portion of the gene (Kwiatkowska, Nandhu, Behera, Chiocca, & Viapiano, 2013). Moreover, viral therapy research involves the creation of a killer virus that destroys cancer cells (Holland, 2000; Shah & Markert, 2004).

Despite the abundant research from a multitude of perspectives, no one really knows what causes GBM. Research has identified three specific risk factors for brain tumors in general: exposure to ionizing radiation, rare genetic mutations, and family history (Bondy & Ligon, 1996; DeAngelis, 2001; Fisher, Schwartzbaum, Wrensch, & Wiemels, 2007; Inskip, Linet, & Heineman, 1995). Unfortunately, only a very small proportion of brain malignancies are attributable to these risk factors (Fisher et al., 2007).

Other potential risk factors like cell phone use, smoking, and environmental exposures have been explored in the development of brain neoplasms. However, these studies were not definitive (Bondy et al., 2008; Connelly & Malkin, 2007; Gomes, Al Zayadi, & Guzman, 2011). What is known is that in the United States, cancer incidence varies from state to state (Centers for Disease Control and Prevention, 2013). In 2011, the age-adjusted brain and spinal tumor incidence for the United States was 6.4 per 100,000 people (all races), and state incidences ranged from 3.4 to 10.3 (Howlader et al., 2014). In 2011, the age-adjusted incidence for GBM was 4.3 per 100,000 people (Howlader et al., 2014). In this introductory chapter, I present a comprehensive overview for this study; that is, an examination of the urban/rural variations of a specific brain tumor known as GBM. The following topics specific to this study will be covered: background, problem statement, purpose, theoretical foundation, major assumptions, scope and delimitations, limitations, and significance.

Background of the Study

Cancer is a significant health issue worldwide. In 2012, over 14 million people worldwide were diagnosed with cancer with a projected increase to 24 million by 2035 (Ferlay et al., 2013). An interesting pattern of brain cancer and various nervous system cancers have emerged in the United States: higher rates in the southeast, northwest, and midwest, and lower rates in the Rocky Mountains, northeast, and southwest (Devesa et al., 1999).

One of the most pressing issues facing the field of public health is trying to ascertain what makes some people healthy while other people are unhealthy. When

attempting to determine the factors that influence the health of people, the traditional perspectives are categorized as follows: biological, environmental, lifestyle, psychosocial, and access to health-related services (Turnock, 2009). The combination of these factors is known as the determinants of health, and the interrelationships of these factors contribute to the health or lack of health for individual and populations (Turnock, 2009; United States Department of Health and Human Services, 2014). Access to health services and the quality of those health services influence health. In the 1980s, a great deal of research examined access to healthcare resources from an urban versus rural perspective. Studies showed that rural areas had fewer providers and hospitals than urban areas (Reschovsky and Staiti, 2005; Ricketts, 2000). Consequently, rural populations had less access to healthcare, used less healthcare resources, and paid more for healthcare (Hartley, 2004). Newer urban/rural research has focused on the health of populations from an environmental perspective, and the resultant effect on health behaviors (Arcury et al., 2005; Goodman, Fisher, Stukel, & Chang, 1997; Higginbotham, Moulder, & Currier, 2001). In this study, I will examine variables that affect health and potentially identify factors that may contribute to different health outcomes for urban and rural residents. Urban and rural environments will be thoroughly discussed in Chapter 2.

A tumor or neoplasm is defined as an abnormal tissue mass that can be either benign or malignant (National Cancer Institute, n.d.). More specifically, a neoplasm of the brain is defined as a mass of abnormal cells growing in the brain, and a malignant brain tumor is one that is considered cancerous because the growth of abnormal cells are out of control and destructive to healthy brain tissue (National Cancer Institute, n.d.).

While most malignant tumors metastasize or spread to other body parts, malignant brain tumors are not metastatic. Rather, malignant brain tumors infiltrate healthy brain tissue and cause massive destruction (National Cancer Institute, 2009).

The most common malignant brain tumor in adults is known as a GBM (National Cancer Institute, 2009, 2012). Patients with GBM may experience any of the following conditions: persistent headaches, visual disturbances, mood and/or personality changes, seizures, changes in ability to think, loss of appetite, vomiting, and/or difficulty with the spoken word (Brandes et al., 2008; Davis & Stoiber, 2011; Fox, Lyon, & Farace, 2007; Nolan & Gavrilovic, 2010). Patients who complain of the aforementioned symptoms will usually undergo specific radiologic procedures known as computed tomography (CT) and/or magnetic resonance imaging (MRI; Fink & Fink, 2013). CT and MRI scans can only ascertain that a brain tumor exists. The way to determine the type of brain tumor is through biopsy or tumor removal (Davis & Stoiber, 2011). The prognosis is quite poor for patients diagnosed with GBM; that is, once diagnosed, median survival is 12 to 15 months from diagnosis (Deorah, Lynch, Sibenaller, & Ryken, 2006).

In any given cancer diagnosis, the size of the tumor is a significant prognostic indicator of survival; that is, a smaller tumor size is a better prognosis for survival than a larger tumor. In the case of GBM, patient symptomatology is usually related to a larger tumor size found at diagnosis. It is not uncommon for GBM patients to be asymptomatic until the tumor reaches an enormous size (Iacob & Dinca, 2009).

Another prognostic indicator of survival is the type and extent of treatment options offered to patients diagnosed with GBM. Since the GBM tumor is aggressively

fast-growing, highly vascular, and invasive in nature, treatment by necessity usually includes surgery followed by adjuvant therapies of radiation and chemotherapy (Hentschel & Lang, 2005). Surgery is usually the initial intervention in treatment of GBMs, and the question most often raised is the degree of surgical aggressiveness (Hentschel & Lang, 2003). The overall goals of surgical resection are three-fold: diagnostic confirmation of GBM, symptom management, and improving overall survival. According to Hentschel and Lang (2003), diagnostic confirmation relies on obtaining adequately sized tissue samples for accurate histological diagnosis. Symptom management involves a thorough understanding of the neurological symptoms caused by GBMs. Hentschel and Lang noted that GBM tumors affect patients in two separate and distinct ways: diffuse neurological symptoms or focal neurological deficits. Diffuse neurological symptoms result from increased intracranial pressure that is due to the size of the tumor and the edema (swelling) that it produces (Ammirati, Vick, Liao, Ciric, & Mikhael, 1987; Fadul et al., 1988; Lacroix et al., 2001; Prabhu, 2007; Sawaya et al., 1998). Symptoms of increased intracranial pressure are headache, nausea, vomiting, blurred vision, alteration in the level of consciousness, and/or seizures. Examples of focal neurological deficits would be a gradual decline in memory, judgment, language problems, personality changes, and mobility and sensory changes (Ammirati et al., 1987; Fadul et al., 1988; Prabhu, 2007; Sawaya et al., 1998). In most other areas of oncologic tumors, the goal of surgery is complete tumor removal along with removal of large areas of normal tissue surrounding the tumor (Hentschel & Lang, 2003). However, the invasive nature of GBMs prevents the neurosurgeon from being able to completely

remove the entire tumor as well as normal brain tissue (Hentschel & Lang, 2003; Sahebjam, McNamara, & Mason, 2012). Surgical resection helps to reduce the diffuse neurological symptoms caused by GBMs. In contrast, surgical resection may or may not improve focal neurological symptoms. According to Stummer, van den Bent, and Westphal (2011), the extensiveness of tumor removal is considered one of the strongest prognostic factors in prolonging survival, decreasing tumor size, and managing symptoms in GBM patients.

The hypothesis of this particular study is that rural GBM patients will have larger tumors, experience fewer surgical resections, undergo fewer adjuvant therapies of radiation and chemotherapy, and have decreased survival when compared to their urban counterparts. This hypothesis is based on the following assumptions: rural populations have limited access to health services, travel greater distances to access health services, are in poor health, and have limited financial means.

Problem Statement

The impact of cancer on the United States population is multifaceted. According to Gosschalk and Carozza (2003), studies have demonstrated variations in incidence, mortality, and staging of particular cancers when examining the variables of race, geographic areas of the United States, gender, and age. GBM is an aggressive brain cancer with an abysmal mortality of 12 to 15 months once diagnosed (Ng, Kesari, Carter, & Chen, 2011; Wen & Kesari, 2008). By the time GBM patients are diagnosed, their tumor size is quite large, and the treatment options of surgery, radiation, and chemotherapy are used to lengthen survival time beyond a year.

Past GBM research has focused on environmental and occupational exposures with ambiguous results (Connelly & Malkin, 2007; Gomes et al., 2011). Population-based studies have examined the incidence of brain tumors and survival rates from a gender perspective (Ohgaki et al., 2004; Ohgaki & Kleihues, 2005). However, there are no studies that have examined the occurrence and survivability of GBM tumors from the geographic perspective of living in rural versus urban regions. Consequently, the nature of the relationship between living in urban versus rural regions and GBM is unclear. Given the high mortality rates of GBM patients, if there is an association linking place of residence and survival rates of GBM patients, then reduction of the barriers and disparities that contribute to these negative outcomes might be achieved.

Significance

Anyone can develop cancer. Despite modern technology and cutting-edge research to reduce cancer incidence and mortality, cancer prevalence is on the rise due to an aging population (American Cancer Society, 2012; Gosschalk & Carozza, 2003). The literature review in Chapter 2 provides significant and noteworthy information. For example, the relationship between urban and rural populations and early cancer detection is uncertain (Blair et al., 2006). Additionally, patients diagnosed with GBM have unusually high mortality rates coupled with low survival rates owing, in part, to delays in diagnosis and treatment (Mathiesen, Paredo, & Lönn, 2011). Furthermore, the GBM tumor itself is characterized by aggressive growth and extensive infiltrative and invasive vasculature. While some studies have examined the association of increased incidence of certain cancers in rural populations (Gosschalk & Carozza, 2003; Singh, Williams,

Siahpush, & Mulhollen, 2011), there are no studies that have investigated whether rurality is a prognostic indicator for patients diagnosed with GBM.

Purpose of the Study

The purpose of this retrospective, quantitative study is to ascertain whether there are variations in tumor size, treatment options, including surgical resection and adjuvant therapies of radiation and chemotherapy, and survival rates between rural and urban residents diagnosed with GBM. This study will use secondary data obtained from the Surveillance and Epidemiology End Results (SEER) database. Rural and urban residents are defined as men and women who are 20 years of age and older. Urban and rural areas will be based exclusively on the SEER definition of using rural-urban continuum codes (RUCCs) to distinguish urban from rural regions. This classification system differentiates urban counties by population size. Alternatively, rural counties are differentiated by the degree of growth, development, expansion, and proximity to an urban county. This study will use the SEER database to ascertain if variations in tumor size, treatment options, and survival rates exist among urban and rural area GBM patients living in the United States.

Nature of the Study

The focus of this cohort study is on newly diagnosed GBM adult patients 20 years of age and older. Participants will be drawn from the SEER database from 1988 through 2011. From a quantitative perspective, tumor size will be measured in centimeters as reported in the SEER database. Patients with GBM tumors undergo surgery followed by radiation therapy and chemotherapy (Hentschel & Lang, 2003). Surgery is the first

course of treatment, and there is a great deal of controversy in the neurosurgical community concerning the degree of surgical resection; that is, biopsy versus surgical resection (Hentschel & Lang, 2005; Koul, Dubey, Torri, Kakumanu, & Goyal, 2012). Some neurosurgeons initially prefer to perform a biopsy while other neurosurgeons advocate for aggressive surgical resection. Over the last 2 decades, studies have demonstrated the value of aggressive resection of GBMs by affecting overall survival (Ammirati et al., 1987; Hentschel & Lang, 2003; Keles, Anderson, & Berger, 1999; Lacroix et al., 2001; Sawaya et al., 2001). It is customary to follow aggressive surgical resection with adjuvant therapies of radiation treatment and chemotherapy. Groundbreaking research has shown definitively that surgery followed by radiation therapy and chemotherapy has increased survival from a little more than 3 months to 7 to 12 months (Stupp et al., 2005). Finally, survival rates, otherwise known as survival statistics, show the proportion of patients who survive cancer for a specified amount of time. This study will use a common cancer statistic known as the 5-year survival rate (Centers for Disease Control, 2014), or the proportion of patients who remain alive 5 years from initial diagnosis (Mayo Clinic, 2013).

Differentiating rural from urban areas is critical to this study. As a way of discerning an urban region from a rural region, the United States Department of Agriculture (2013) developed a classification system comprised of nine codes corresponding to population size and adjacency to a metropolitan area. Every county in the United States is consigned to one of the nine codes referred to as RUCCs. The SEER database uses the RUCC system.

Research Questions and Hypotheses

The following research questions and hypotheses form the basis for this quantitative study:

Research Question 1: When comparing urban and rural patients with GBM, is there a significant difference in GBM tumor size at diagnosis?

$H_0$1: When comparing urban and rural patients with GBM, there is no significant difference in GBM tumor size.

$H_1$1: When comparing urban and rural patients with GBM, there is a significant difference in GBM tumor size.

Research Question 2: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced surgical resections?

$H_0$2: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced surgical resections.

$H_1$2: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced surgical resections.

Research Question 3: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy?

$H_0$3: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

$H_1$3: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

Research Question 4: When comparing urban and rural patients with GBM, is there a significant difference in survival rates?

$H_0$4: When comparing urban and rural patients with GBM, there is no significant difference with survival rates.

$H_1$4: When comparing urban and rural patients with GBM, there is a significant difference in survival rates.

Research Question 5: In the study population of GBM patients, is there a significant difference in survival rates when controlling for region, race, age, sex, educational level, and median family income?

$H_0$5: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is no significant difference in survival rates.

$H_1$5: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is a significant difference in survival rates.

The sample was drawn from the SEER database and consisted of subjects diagnosed with GBM with the following attributes: (a) adult males and females, 20 years of age and older, (b) urban or rural place of residence, (c) age at diagnosis, (d) year of diagnosis between 1988 and 2011, (e) tumor size, (f) race/ethnicity: all races/ethnicities

reported, (g) surgical resection, (h) adjuvant therapies: radiation therapy and chemotherapy, and (i) survival time: 5 years after diagnosis. The data were analyzed using the latest version of SPSS. For the purpose of this study, the independent variable was region, apportioned to urban and rural regions using RUCCs. The level of measurement of the independent variable was nominal. There were four dependent variables: tumor size at initial diagnosis, surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rate. The level of measurement for tumor size was ordinal; that is, tumor size was measured in centimeters. Ordinal measurements assign observations into categories that can be put into rank order and do not quantify differences (Gerstman, 2008, p. 5). Since rank orders do not quantify differences, conditions of normality and equal variance are absent. Thus, a nonparametric statistic was used. Data analysis for the first research question used the independent samples *t* test. For the second (surgical resection) and third research questions (adjuvant therapies of radiation treatment and chemotherapy), the level of measurement was nominal. GBM patients were identified as to whether or not they experienced surgical resections (yes/no), radiation treatment (yes/no), and chemotherapy (yes/no). Data analysis for surgical resections, radiation treatment, and chemotherapy used the independent samples *t* test. The fourth research question involving survival rate used a combination of Kaplan-Meier for univariate analysis and Cox proportional hazards (regression analysis) for multivariate analysis of survival differences between groups (metropolitan and nonmetropolitan). Finally, the fifth research question used multiple regression modeling to determine the best predictive model based on the independent

variables of region, age, marital status, race, educational level, and family income in the study population of GBM cases (Klein, 2010; Klein, Ji, Rea, & Stoodt, 2011).

Theoretical Base

The theoretical framework used for this study was Andersen's behavior model of health services use developed in the late 1960s (Andersen, 1995). With a major focus on accessing health care, this model has undergone several iterations over the last 40 years. The original focus was on the family unit while the later models explored the individual. Regardless of the focus, the model sought to understand how and why health services were used as well as any factors that contributed to or hindered one's access to medical care. Andersen (1995) postulated that there were three essential factors that affected one's use of health care services or access to medical care: predisposing factors, enabling factors, and need factors. Predisposing factors are defined as demographic features of human beings like age, gender, ethnicity, education level, occupational background, and ethnicity, and basic health beliefs (Andersen, 1995). Enabling factors are viewed as resources that contribute to one's use of health services like income, insurance coverage, and the geographic region where one lives (Andersen, 1995). Finally, need factors are defined as the most immediate reasons why an individual would seek health care like illness or trauma (Andersen, 1995). Placing this study within the context of the theoretical foundation, it is possible that because of the predisposing characteristics and enabling resources specific to rural patients, delays in accessing health care resources might lead to larger tumor size, decreasing KPS, and poorer survival rates of rural GBM

patients. This model will be further explored in Chapter 2. Figure 1 shows the health behavior model by Andersen.

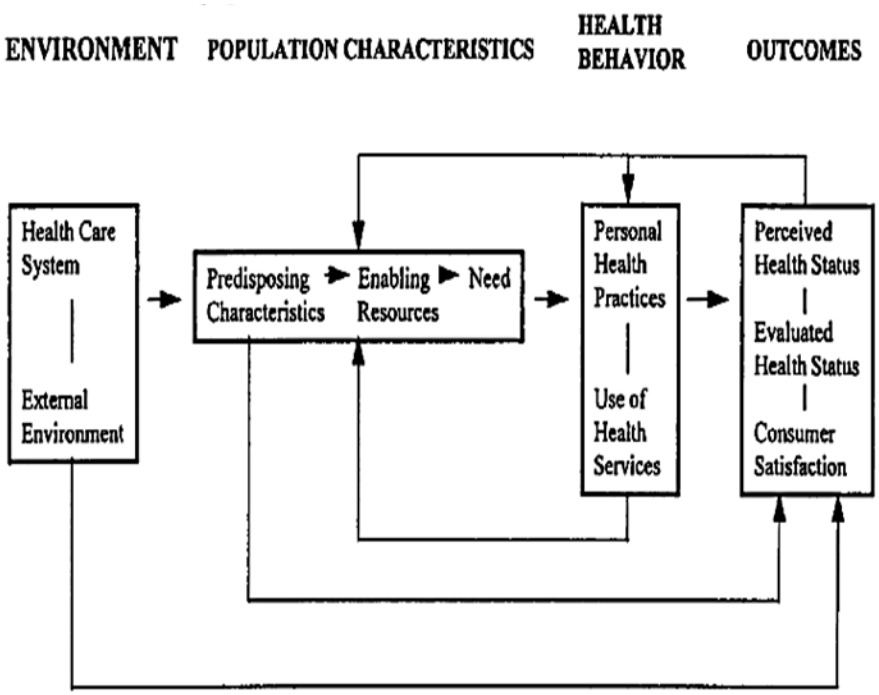

Figure 1. The health behavior model as put forth by Andersen. Andersen, R.M. (1995). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Health and Social Behavior, 36*(1), 1-10. Reprinted with permission (Appendix B).

For this study, the following constructs of the health behavior model form the basis of data collected from the SEER database:

- Health Care System: Location, that is, rural versus urban areas using the RUCCs used by the SEER database.
- Predisposing characteristics: Demographic factors such as age, gender, and race obtained through the SEER database. Educational level or

median family income is not available from the SEER database but is available at the county level. For this study, educational level and median family income were obtained from county data.

- Enabling resources: Financial resources, insurance coverage, rurality, or the degree of urban versus rural locations (distance from healthcare resources, access to transportation as defined by RUCC in the SEER database).
- Need: The reason that causes the individual to seek healthcare services (diagnosis of GBM) and measured by tumor size, treatment options, and survival rates from the SEER database. Please see Table 1.

Table 1

HBM Constructs and Relationship to Study Variables

HBM construct	Description	Database	Study variable
Health care system	Location	SEER: RUCC Codes (urban or rural)	Independent
Predisposing characteristics	Demographic data	*SEER: Age-Sex-Race *County Data: Educational level and median family income	Dependent
Enabling resources	*Financial data *Insurance *Rurality	*SEER: RUCC Codes *County Data: median family income and insurance	Independent Dependent
Need	Diagnosis of GBM	SEER: tumor size-treatment options-survival rate-mortality rate	Dependent

Definition of Terms

Glioblastoma Multiforme (GBM): A malignant brain tumor known as a Grade-4 glioma.

Glioma: A broad term that describes a tumor that originates from glial cells specific to the brain. Glial cells provide support and protection to the nervous system.

Rural-urban classification code: The SEER database uses the geographical region known as a county to define urban and rural regions. An urban county is defined by population size. Alternatively, a rural county is defined by how close it is to an urban area. See Table 2 below.

Table 2

Urban and Rural Continuum Codes

Metropolitan counties Code	Definition
1	Metro area with 1 million or more people
2	Metro area with 250,000 to 1 million people
3	Metro area with fewer than 250,000 people
Nonmetropolitan Counties	
Code	
4	Adjacent to metro area, 20,000 or more people
5	Nonadjacent to metro area, 20,000 or more people
6	Adjacent to metro area, 2,500 to 19,999 people
7	Nonadjacent to metro area, 2,500 to 19,999 people
8	Adjacent to metro area, < 2,500 people or totally rural
9	Non adjacent to metro area, < 2,500 or totally rural

Note. United States Department of Agriculture (2013). *Rural-urban continuum codes.* Retrieved from http://www.ers.usda.gov/data-products/rural-urban-continuum-codes/documentation.aspx. Table is in the public domain. Permission to reproduce was not required.

Survival rate: Survival rate is a term used when examining survival analysis, indicative of a certain percentage of people in a study who are alive for a given period of

time after diagnosis (National Cancer Institute, n.d.). This study will express survival rate as the percent of adults diagnosed with GBM still alive after 5 years.

Tumor size: For the purpose of this study, a classification system developed by SEER will be used to determine GBM tumor size. This system, known as the Extent of Disease, uses a 3-digit numerical code to describe tumor size (National Institute of Health, 2007). Using the largest diameter of the tumor, the size of the tumor is coded (NCI, 1998). These data are used by health care providers to determine the extent of a patient's disease and prognosis of the particular cancer involved. It is often referred to as collaborative staging. Every type of neoplasm has its own collaborative stage for tumor size. Table 3 is specific to brain tumors.

Table 3

Brain: Collaborative Stage for Tumor Size

Code	Description
000	No mass or tumor found
001-988	001 – 988 millimeters (mm). Exact size to nearest mm
989	989 mm or larger
990	Microscopic only and no size of given
991	Tumor is "less than 1 centimeter (cm)"
992	Tumor is "less than 2 cm" or "greater than 1 cm" or "between 1 cm and 2 cm"
993	Tumor is "less than 3 cm" or "greater than 2 cm" or "between 2 cm and 3 cm"
994	Tumor is "less than 4 cm" or "greater than 3 cm" or "between 3 cm and 4 cm"
995	Tumor is "less than 5 cm" or "greater than 4 cm" or "between 4 cm and 5 cm"
999	Size not known due to lack of documentation

Note. Adamo, M., Dickie, L., & Ruhl, J. (May 2014). *2014 SEER Program Coding and Staging Manual*. National Cancer Institute, Bethesda, MD: United States Department of Health and Human Services. Table is in the public domain. Permission to reproduce was not required.

Assumptions

In this study, I focused on differences in GBM tumor size at diagnosis, treatment options, and survival rates in urban and rural GBM patients across SEER registries. The following assumptions are important in understanding the context of this particular study. First, the scope of this study is limited to an examination of urban and rural GBM patients. Second, a GBM tumor is a Grade 4 neoplasm, and by the time symptoms appear, it is considered to be in an advanced stage of development. Third, rural populations differ from their urban counterparts. Fourth, there are specific features of the rural environment that create obstacles to one's ability to access healthcare like a lack of health insurance or financial resources to pay for needed healthcare services, lack of healthcare resources themselves, and/or the distance and travel time to healthcare resources. Fifth, urban regions have a greater concentration of physicians, hospitals, specialty healthcare centers, and advanced diagnostic capabilities than rural regions.

Scope and Delimitations

Since this study is descriptive in nature only, one cannot draw conclusions of causation. Furthermore, this study focuses only on the subpopulation of adult patients diagnosed with GBM. Consequently, there is an inherent sample bias that undermines the study's external validity.

Limitations

First and foremost, this study is based exclusively on secondary data obtained from the SEER database representing 28% of the United States population (National Cancer Institute, n.d.). This limits the generalizability of results to all populations. To

minimize this limitation, descriptive statistics will be used to describe study results, and confounding variables will be controlled. Second, confounding conditions of the study population pose a threat to internal validity (Graves, 2011). Since GBMs are most common in the elderly who have complex health issues, survival could be affected by potential confounding conditions other than the GBM itself. The SEER database reports only on cancer information and incidence. It does not address lifestyle factors or causes of cancer. Since this is a quantitative, retrospective cohort study, the use of descriptive statistics should minimize this particular limitation. Third, since the database will cover a 23-year timeframe from 1988 to 2011, the loss of patients to follow-up could result in either an overestimate or underestimate of study results. Loss of patients from SEER registries are primarily due to patient interest, name and address changes, and/or death. With the GBM population, survival is usually 12 to 15 months or less from time of diagnosis. Since SEER does follow all patients until death, and the survival rate for GBM patients is poor, the likelihood of losing patients to follow-up should be minimal. Fourth, this particular study is based exclusively on the SEER definitions of RUCCS, which ultimately affect the generalizability of results. There is no single, universally accepted definition of rural. However, counties are the most commonly used geographic component of rural definitions. The advantages of using "counties" to describe urban from rural areas are that they are simple to understand and their boundaries are very stable over time. Additionally, many national health data sets use counties as a core geographic unit. Finally, RUCCs data are provided as a numeric continuum, and as such,

must be treated as ordinal data since there is no equal distance between codes (Hall, Kaufman, & Ricketts, 2007).

Significance of the Study

With the recent advances in genetics and genomes, a plethora of research has focused on the identification of genes specific to GBM. In contrast, very little research has been done to study brain cancer from a geographical perspective. This project is unique in that examining patients diagnosed with GBM from an urban-rural perspective has never been done before, highlighting a significant gap in the literature. Specifically, I will examine the association between exposure to rural versus urban locations on tumor size at diagnosis, the number of patients that experienced surgical resection, the number of patients who experienced adjuvant therapies of radiation treatment and chemotherapy, and survival of GBM patients. The independent variables are region, dichotomized to urban or rural areas, race, age, sex, educational level, and family income. The dependent variables are tumor size, surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rates. GBMs are a significant public health issue. Identification of the associations of these variables may provide insight into earlier detection resulting in improved survival rates GBM patients. This study can significantly impact social change by identifying geographical predictive variables associated with health outcomes of GBM patients, thereby leading to earlier detection and improved survival rates of individuals and populations.

Summary and Transition

Cancer is a worldwide health issue. GBM is a malignant brain tumor in adults, distinctively characterized by its aggressiveness to spread rapidly, invade deeply and infiltrate healthy brain tissue, and result in death 12 to 15 months after initial diagnosis. Delays in detection and treatment contribute to its dismal prognosis. In this study, I examined the relationship between GBM patients and the geographic regions where they live and work. I also explored the variables of tumor size, the treatment modality of surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival of GBM patients in urban and rural regions. Using the SEER database covering 1988 through 2011, descriptive and multivariable analyses of data provided an examination into the complex phenomena of GBM in rural and urban populations. Analysis of this type can provide valuable information to those responsible for the creation of healthcare policies and the allocation of healthcare resources.

Chapter 2 includes a review of the existing literature on GBM in adult populations, the theoretical framework associated with this study, and a discussion of healthcare access. Chapter 2 also includes a discussion of geographic variations of healthcare in general, including rural and urban differences in GBM incidence and survival, provides an overview of brain tumors and the epidemiology of GBM, and identifies the gap in the literature with respect to geographic differences specific to the GBM population. I conclude Chapter 2 with an explanation for ongoing GBM research.

Chapter 2: Literature Review

In this chapter, I provide a systematic review of the literature pertinent to this study. I first explore the theoretical framework used for this study. Additionally, I discuss the geographic variations of GBM in the United States. I then explore the clinical attributes of GBM including its definition, symptomatology, detection, prognostic characteristics, diagnosis, and treatment options followed by the epidemiological characteristics of GBM from a person, place, and time perspective based on the most current literature. Major studies on GBM will be reviewed and summarized. Specifically, this discussion compares and contrasts urban and rural regions of the United States by examining tumor size at diagnosis, the number of patients that experienced surgical resection, the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy, and survival rate. Finally, an analysis of this literature review highlights a knowledge gap regarding urban and rural variations in tumor size, the treatment modality of surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rate in GBM patients.

The literature review included an evaluation of the following databases available through the internet: the Academic Search Premier database of Walden University, MEDLINE, PUBMED, Science Direct, and ProQuest for dissertations. This approach generated hundreds of peer reviewed articles on GBM. Peer-reviewed journal articles were included if they were published in English and without date limitations. Publications referenced in peer-reviewed articles specific to GBM were also included in the search strategy. Key terms used in the search strategy included *glioblastoma*

multiforme, GBM, gliomas, and *brain tumors* combined with the following terms: *geography, geographic variation, regional, regional variation, urban-rural, metropolitan-nonmetropolitan, brain tumors, primary brain tumors, gliomas, GBM epidemiology, prognosis*, and *SEER*.

Theoretical Framework

This study used Andersen's behavioral model of health services use (1995) as its theoretical framework. This theoretical framework has been used in studies that examined access to healthcare, determined the quality of care delivered, and evaluated associated outcomes (Blustein & Weitzman, 1995; Fryer et al., 1999; Love & Lindquist, 1995). The framework for this study is based on the hypothesis that late access to general and cancer diagnostic services for patients experiencing GBM may potentially lead to increased tumor size, decreased treatment options, and decreased survival rates.

Concerned with inequalities to medical care access, Andersen initiated studies on the concepts of access in 1968. The behavioral model (Figure 2) focused on the family unit, how and why the family used health services, and access to medical care.

Figure 2. The initial behavioral model (1960s).Andersen, R.M. (1995). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Health and Social Behavior, 36*, 1-10. Reprinted with permission.

Andersen's (1995) model infers that an individual's use of healthcare relies on one's general predisposition concerning health services, issues that enable or block utilization of services, and one's inherent need to seek health care. Andersen and Aday (1974) further examined concepts of medical care access and developed a more cohesive theoretical framework showing initial measures of access to medical care (Figure 3). Andersen (1995) noted that the purpose of the initial measures of access was to identify situations that either enhance access to healthcare services or obstruct access to the same services.

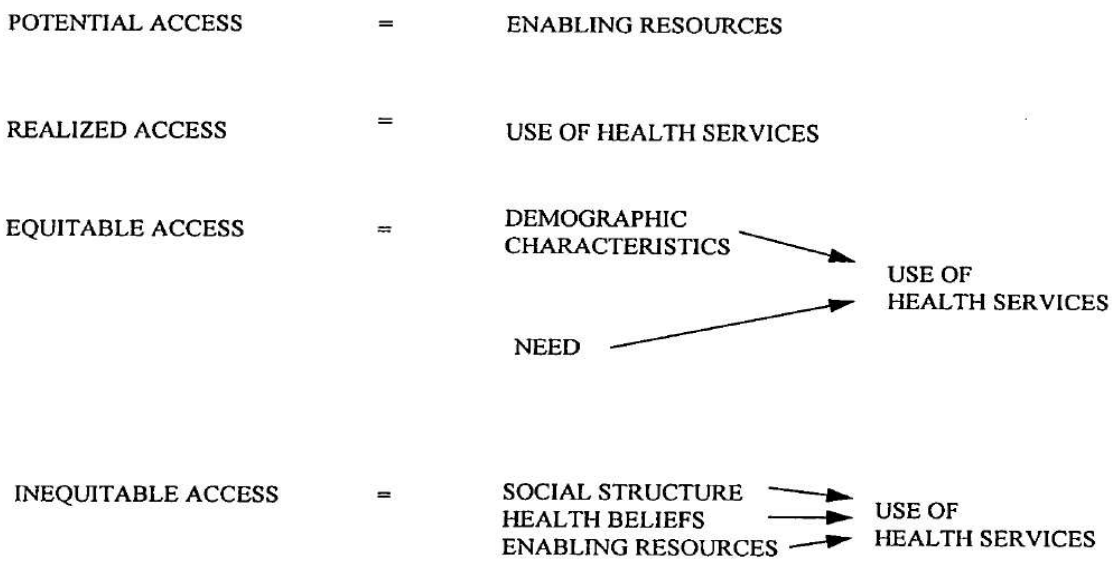

Figure 3. Initial measures of access of the health behavior model. Andersen, R.M. (1995). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Social Behavior, 36*, 1-10. Reprinted with permission.

By 1995, Andersen revised the original focus on access to a behavioral approach of health services use with the assertion that using health services should either maintain the health status of the population served or improve the population's health status, both perceived by the population and/or evaluated by health professionals (Andersen, Davidson, & Ganz, 1994; Figure 7). The model also recognizes the importance of how the external environment contributes to the use of health services. Andersen (1995) noted that this final model shows the many influences of health services use and eventually health status. This model provides feedback loops indicated by the arrows in the diagram that highlight the interrelatedness of all the factors that make up this model (Andersen, 1995).

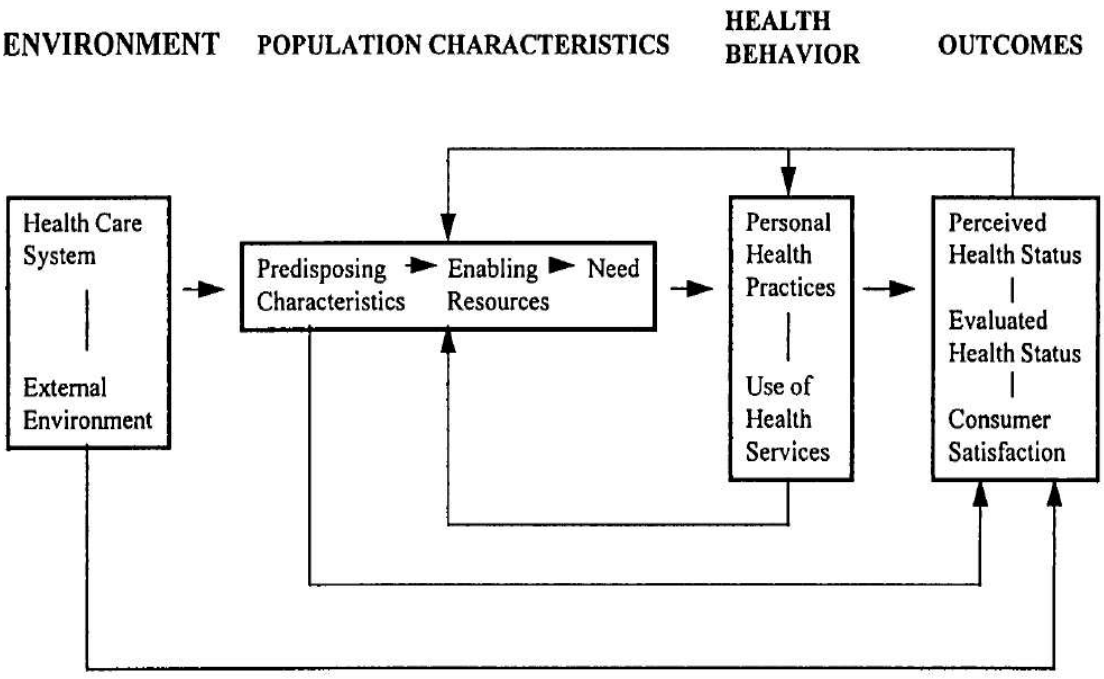

Figure 4. An emerging model identified as Phase 4 of the health behavior model. Andersen, R.M. (1995). Revisiting the behavioral model and access to medical care: Does it matter? *Journal of Social Behavior, 36*, 1-10. Reprinted with permission.

The following concepts, identified by Aday and Andersen (1974), are critical to understanding the behavioral model:

1. Health policy: Viewed as a starting point for understanding access to health care. Aday and Andersen (1974) acknowledged that those professionals involved with health planning and creating policy are concerned with effecting health policy in order to improve access to medical care.
2. Health care delivery system: Comprised of resources and organization.
    a. Resources are defined as the workforce and funds devoted to health care including health care personnel, physical structures where health care is

delivered, and equipment and supplies used to provide health care services.

b. Organization refers to what and how the system handles its resources. The components of organization are entry and structure.

i. Entry is the process of entering the healthcare system, otherwise known as access.

ii. Structure refers to the characteristics of the system that determines the needs of the patient at the time of service.

3. Characteristics of the population at risk: Viewed as the individual's determinants of health care utilization.

a. Predisposing factors are the sociocultural aspects of individuals that exist like age, gender, educational level, occupation, race, and ethnicity (Andersen, 1995).

b. Enabling factors involve resources that promote the use of health care such as adequate income and insurance coverage (Andersen, 1995). Additionally, the location of healthcare services is significant for people's ability to access health services (Aday & Andersen, 1974).

c. Need factors are the reasons why health care is sought (illness, accident) (Andersen, 1995).

4. Utilization of health care services: Those characteristics that identify what happens to the individual upon entry (or nonentry) into the system (Aday & Andersen, 1974; Andersen, 1995).

5. Consumer satisfaction: Measures users' satisfaction with the quantity or quality of care actually received. This dimension of access is measured by subjective perceptions in relation to convenience, coordination, cost, courtesy, and information provided.

Andersen's (1995) model is most meaningful in considering access from the perspective of whether those people who need care actually get into the system. A more precise model for measuring or quantifying access will improve awareness of the availability and utilization of health services by certain subgroups within the population. Graves (2011) noted that understanding the specific needs, predisposing factors, and enabling resources of people living in particular regions can ultimately effect alterations in health outcomes. The assessment of tumor size, treatment options, and survival rates for GBM patients and the relationship to location of health services (urban versus rural areas) can potentially improve survival rates. Therefore, the adaptation of Andersen's HBM model to the GBM population in urban versus rural areas is presented in this study.

Healthcare Access

Aday and Andersen (1974) defined access as the ability to utilize healthcare services whenever and wherever the need arises. Alternatively, potential access refers to having the resources that promote the use of healthcare services, otherwise known as enabling resources (Andersen, 1995; Graves, 2011). Therefore, if one possesses more enabling resources, chances are that the healthcare system will be used. Alternatively, a shortage or absence of enabling resources could ultimately result in one's decreased ability to enter the health care system. A 1973 report by the United States Department of

Agriculture examined the provision of healthcare services in rural versus urban regions and concluded that populations living in rural regions do not have equal access to healthcare compared to their urban counterparts. The report goes on to say that rural regions are deficient in medical personnel and healthcare facilities, and populations in rural regions do not have the economic capabilities to afford the costs of illness (Lepine & Le Nestour, 2012).

The concept of access describes the association or connection between the basic need for healthcare and the actual delivery of healthcare. From a conceptual perspective, access is further divided into the following categories: acceptability, accessibility, accommodation, affordability, and availability. Accessibility is subdivided into socio-organizational and geographical aspects such as distance transportation and travel time to and from health care services (Aday & Andersen, 1974). However, most measures of access highlight the actual location of healthcare services and how the needs of the associated population in question are being met (Graves, 2009).

In 1971, Hart described the state of heath care services in Great Britain as an imbalance between need and provision. Hart observed that the lower social classes in Great Britain had higher morbidity and mortality rates than those in higher social classes. He proposed the Inverse Care Law where "the availability of quality medical care varies inversely with the need for care in the particular population served" (Hart, 1971, p. 405). Despite present-day advances in healthcare, the inverse relationship of need and provision persists. According to Murray and Lopez (1997), this inverse relationship is most evident in developing countries. Gatrell (2002) noted that in 1990, developing

countries had 90% of the disease burden but only 10% of global health expenditures. Current literature on developed countries has suggested that this inverse relationship continues to exist in Britain's healthcare system today (Lovett, Haynes, Sunnenberg, & Gale, 2002).

Access and Health Outcomes

Aday and Andersen (1974) identified health outcomes as the end products of access and include the indicators of health status, satisfaction, and quality of life. Past research has demonstrated differences in health outcomes by specific subpopulations who faced barriers to accessing high quality health care (Black, Langham, & Petticrew, 1995; Blustein & Weitzman, 1995; Bullen, 1996; Goodman et al., 1997; Sempos, Cooper, Kovar, & McMillen, 1988; Weitzman et al., 1997). Differences in health outcomes might be how frequently a disease affects a group or how often the disease results in death. These differences in health outcomes are known as healthcare disparities, and when disparities are identified, it is assumed that inequalities in healthcare could exist (Agency for Healthcare Research and Quality, 2013). Inequalities result in underserved, at-risk populations like minority groups, the elderly, women, children, the elderly, low-income populations, rural residents, and special needs populations (Agency for Healthcare Research Quality, 2004).

Access and Rural Health

There are numerous definitions of rural regions or rurality that have been used by various federal agencies of the United States. For this particular study, the definition developed by the United States Department of Agriculture (USDA) will be examined.

The Economic Research Service (ERS), a division within the USDA created a model known as RUCCs to describe the distinctions between rural regions and urban regions (USDA, 2002). The RUCCS model is based on metropolitan (urban) versus nonmetropolitan (rural) regions of the United States. In Table 4, the model starts with metro or urban regions classified into three separate categories by the size of the population. Conversely, nonmetropolitan regions are classified by how close they are to urban regions, often referred to as adjacency. In Table 4, Codes 1 through 3 refer to urban counties by population size, while Codes 4 through 9 identify rural counties by their proximity or adjacency to an urban area with a given population size (USDA, 2002).

Table 4

Urban and Rural Classifications

Metropolitan Counties	Definition
Code	
1	Metro area with 1 million or more people
2	Metro area with 250,000 to 1 million people
3	Metro area with fewer than 250,000 people
Nonmetropolitan Counties	
Code	
4	Adjacent to metro area, 20,000 or more people
5	Nonadjacent to metro area, 20,000 or more people
6	Adjacent to metro area, 2,500 to 19,999 people
7	Nonadjacent to metro area, 2,500 to 19,999 people
8	Adjacent to metro area, < 2,500 people or totally rural
9	Non adjacent to metro area, < 2,500 or totally rural

Note. Economic Research Service (2013). *2013 rural-urban continuum codes*. Retrieved from http://www.ers.usda.gov/data-products/rural-urban-continuum-codes/documentation.aspx.Table is in the public domain. Permission to reproduce is not required.

Geographic Perspectives: Urban Versus Rural Regions

From a public health perspective, there has always been significant interest in the health of populations from a geographic vantage point of where people reside. Research has demonstrated the important connection between place of residence and health (Eberhardt & Pamuk, 2004; Tunstall, Shaw, & Darling, 2004). Specifically, there is a dearth of research on health care and health outcomes in rural and urban areas. This research originally focused on access, cost, and the distribution of healthcare resources like medical providers, clinics, and hospitals (Aday & Andersen, 1974; Hartley, 2004; Vlahov, Galea, & Freudenberg, 2005). Current research in the rural-urban arena is on the determinants of health and the resultant similarities and differences on health behaviors and outcomes (Meade & Emch, 2010).

At least half of the world's population lives in urban regions (United Nations Population Fund, 2011). From a social and environmental perspective, urban life is quite different from rural life. Urban life is distinguished by the following characteristics: dense and diverse populations, complex systems, extensive social and political networks, increased growth of slums, a dearth of hazardous waste sites, increased indoor and outdoor pollution, noise exposure, and inadequate, over-crowded living conditions (Lauber & Tidball, 2014; Vlahov et al., 2005).

Alternatively, rural regions show populations that are more spread out across wider farmland type areas and characterized by a lower socioeconomic status, earlier mortality before 75 years of age (Eberhardt & Pamuk, 2004), along with higher mortality rates from accidents and suicide (Eberhardt et al., 2001). Rural populations tend to

smoke excessively (Monroe, Ricketts, & Savitz, 1992), and have higher mortality rates from chronic obstructive pulmonary disease (Eberhardt et al, 2001). Research has shown mixed results for cancer mortality rates across rural regions of the United States. For example, Yabroff et al. (2005) demonstrated higher mortality rates due to cervical cancer in women living in the central California valley, southern portions of the United States, and rural Appalachia, compared to their urban counterparts. A 2011 study examined the mortality rates for all cancers in the United States, and found that rural residents had higher cancer mortality of the prostate, cervix, lung, and colon (Singh et al., 2011). Research has also demonstrated that populations living in rural regions travel longer distances and to urban areas to obtain needed medical care (Chan, Hart, & Goodman, 2006). Ricketts (2000) specifically pointed out that rural areas are constantly suffering from physician shortages since only 11% of all physicians practicing in the United States are based in rural areas. Reschovsky and Staiti (2005) determined that the physician shortage is far greater among specialists in rural areas. Since rural patients have a lower socioeconomic status, they are less likely to have insurance which discourage them from seeking needed medical care. When illness becomes so great and patients have to obtain needed care, they have to wait longer for appointments due to physician shortage, have to travel far greater distances to see specialists, and are usually in advanced stages of disease progression.

Brain Tumors: General Overview

The brain and spinal cord, taken together are known as the Central Nervous System (CNS; Buckner et al., 2007). The CNS regulates all the vital functions of the

body such as all body movements, speech, and thoughts (Buckner et al., 2007). When a brain tumor occurs in the CNS, it can significantly affect one's thought processes, communication abilities, and movement capabilities (American Society of Clinical Oncology, 2012). Brain tumors occur when normal brain cells change and grow uncontrollably ultimately forming a collection of abnormal cells (National Cancer Institute, 2009). Brain tumors are classified as primary or secondary. Primary brain tumors start in the brain, and rarely metastasize to other parts of the human body (National Cancer Institute, 2009). Secondary brain tumors, otherwise known as metastatic brain tumors, occur when cancer cells from another part of the body, such as the lung, breast, or colon, spread or metastasize to the brain via the bloodstream (National Cancer Institute, 2009). The distinction between primary and secondary brain tumors is clinically important since treatment modalities are quite different.

There are over 100 different types of primary brain tumors that are identified and categorized by microscopic examination otherwise known as histopathologic classification. Approximately 50% of these brain tumors come from a specific cell in the brain known as a glial cell (Jellinger, 1978). First identified by the German pathologist, Rudolf Virchow, in 1860, these primary brain tumors are known as gliomas, and Virchow used terms like *teleangiectatic* and *hemorrhagic* to further describe these tumors (Jellinger, 1978). Gliomas originate from primitive cells known as astrocytes, and brain tumors that originate from astrocytes are called astrocytomas (Jellinger, 1978). Astrocytomas are given a grade from I to IV for how much the tumor looks like normal brain tissue and how quickly the cells grow often referred to as aggressiveness (American

Society of Clinical Oncology, 2014). This grading system, specific to brain tumors, is primarily used to determine a patient's prognosis. Lower grades are less abnormal and slow-growing while higher grades are more abnormal and fast-growing. The World Health Organization (WHO) classifies astrocytomas in the following ways:

- Grade I (Pilocytic Astrocytoma): A brain tumor that grows slowly, does not metastasize to other areas of the CNS, the least malignant, and accounts for 2% of all brain tumors (American Society of Clinical Oncology, 2014).
- Grade II (Low-grade Astrocytoma): A relatively slow-growing brain tumor that may or may not metastasize to other parts of the CNS, tends to recur post-treatment, and accounts for 3% of all brain tumors (American Society of Clinical Oncology, 2014).
- Grade III (Anaplastic Astrocytoma): A malignant brain tumor that grows quickly, invades nearby brain tissue, and accounts for less than 5% of all brain tumors (American Society of Clinical Oncology, 2014; Louis et al., 2007).
- Grade IV (GBM): An extremely aggressive and highly malignant brain tumor that rapidly invades normal brain tissue, characterized by areas of necrosis (dead cells) in the center of the tumor when viewed under a microscope, and accounts for 25% of all primary brain tumors (American Society of Clinical Oncology, 2014; Louis et al., 2007; Wang et al., 2011).

Glioblastoma Multiforme: Definition and Description

The term *glioblastoma multiforme* was first used in 1925 by Globus and Straus as a replacement for the category known as spongioblastoma multiforme. On microscopic

examination, a GBM is typically recognized as having large areas of necrosis and microvascular proliferation (the formation of new blood vessels from preexisting blood vessels), a hallmark sign in aggressive cancers (Shabason, Tofilon, & Camphausen, 2011). In general, GBM tumors have the appearance of malignant cells surrounding areas of necrosis and hemorrhage (Louis, Holland, & Cairncross, 2001; Shabason et al., 2011). Due to its hemorrhagic, proliferative, and aggressive qualities, the median survival time for a newly diagnosed patient is approximately one year (Aldape, Okcu, Bondy, & Wrensch, 2003).

Epidemiology of Glioblastoma Multiforme: Person, Place, and Time

In the United States, primary malignant brain tumors are rare, accounting for approximately 2% of all adult cancers (American Cancer Society, 2012a; Patel et al., 2014). Despite their rarity, brain cancer incidence has increased over the last 30 years while survival rates remain abysmally poor (Deorah, Lynch, Sibenaller, & Ryken, 2006). From 1973 to 2001, over 38,000 cases of malignant brain tumor were reported to the SEER 9 database, and almost 17,000 cases were diagnosed as GBM (Deorah et al., 2006). GBM is the most commonly-occurring brain neoplasm in adults. .The following epidemiological facts are known about GBM:

- 1.6 times more common in men than women (Ivan, Tate, & Clarke, 2012).
- Two to three times higher among Caucasians than blacks, American Indians and Alaskan natives, and Asian-Pacific Islanders race groups (Ohgaki & Kleihues, 2005).

- Occurs more frequently in older adults (Dolecek, Propp, Stroup, & Kruchko, 2012), and increase with age with primary occurrence in adults from 45-70 years old although the highest rates occur in the 75 to 84 year-old age group (Ivan, Tate, & Clarke, 2012; National Cancer Institute, 2012).
- In most elderly patients, GBMs arise abruptly and grow quickly, impairing cognition and drastically reducing functional independence (Hutterer, 2009). Furthermore, GBM treatments in older people are less effective and more toxic than in younger people.

As in the United States, GBM is the most common primary brain tumor worldwide, with an incidence of 2-3 new cases per 100,000 people per year (Central Brain Tumor Registry of the United States, 2012). The relative survival estimates for patients diagnosed with GBM show less than 5% of patients surviving five years post-diagnosis (Central Brain Tumor Registry of the United States, 2012). Aldape et al. (2003) noted that the median survival for patients newly diagnosed with GBM and undergoing typical treatment options is 12 months. Despite the advent of modern-day diagnostic capabilities along with improved and enhanced treatment modalities, survival time has not significantly improved.

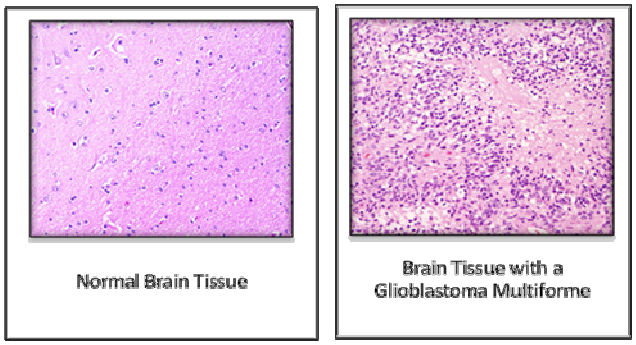

Figure 5. Microscopic view of normal brain tissue and brain tissue with a GBM.
Note. College of American Pathologists (2012). *Brain tumor: Glioblastoma.* http://www.cap.org/apps/docs/reference/myBiopsy/glioblastoma.html. Figure is in the public domain. Permission to reproduce not required.

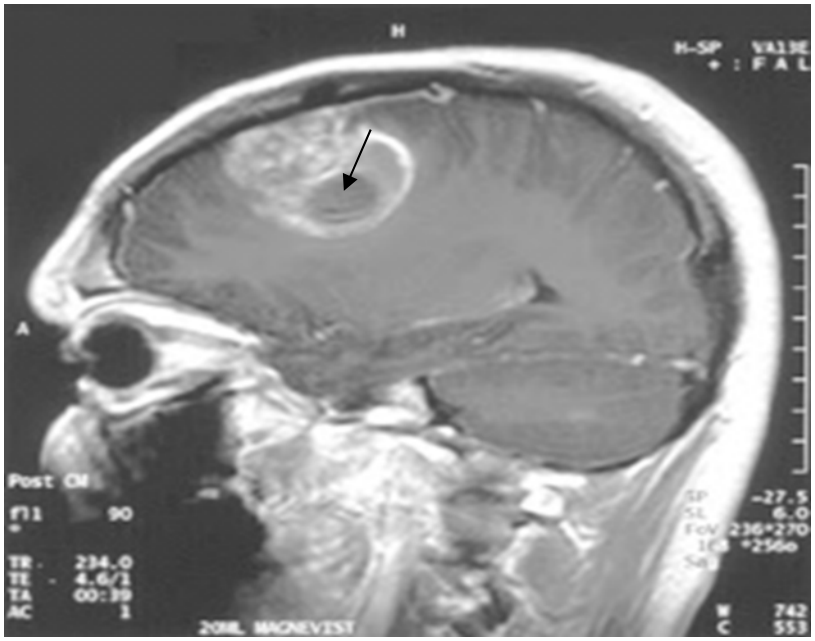

Figure 6. Magnetic resonance image (MRI) revealing a mass in the brain that was later shown to be a glioblastoma multiforme (indicated by arrow).
Note. National Institutes of Health (2014). Glioblastoma multiforme. *The Cancer Genome Atlas.* Retrieved from http://cancergenome.nih.gov/cancersselected/glioblastomamultiforme. Figure is in the public domain. Permission to reproduce not required.

Treatment Modalities of GBM

The management of GBM has progressively evolved over the last two decades with new technological advances that have led to improve diagnosis, site-specific radiation techniques, surgical procedures, and improved chemotherapies. Yabroff, Harlan, Zeruto, Abrams, and Mann (2012) note that GBM treatment is limited by its primary location (brain) and its infiltrating vascularity. According to Ivan, Tate, and Clarke (2012), prior to 2005, the typical standard of care for newly diagnosed GBM patients was surgical removal of the tumor followed by radiation therapy (adjuvant radiotherapy). Whether or not chemotherapy administration was beneficial in the treatment of GBM was not clear (Yabroff et al., 2012). However, in 2005, a landmark study demonstrated that overall survival was prolonged if the patient had maximal surgical resection of the tumor followed by concomitant therapies of radiation and administration of a chemotherapeutic agent identified as temozolomide (Stupp et al., 2005).

Prognostic Factors of GBM

The neuro-oncologic community universally agrees that a diagnosis of GBM is associated with a dismal prognosis (Stupp et al., 2005; Yuile, Dent, Cook, Biggs, & Little, 2006;Yabroff et al.,2012). The prognosis of GBM remains poor despite ongoing therapeutic advancements. Median survival from initial diagnosis is, at best, approximately one year. Given the dismal prognosis, multimodal aggressive therapy consisting of surgical resection of the GBM tumor, radiation therapy, and chemotherapy administration is done in an attempt to prolong survival time. In an attempt to understand

contributory factors associated with the development of GBM, studies have explored a multitude of exogenous factors such as smoking, diet, cell phone use, ionizing radiation, electromagnetic fields, immunological status, allergies, and viral infections just to name a few. Unfortunately, there is no definitive evidence implicated in the development of GBM except for prolonged exposure to ionizing radiation.

The difficulty in treating GBM is well recognized. Researchers have sought to evaluate those factors that contribute to worsening survival times and/or prolonging survival times. In order to optimize treatment modalities for individual patients, it is critical to evaluate prognostic factors that will enhance survival. Data from the Glioma Outcomes Project demonstrated that patient age, functional status, and complete resection of the tumor were statistically significant prognostic indicators for patient survival (Laws et al., 2003).

- Age is the most significant prognostic factor for survival. It is noted that age younger than 60 years is a favorable prognostic factor (Mineo et al., 2007; Chandana, Movva, Arora, & Singh, 2008).
- In an attempt to understand how well GBM patients are doing physically, medical providers will assess their ability to carry out everyday activities, or their functional capacity. There are different kinds of functional tests that practitioners use to determine a patient's level of functioning. One of the most commonly used tests is identified as the Karnofsky Performance Scale (KPS) developed in 1949 by Karnofsky and Burchenal. A patient can score anywhere from 0 to 100, with 0 representing death while 100 is considered normal with no evidence of disease. A

score of 80 or greater is considered a good prognostic indicator for GBM patients (Stark, Stepper, & Medhorn, 2010).

- Removal of the entire GBM tumor is impossible because of the hyper-vascularity and invasiveness of the tumor. Therefore, surgeons strive to remove as much of the tumor as possible to decrease the tumor size, relieve pressure on the brain known as intracranial pressure (ICP), and prolong survival (Chandana et al., 2008). Hentschel and Lang (2004) noted that aggressive resection where more than 98 % of the GBM tumor is removed is associated with a statistically significant improved survival rate.
- Epilepsy or seizures represent a significant prognostic factor because it leads to earlier diagnosis (Mineo et al., 2007; Chandana et al., 2008). However, there are many GBM patients who never experience seizures.
- Patients who present with acute onset or significantly disturbing symptoms show improved survival when compared to patients who experience symptoms that are subtle or slower to evolve (Yulie et al., 2006).

Summary

This chapter included a review of the literature pertinent to this study. I described Andersen's Health Behavioral Model which serves as the theoretical framework used for this study. Additionally, this chapter included a discussion of the geographic variations of GBM in the United States, the clinical attributes of GBM including its definition, symptomatology, detection, prognostic characteristics, diagnosis, and treatment options followed by the epidemiological characteristics of GBM from a person, place, and time

perspective based on the most current literature. Major studies on GBM were reviewed and summarized. Finally, analysis of this literature review highlighted a knowledge gap regarding urban and rural variances in tumor size, treatment options, and survival rate in GBM patients.

Almost 20 % of the population in the United States lives in a rural setting, are generally older, usually unemployed, experience greater poverty, tend to be in poor health, and are usually uninsured (Hart et al., 2005). Rural residents are challenged with barriers when trying to access health care services such as traveling longer distances to reach health care facilities, and have fewer doctors and hospitals than urban residents. By the time rural residents do access the healthcare system, their health issues may be more serious or far advanced. This study will help fill the knowledge gap related to geographic variations in GBM tumor size, treatment options, and survival rate. Research that focuses on early detection of GBM, increasing GBM awareness, and geographic variation has received inadequate attention. This study may help to fill the void in the current state of affairs related to GBM, and thereby lead to future research that will improve survival rates in this deadly disease.

In Chapter 3, I discuss the study methodology that used to address the primary research question: Are there differences in tumor size, treatment options, and survival rate between urban and rural GBM patients? Chapter 3 describes the research design, setting, sample and eligibility criteria. Additionally, Chapter 3 offers a thorough discussion of instrumentation and materials, data collection, and analysis. Finally,

Chapter 3 closes with a discussion on maintaining quality assurance and confidentiality, and ensuring protection of human subjects.

Chapter 3: Research Method

Introduction

In this study, I focused on patients 20 years and older who have been diagnosed with GBM. My purpose was to determine if differences in tumor size, treatment options, and survival rate occur in GBM patients living in urban versus rural regions of the United States. This chapter delineated the research design, data setting, and sample. A discussion of the research design section included the rationale for the design of the study. The setting and sample section included a description of the study's sample population and criteria for inclusion. The instrumentation and materials section included a discussion of the SEER database and cancer registries. The data collection and analysis section addressed the research questions and study variables. The final section provided a discussion of quality assurance, confidentiality of study subjects, and protecting human research participants.

Research Design and Approach

This retrospective study explored the differences in GBM tumor size, treatment options, and survival rate in urban versus rural patients. The independent variables were urban (metropolitan) and rural (nonmetropolitan) areas. The dependent variables were tumor size at diagnosis, treatment options (surgical resection and adjuvant therapies of radiation treatment and chemotherapy), and survival rate. Using secondary data sets available through the SEER program, this was a quantitative, retrospective cohort study. The SEER Program is a division of the National Cancer Institutes (NCI) involved in the collection of cancer data across the United States. Cancer data is collected by specially-

trained personnel from 18 cancer registries representing 28% of the United States population (SEER, 2013). The SEER registries consistently collect the following types of data: patient information, type of cancer, primary location of the cancer or tumor, tumor size, microscopic composition of the tumor, stage and grade of the tumor, treatment options, and survival data (SEER, 2013). Once the data are collected, the data are then analyzed for cancer trends in the United States, including cancer incidence for specific cancers, population characteristics, treatment options, and survival and mortality data.

The primary benefits of a retrospective cohort design are that it is less expensive, easier to conduct, less prone to bias, and optimal for multiple outcomes analysis (Mann, 2003). Additionally, since the SEER database is linked to census data, researchers can examine disease patterns across numerous demographic and socioeconomic variables (SEER, 2013). A major disadvantage of a retrospective cohort design involves collection of data prior to the study. For instance, failure to adhere to data standardization procedures may lead to incomplete or erroneous entries. Another disadvantage of retrospective cohort studies is the inability to control for confounding variables (Mann, 2003). Finally, retrospective cohort studies may be prone to bias given the manner in which study subjects are selected and the potential for subjects to drop out of the study.

Setting and Sample

Adult patients 20 years of age and older diagnosed with GBM served as the study population. Data were collected and analyzed retrospectively using the most recent

SEER database covering the years 1973 through 2011. For the purposes of this particular study, data were collected on GBM patients diagnosed from 1988 to 2011.

Eligibility Criteria

The sample consisted of subjects with the following eligibility characteristics: (a) adults diagnosed with GBM, (b) age at diagnosis: all ages, (c) place of residence: urban (metropolitan) or rural (nonmetropolitan), (d) year of diagnosis: 1988 to 2011 inclusive, (e) race and ethnicity: all races and all ethnicities reported, (f) tumor size, (g) surgical resection (yes/no), (h) adjuvant therapies: radiation treatment (yes/no) and chemotherapy (yes/no), and (i) survival time: 5 years after diagnosis. The SEER database specifically classifies tumors by a collaborative staging code most commonly referred to as a CS code, and used to identify the part of the body where the tumor is found. CS codes specific to GBM tumors corresponded to the particular lobe or area in the brain where the tumor was located. The CS codes for GBM tumors included C70.0 and C71.0-71.9. See Table 5 for location of brain tumors.

Table 5

Brain/Cerebral Meninges

CS code	Location
C70.0	Cerebral meninges
C71.0	Cerebrum
C71.1	Frontal lobe
C71.2	Temporal lobe
C71.3	Parietal lobe
C71.4	Occipital lobe
C71.5	Ventricle, NOS*
C71.6	Cerebellum, NOS*
C71.7	Brain stem
C71.8	Overlapping lesion of brain
C71.9	Brain, NOS* (not otherwise specified)

Note. Beahrs, O. H., Henson, D. E., Hutter, R. V. P., & Kennedy, B. J.(1992). *Manual for staging of cancer (4th ed.)*. Philadelphia, PA: J. B. Lippincott Company.

Power Analysis

The power of a statistical test allows the researcher to decide the size of the sample needed to produce accurate and reliable results. For this study, statistical power was calculated using a priori power analyses conducted using *G Power. An a priori analysis was done to ascertain the required sample size that will achieve a given statistical power. More specifically, the statistical power of a test detected that a phenomenon does in fact exist (Cohen, 1988; High, 2000).

For this study, the expectation was that the null hypothesis would be rejected for all research questions noted in the following:

- Research Question 1: There is no significant difference in GBM tumor size between urban and rural patients.

- Research Question 2: There is no significant difference in the treatment option of surgical resection.
- Research Question 3: There is no significant difference in the adjuvant therapies of radiation treatment and/or chemotherapy between urban and rural patients.
- Research Question 4: There is no significant difference in GBM survival rates between urban and rural patients.
- Research Question 5: There is no significant difference in GBM survival rates controlling for region, race, age, sex, educational, and family income in the study population of GBM cases.

Using G*Power v3.1.0 to determine the sample size, the test family of *t* tests were used. A calculation estimating the effect size was determined to be 0.32, or medium effect, and a power of 0.80 was selected. Power analysis was done by entering the proportions for the null hypotheses (rural patients diagnosed with GBM will not present with larger tumor, limited treatment options, or have poorer survival) against proportions expected to be seen. The G*Power Analysis calculator, developed by Faul, Erdfelder, Lang, and Buchner (2007) was set at the test family of *t* tests using the Mann-Whitney U test , the a priori total sample size was calculated at 256 (equal sample size in urban and rural groups). Table 6 shows the G*Power Analysis Calculator.

Table 6

*G*Power Analysis Calculator (a priori) Independent Samples t Test Using the Mann-Whitney U test*

Input	Calculation
Effect size w	0.32
α err prob	0.5
Power (1-β err prob)	0.80
Allocation ratio N2/N1	1
Input	Calculation
Noncentrality parameter λ	2.5016449
Critical t	1.6511624
Sample size group 1	128
Sample size group 2	128
Df	242.462
Total sample size	256
Actual power	0.8022824

Note. To calculate the sample size for the Kaplan Meier and Cox Proportional Hazard Ratio, the MedCalc version 12.7.7 (Medcalc Software, 2013) was used. The a priori sample size was calculated at 196 (equal sample size in urban and rural groups).

Table 7

Survival Analysis (logrank test): MedCalc (a priori): Compute Required Sample Size

Options

Type I error (alpha, significance)	0.05
Type II error (Beta, 1-Power)	0.20

Data

Survival rate Group 1	0.6
Survival rate Group 2	0.4
Ratio of Sample Sizes in Group1/Group 2	1

Result

Number of cases required in Group 1	98
Number of cases required in Group 2	98
Total sample size (both groups together)	196

Data Collection and Analysis

The SEER Program provided a cancer database considered the preeminent source of cancer-specific and population statistics for the United States (SEER, 2013). In addition to cancer-specific data, the SEER database captured population-based data like gender, race/ethnicity, age, date of original diagnosis, the geographic location of residence, patient-specific treatments, tumor stage and size, and patient survival data (SEER, 2013). The advantages of using the SEER database included the following: (a) It is a relatively inexpensive way to obtain cancer-specific data; (b) its validity and reliability has been established; and (c) its comprehensiveness lends itself to obtaining a large sample size with increased power. Data were manually extracted from the SEER database using SPSS (IBM Statistics Grad Pack Version 20). SPSS has the capability of handling sizeable datasets and the ability to perform data analysis employing an assortment of statistical tests.

This retrospective cohort study used secondary data obtained from the 1973-2011 SEER database to examine the relationship between GBM cases in urban and rural areas, tumor size, functional status, and survival. The data were publically available and readily accessible by signing a SEER Research Data Agreement (SEER, 2013). This agreement stressed the importance of protecting the identities of cancer patients covered in the Protection of Human Subjects. Data can be accessed via the Internet or on a DVD. For this study, a request was made to have access to the data and SEER*Stat software via the Internet. A personalized SEER Research Data Agreement was generated and signed, and

permission to access the data was granted (refer to Appendix A). After permission was granted, a confidential and unique user name and password were assigned by SEER.

All GBM cases noted earlier were assigned to regions and dichotomized to urban and rural counties based on location of residence when diagnosed. To further understand the regional variations, the study evaluated tumor size at diagnosis, the treatment option of surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rate. Five research questions were evaluated:

- Research Question 1: When comparing urban and rural patients with GBM, is there a significant difference in GBM tumor size at diagnosis?
- Research Question 2: When comparing urban and rural patients with GBM, is there a significant difference in the number of GBM patients who experience surgical resection?
- Research Question 3: When comparing urban and rural patients with GBM, is there a significant difference in the number of GBM patients who experience adjuvant therapies of radiation treatment and chemotherapy?
- Research Question 4: When comparing urban and rural patients with GBM, is there a significant difference in GBM survival rates?
- Research Question 5: In the study population of GBM patients, is there a significant difference in survival rates when controlling for region, race, age, sex, educational level, and median family income?

Inclusion criteria included all GBM cases diagnosed in adults 20 years and older reported to SEER between 1988 and 2011. Data on stage at diagnosis have been reported since

1975. However, tumor size has only been reported since 1988 (Farrow, Samet, & Hunt, 1996). Consequently, the SEER data were scrutinized for all GBM cases diagnosed from 1988 through 2010 inclusive of data on tumor size.

Independent Variable

The independent variable for this study is identified as region, apportioned to urban and rural counties. In the SEER database, two other terms describe urban and rural: Metropolitan was used interchangeably with urban, and nonmetropolitan was used interchangeably with rural. The independent variable of region was presumed to influence the dependent variables noted below. The geographic features of urban and rural areas may be critical in accessing healthcare resources, early screening and detection, and providing basic preventive health services (Klein, 2010). Rural populations have poorer access to healthcare facilities and resources that may affect not only access to healthcare in general but also access to preventive cancer screening and specialized health services. Consequently, rural residents will not seek care at the time of need, and when care is finally sought, rural patients are found in advanced disease stages than their urban counterparts (Eberhardt et al., 2002). Complicating this scenario is the fact that rural residents face longer distances and travel times to medical facilities including cancer centers, treatment facilities, and specialized providers (Coughlin et al., 2002).

Dependent Variables

This study addresses four dependent variables: tumor size, surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rate. Past

research identified these variables as prognostic indicators for adults diagnosed with GBM. GBM is usually diagnosed at an advanced stage known as a Grade 4 tumor. Grade 4 tumors are usually larger in size than early-stage tumors. Larger tumors and advanced age at diagnosis are associated with a lower survival rate.

Scales of Measurement

The level of measurement of the independent variable of region apportioned to urban and rural was nominal. There were four dependent variables for this study: tumor size at initial diagnosis, surgical resection, adjuvant therapies of radiation treatment and chemotherapy, and survival rate. The level of measurement for tumor size was ordinal since the SEER database uses categories of tumor size ranges where tumor size is measured in centimeters. Ordinal measurements assign observations into categories that can be put into rank order and do not quantify differences (Gerstman, 2008, p. 5). Since rank orders do not quantify differences, conditions of normality and equal variance are absent. Thus, a nonparametric statistic was be used. Data analysis for the first research question used the Independent Samples *t* test or Mann-Whitney *U* test, depending on normality. The level of measurement for surgical resection as reflected by whether or not the patient experienced surgical resection was nominal, and correlated to a simple classification of yes versus no. Data analysis for the second research question involving surgical resections was conducted using the Independent Samples *t* test or the Mann-Whitney *U* test depending on sample size and normality. The level of measurement for adjuvant therapies of radiation treatment and chemotherapy as reflected by whether or not the patient experienced radiation treatment (yes/no) and/or chemotherapy (yes/no) was

nominal, and correlated to a simple classification of yes versus no for each adjuvant therapy of radiation treatment and chemotherapy. The fourth research question on survival rate used two statistical tests. First, the Kaplan-Meier was used for univariate analysis. Second, the Cox proportional hazards (regression analysis) was used for multivariate analysis of survival differences between groups (urban and rural). The fifth research question involving survival rates used multiple regression modeling to determine the best predictive model based on the independent variables of region, gender, race, age, marital status, education, and family income in the study population of GBM cases (Klein, Ji, Rea, & Stoodt, 2011). Table 8 shows the multiple regression modeling and associated independent variables.

Table 8

Variables for Multiple Regression Modeling

Variables	Rural (n)	Rural %	Urban (n)	Urban %	Total
Race					
Black					
White					
Other					
Unknown					
Marital status					
Single					
Married					
Widowed					
Divorced/Separated					
Education level					
Low					
Medium					
High					
AGE					
< 50					
50-70					
71-80					
> 80					
Median family income					
< $50,000					
$51,000 - $64,000					
> $65,000					

Instrumentation and Materials

The database used is the SEER Program of the National Cancer Institute (NCI) (SEER, 2013). A plethora of data is collected from 18 cancer registries across the United States, as noted in the data collection and analysis section. The registries noted in Table 9 correspond to their geographic location:

Table 9

SEER 18 Registries

Alaska Native Tumor Registry
Arizona Indians
Cherokee Nation
Connecticut
Detroit
Georgia Center for Cancer
Greater Bay Area Cancer Registry
Greater California
Hawaii
Iowa
Kentucky
Los Angeles
Louisiana
New Jersey
New Mexico
Seattle-Puget Sound
Utah

Note. SEER (n.d.). *List of SEER registries.* Washington, D.C.: United States Department of Health and Human Services. Retrieved from http://seer.cancer.gov/registries/list.html. Information is in the public domain. Permission to reproduce not required.

The above noted geographic regions represented 28% of the United States population, and accounted for a broad cross section of the population representing different ethnicities, cultures, and geography (National Cancer Institute, 2010). While the entire United States was not represented in the SEER database, the coverage was broad enough to account for the many population groups living in the United States (SEER, 2010). For the purposes of this study, all of these regions identified in the SEER database were used for data collection, and then categorized into urban and rural areas using RUCCs. Figure 7 shows the location of SEER registries across the United States.

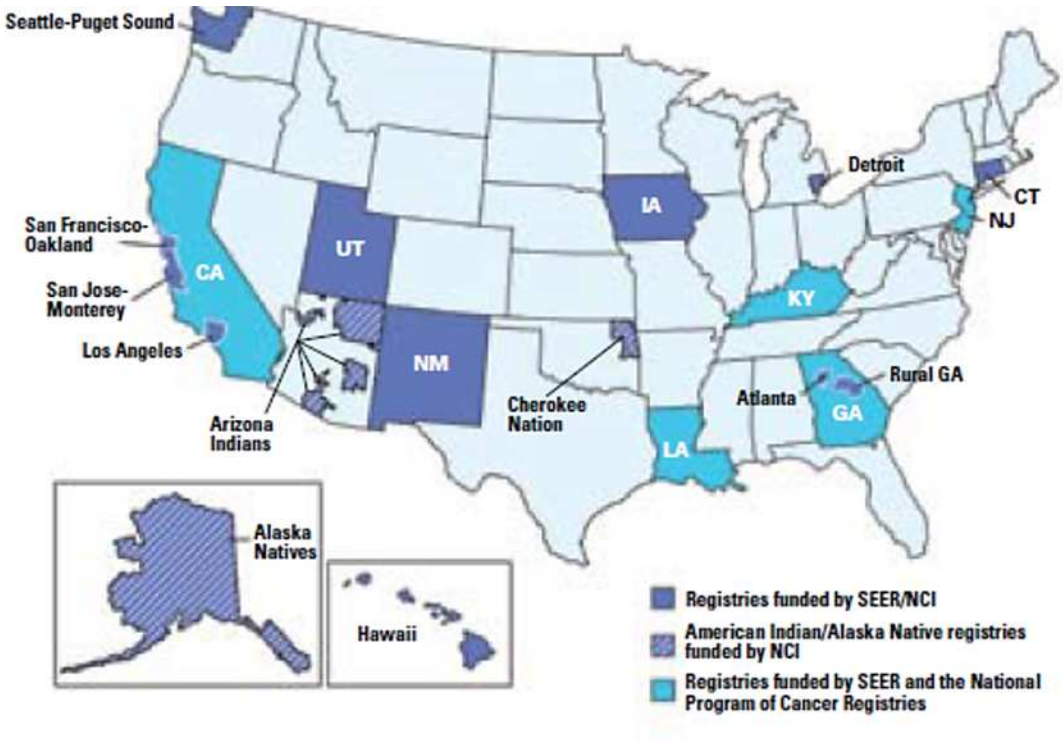

Figure 7. Locations of SEER registries across the United States
Note. SEER (n.d.). *About the SEER registries.* Washington, DC: United States Department of Health and Human Services. Retrieved from http://seer.cancer.gov/registries/. Figure is in the public domain. Permission to reproduce not required.

The 18 population-based registries fall under the auspices of the North American Association of Central Cancer Registries (NAACCR). The NAACCR provides guidance in data collection to all registries as a way of maintaining the integrity, quality, and accuracy of collected data (National Cancer Institute, n.d.). The NAACCR has a rigorous audit and quality control process to ensure the accuracy of collected data (National Cancer Institute, n.d.), and study results are ultimately used to improve documentation of data (National Cancer Institute, n.d.).

In addition to state and regional registries, the SEER Program interfaces with other federal and state agencies as well as nationally-recognized databases for research

purposes. For example, the National Center for Health Statistics provides mortality statistics, and the Census Bureau provides population data for the calculation of cancer rates (National Cancer Institute, n.d.). SEER also works with the Centers for Medicare and Medicaid Services (CMS) to collect data on cancer statistics in the elderly. Finally, SEER has joined forces with the National Longitudinal Mortality Study (NLMS) to explore cancer incidence, tumor characteristics, and survival rates from a socioeconomic and demographic perspective.

Quality Assurance

The SEER database is considered the model of excellence for data quality, and often referred to as the gold standard for data collection. Quality improvement is critical to enhancing and continuously improving data quality. Quality improvement activities include case-finding audits related to data collection procedures, reliability studies that test the skills of registry personnel, and reabstraction studies at central and hospital cancer registries to continuously improve the input of meaningful data. To safeguard all study-related materials and maintain confidentiality, data were secured on a password-protected laptop with anti-virus software and internal firewalls. All study files were backed up daily, and saved on a password-protected flash memory card (thumb drive) maintained in a locked file cabinet. The researcher was the only person with access to the laptop, thumb drive, and key to the file cabinet.

Protection of Human Subjects

This study used secondary data sets from the SEER database. All data were de-identified as noted in the Privacy Rule which evolved from the Health Insurance

Portability and Accountability Act (HIPAA) of 1996. Additionally, the SEER registry program requires the researcher to sign a Limited Use Agreement in order to grant access to the data (Appendix A). Finally, an application for study approval was submitted to the Institutional Review Board (IRB) of Walden University (IRB approval # 01-28-14-0174231). Data collection and analysis moved forward once final approval was received from the IRB.

Dissemination of Findings

Dissemination of research findings is a critical component of any study. Equally important is Walden University's commitment to social change. Therefore, synthesis and dissemination of research findings for this study provides relevant and valid research evidence and implications for social change to colleagues, clinicians, and health policy makers.

Summary

Chapter 3 provided the basic methodology of this quantitative retrospective cohort study. The research design and approach provided the systematic plan to study GBM patients in urban and rural regions in relationship to tumor size, treatment options, and survival rate. The sample population was identified, including a thorough description of the eligibility criteria. The selected instrumentation and materials provided a comprehensive examination of the data sources associated with the SEER registries. Data collection and analysis provided the context for the established research questions, independent and dependent variables and their associated levels of measurement. Quality assurance focused on confidentiality, and the protection of human subjects provided

context around the Privacy Rule which grew out of HIPAA, the limited-use data agreement required by SEER, and subsequent IRB approval through Walden University. The methodology for this study was used to determine if urban and rural GBM patients experience differences in tumor size at diagnosis, surgical resections, adjuvant therapies of radiation treatment and chemotherapy, and survival rates using the U.S. SEER database. Study results are covered in Chapter 4.

Chapter 4: Results

The purpose of this retrospective, quantitative study was to ascertain if there are differences in tumor size, treatment options, and survival rates between rural and urban patients diagnosed with GBM. Research Question 1: Was there a potential relationship of GBM tumor size in urban and rural patients? Research Question 2: Was there a link between the treatment option of surgical resections in urban and rural patients? Research Question 3: Was there a relationship between treatment options of radiation therapy and chemotherapy in urban and rural patients? Research Question 4: Were there differences in survival rates of urban and rural patients. Research Question 5: Were there differences in survival rates of urban and rural patients when controlling for region, race, age, sex, educational level, and median family income? The hypothesis under review is that rural patients diagnosed with GBM will present with larger tumor size, experience fewer treatment options of surgical resections, radiation therapy, and chemotherapy, and have poorer survival rates compared to urban patients diagnosed with GBM.

I begin this chapter with a detailed description of data collection methods and any discrepancies from the outlined plan provided in Chapter 3. Next, descriptive statistics are provided for every variable of the study population. Finally, all statistical analyses specific to each research question are explained in detail.

Data Collection

This retrospective cohort study used secondary data obtained from the 1973 to 2011 SEER 18 database to examine the relationship between GBM cases in urban and rural areas, tumor size, treatment options, and survival. The SEER Program provides a

cancer database, which is the premier source of cancer-specific and population statistics associated by age, race/ethnicity, year of diagnosis, and geographic areas in the United States. Additionally, it is the only comprehensive source of population-based data in the United States that documents tumor size at diagnosis and survival data (SEER, 2013). The SEER 18 Registries of the NCI collects and analyzes cancer incidence, prevalence, and survival data from 18 population-based cancer registries covering approximately 28% of the total U.S. population (SEER, 2013). Refer to Table 9 in Chapter 3 for a complete listing of the registries. While the entire United States is not represented in the SEER database, the coverage is broad enough to account for the various diverse populations throughout the United States (SEER, 2010).

Using the SEER 18 database, cases were selected specific to this study that included all adults greater than 20 years old diagnosed with GBM in the United States between 1988 and 2011. This selection resulted in 33,202 eligible cases. Permission to view the selected cases was granted by both the Walden University IRB approval # 01-28-14-0174231 and the SEER Program.

Demographic information collected for this analysis included the following: a unique patient identifier, age, gender, race, marital status, registry location, location of residence categorized by either urban or rural area, median family income, educational level (< 9^{th} grade, high school, or bachelor's degree), GBM tumor size in millimeters, whether or not the patient underwent surgical resection of the brain tumor (yes/no), whether or not the patient underwent radiation therapy (yes/no), and survival time noted in months. It should be noted that data for the adjuvant therapy of chemotherapy

administration were going to be obtained from the SEER database. Unfortunately, these data were no longer included in the SEER database made available to the public. This will be further explained in Chapter 5. Since this was a retrospective study where de-identified patient information was used, informed consent was not required.

The study sample of 33,202 patients appears to exhibit appropriate external validity in that the sample consisted of patients representing all 18 registries of the SEER database. Furthermore, the sample includes both males and females diagnosed with GBM as well as all races, 20 years and older, representing urban and rural areas. It is worth noting that there are no studies to date that have examined the demographic variables of GBM from the geographic perspective of urban versus rural locations. As described in the following results section, descriptive statistics appropriately examined the study sample, and inferential statistics explored the aforementioned research questions and associated hypotheses.

Demographic Results

Initially, a series of descriptive statistics was conducted on these data to summarize characteristics of the study population. First, Figure 8 shows the number of GBM cases diagnosed from 1988 through 2011 in the United States. In general, diagnosed cases have increased annually with a sharp spike in 2000.

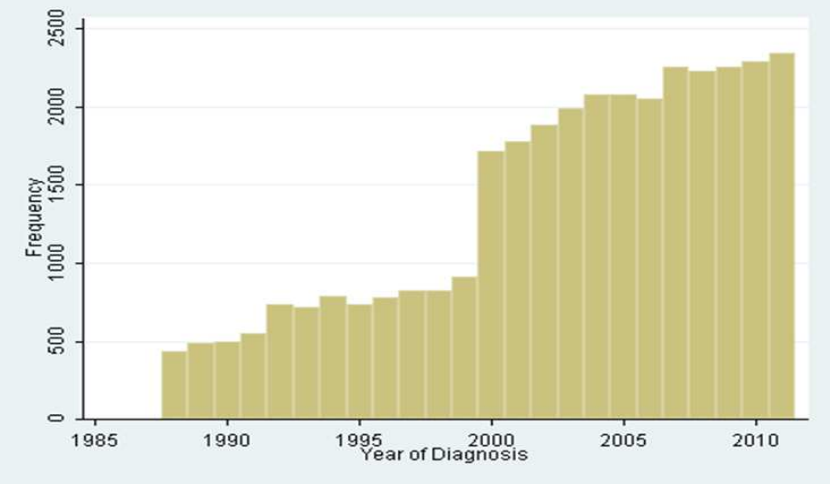

Figure 8. Glioblastoma multiforme cases diagnosed in the United States from the SEER data base, 1988-2011.

The sample included 12,430 females (37.44%) and 20,772 males (62.56%). As shown in the following table, the vast majority of the sample was white (91%), followed by black (5.14%) and other (4.19%). Finally, less than 1% of respondents did not have valid data on race.

Table 10

Percent Distribution of Study Subjects by Race (N = 33,202)

Category	*N*	%
Black	1,706	5.14
Other	1,391	4.19
White	30,049	90.50
Unknown	56	0.17
Total	33,202	

Table 11 summarizes the descriptive statistics conducted focusing upon respondent age. As shown, a broad range in responses was found, with the majority of patients being between the ages of 50 and 74.

Table 11

Frequency Distribution of Study Subjects by Age. (N = 33,202)

Category	*N*	%
20-24 years	215	0.65
25-29 years	371	1.12
30-34 years	520	1.57
35-39 years	873	2.63
40-44 years	1,545	4.65
45-49 years	2,576	7.76
50-54 years	3,586	10.80
55-59 years	4,364	13.14
60-64 years	4,771	14.37
65-69 years	4,434	13.35
70-74 years	4,134	12.45
75-79 years	3,260	9.82
80-84 years	1,816	5.47
85+ years	737	2.22
Total	33,202	100.00

Table 12 summarizes the descriptive statistics conducted with relation to marital status at time of diagnosis. Slightly over 76% of the sample was found to be married, with slightly over 9% being divorced. Slightly over 13% of respondents were single/never married, with close to 1% being separated.

Table 12

Frequency Distribution of Study Subjects by Marital Status (N = 33,202)

Category	*N*	%
Divorced	3,134	9.44
Married	25,308	76.22
Separated	286	0.86
Single (never married)	4,474	13.48
Total	33,202	

Table 13 summarizes from which registry location these data were derived. As shown, a very wide range was found with regard to the source of these data, suggesting that while not a probability sample, these data are representative of a broad population of patients. With respect to region, 29,140 (88.29%) patients lived in urban (metropolitan) regions, while 3,864 (11.71%) live in rural (nonmetropolitan) regions.

Table 13

Frequency Distribution of Study Subjects by Location of Registry

Category	*N*	%
Alaska Natives - 1992+	19	0.06
Atlanta (Metropolitan) - 1975+	1,179	3.55
California excluding SF/SJM/LA - 2000+	6,005	18.09
Connecticut - 1973+	2,397	7.22
Detroit (Metropolitan) - 1973+	2,213	6.67
Greater Georgia - 2000+	1,681	5.06
Hawaii - 1973+	418	1.26
Iowa - 1973+	2,118	6.38
Kentucky - 2000+	1,254	3.78
Los Angeles - 1992+	3,476	10.47
Louisiana - 2000+	1,214	3.66
New Jersey - 2000+	2,843	8.56
New Mexico - 1973+	809	2.44
Rural Georgia - 1992+	61	0.18
San Francisco-Oakland SMSA - 1973+	2,560	7.71
San Jose-Monterey - 1992+	1,132	3.41
Seattle (Puget Sound) - 1974+	2,690	8.10
Utah - 1973+	1,133	3.41
Total	33,202	100.00

Table 14 summarizes the descriptive statistics conducted with regard to all continuous measures of interest included within the data. This consisted of tumor size, median family income measured in $10,000s, the percentage of the population with less than a high school degree, the percentage with a bachelor's degree or above, survival (measured

in months), and year of diagnosis. Mean scores were focused upon as a measure of central tendency for these measures, as mean and median scores were found to be very similar with the exception of survival time. Mean tumor size is measured in millimeters and relates to a new measure that combined the two initial measures of tumor size after having removed all missing and invalid data. Average tumor size was found to be close to 34 mm. Next, with regard to median family income, this was found to be close to $73,000. The percentage of individuals with less than a high school degree was found to be close to 15%, with the percentage having at least a bachelor's degree found to be close to 31%. Mean survival time was close to 12 months with a median of 7 months.

Table 14

Frequency Distribution of Study Subjects by Continuous Measures

Measure	Valid *N*	Mean	Median	*SD*	Min	Max
Tumor Size (mm)	33202	33.553	36	37.418	0	989
Family Inc. (in $10k)	33201	7.267	6.948	1.700	2.565	12.381
% less than High School	33201	14.885	13.52	6.180	1.390	43.89
% at least BA Degree	33201	30.591	29.61	10.226	45.90	63.94
Survival (Months)	33176	11.824	7	18.361	0	287

Additionally, Table 15 looks at the sociodemographic variables of race, marital status, educational level, age, and median family income by rural and urban regions.

Table 15

Frequency Distribution of Study Subjects by Sociodemographic Characteristics

Variables	Rural (N)	Rural %	Urban (N)	Urban %	Total
Race					
Black	126	7.39%	1580	92.61%	1706
White	3779	12.58%	26270	87.42%	30049
Other	155	11.14%	1236	88.86%	1391
Unknown	2	3.57%	54	96.43%	56
Total	4062	12.2%	29140	87.8%	33202
Marital status					
Single	392	8.76%	4082	91.24%	4474
Married	3286	12.98%	22022	87.02%	25308
Divorced	360	11.49%	2774	88.51%	3134
Separated	24	8.39%	262	91.61%	286
Education level					
Low	–	64.22%	–	69.55%	–
Medium	–	15.88%	–	14.75%	–
High	–	18.97%	–	32.21%	–
Age					
< 50	635	10.41%	5465	89.59%	6100
51-70	2099	12.24%	15056	87.76%	17155
71-80	1018	13.77%	6376	86.23%	7394
> 80	310	12.14%	2243	87.86%	2553
Median family income					
< $50,000	1325	63.04%	777	36.96%	2102
$51,000 - $64,000	1908	17.40%	9060	82.60%	10968
> $65,000	828	4.11%	19303	95.89%	20131

Finally, several new measures were constructed for the purpose of these analyses. With regard to surgical resection, 8,709 (26.23%) patients did not receive resection, while

24,493 (73.77%) did. Regarding radiation, 8,075 (24.80%) patients did not receive radiation therapy, while 24,484 (75.20%) did.

Research Questions and Hypotheses Results

Research Question 1: Results

Research Question 1: When comparing urban and rural patients with GBM, is there a significant difference in GBM tumor size at diagnosis?

$H_0$1: When comparing urban and rural patients with GBM, there is no significant difference in GBM tumor size.

$H_1$1: When comparing urban and rural patients with GBM, there is a significant difference in GBM tumor size.

In order to test the first research question, initially, measures of skewness and kurtosis indicated strong nonnormality with respect to tumor size. However, the very large sample size present in this data set would make nonnormality less important with respect to an independent samples *t* test; for this reason, both a *t* test as well as a Mann-Whitney *U* test was conducted in order to test this research question. In these analyses, tumor size at the time of diagnosis was analyzed as the outcome measure of interest, with regional status included as the dichotomous predictor variable.

First, Table 16 summarizes the descriptive statistics associated with the Mann-Whitney *U* test. As shown, moderate differences were present when comparing the rank sums and expected values. This test itself was found to achieve statistical significance, $z = -2.632$, $p = .0085$. These results indicate that patients residing in rural areas had a

significantly larger mean tumor size as compared with those residing in urban regions. Therefore, the null hypothesis is rejected.

Table 16

Descriptive Statistics of Urban/Rural Areas Using the Mann-Whitney U test

Category	Valid *N*	Ranksum	Expected
Urban	29140	4.794E8	4.809E8
Rural	3864	65212919	63765660
Combined	33004	5.446E8	5.446E8

Next, Table 17 summarizes the descriptive statistics associated with the independent-samples *t* test conducted. Again, these results indicate a higher mean tumor size with regard to individuals residing in non-metropolitan regions. The independent-samples *t* test also achieved significance, $t\ (33002) = -2.3722$, $p = .018$. Therefore, the null hypothesis is rejected.

Table 17

Descriptive Statistics of Urban/Rural Regions Using the Independent-Samples t-test

Category	Valid *N*	Mean	*SD*
Urban	29140	33.391	.215
Rural	3864	34.913	.682
Combined	33004	33.569	.206
Difference		-1.522	.641

Research Question 2: Results

Research Question 2: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced surgical resections?

$H_0$2: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced surgical resections.

$H_1$2: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced surgical resections.

Initially, a new measure was created which consisted of a dummy measure of whether or not respondents had a surgical resection. In the overall sample of 33,202 patients, 24,493 (73.8%) had a surgical resection, while 8,709 did not (26.2%). A chi-square analysis was then conducted to determine if a significant association existed between these two measures. First, Table 18 presents the cross tabulation conducted between these two measures. As shown, no distinct relationship is apparent.

Table 18

Cross Tabulation Results Between Surgical Resection and Regional Status

Region		Resection	
Category	No	Yes	Total
Urban	7617	21523	29140
Rural	1032	2832	3864
Total	8649	24355	33004

Second, the chi-square analysis conducted in relation to this hypothesis also failed to achieve statistical significance, $\chi 2$ (1) = .5707, p = .450. Therefore, the null hypothesis is accepted.

Research Question 3: Results

Research Question 3: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy?

$H_0 3$: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

$H_1 3$: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

For this research question, initially, a new variable was constructed which consisted of a dummy variable measuring whether patients received radiation treatment. This measure was coded 1 for patients that received any kind of radiation therapy including the categories of beam radiation, combination of beam with implants or isotopes, radiation NOS method or source not specified, radioactive implants, and radioisotopes, and was coded 0 in cases of no radiation, and missing if responses to this question were refused. Out of this sample of 32,366 patients, it was found that 24,333 (75.2%) patients received radiation therapy while 8,033 (24.8%) patients did not receive radiation therapy. The use of radiation was slightly more common among patients

residing in urban regions compared to rural areas. The chi-square analysis conducted is found to achieve statistical significance, χ^2 (1) = 18.3962, $p < .001$. Therefore, the null hypothesis is rejected. See Table 19.

Table 19

Frequency Distribution of Study Subjects Comparing Radiation Therapy by Region

Region	Radiation		
Category	No	Yes	Total
Urban	6987 (24.4%)	21596 (75.6%)	28583
Rural	1046 (27.6%)	2737 (72.4%)	3783
Total	8033 (24.8%)	24333 (75.2%)	32366

Research Question 4: Results

Research Question 4: When comparing urban and rural patients with GBM, is there a significant difference in survival rates?

$H_0$4: When comparing urban and rural patients with GBM, there is no significant difference with survival rates.

$H_1$4: When comparing urban and rural patients with GBM, there is a significant difference in survival rates.

Of the overall sample of 33,176 patients, 4,056 (12.2%) rural patients survived 10.3 months while 29,120 (87.8%) urban patients survived 12.04 months as seen in Table 20.

Table 20

Frequency Distribution of Study Subjects by Survival Time in Months

Category	*N*	Mean	SD
Rural	4,056	10.286	16.119
Urban	29,120	12.039	18.642
Total	33,176		

Survival data is commonly depicted with a Kaplan-Meier curve noted in Figure 10. To further explore this fourth research question, a Cox regression was conducted in which region was used to predict survival time. This analysis again incorporated a total of 33,176 cases with the same number of failures and a total time at risk of 392,283 months. Urban region was found to achieve statistical significance, with a hazard ratio of .882 (robust $SE = .015$), $p < .001$, 95% CI = [.853, .913]. Additionally, this regression model was found to achieve statistical significance, Wald $\chi^2 (1) = 52.94$, $p < .001$. Therefore, the null hypothesis is rejected as noted in Figure 9..

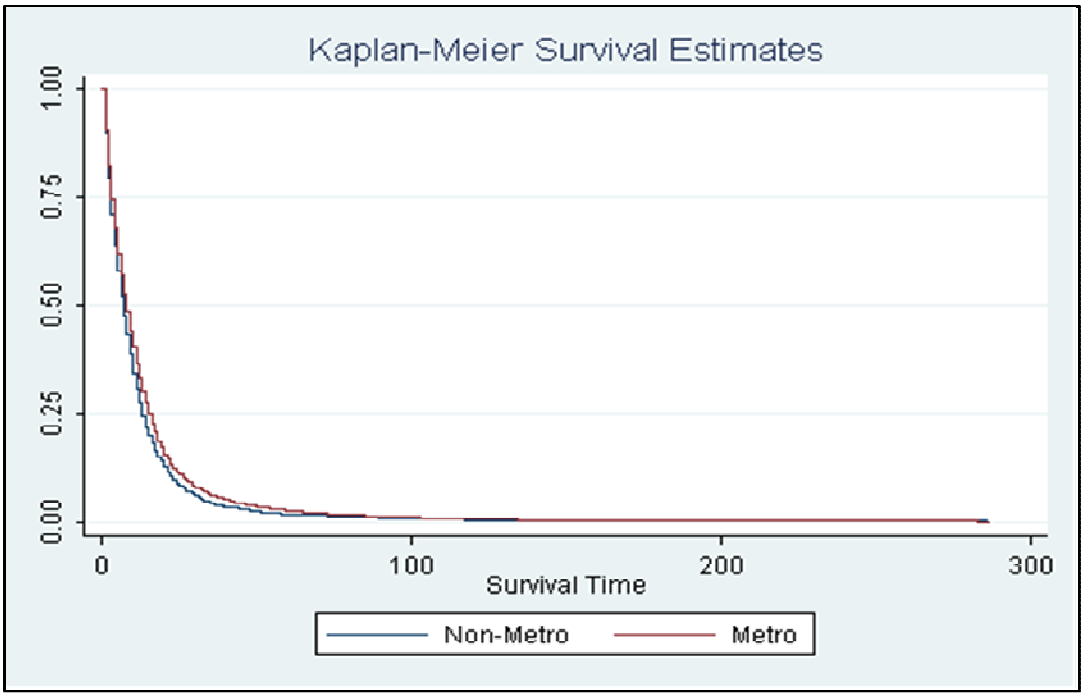

Figure 9. Kaplan-Meier survival estimates for urban (metro) and rural (nonmetro) GBM patients.

Research Question 5: Results

Research Question 5: In the study population of GBM patients, is there a significant difference in survival rates when controlling for region, race, age, sex, educational level, and median family income?

$H_0$5: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is no significant difference in survival rates.

$H_1$5: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is a significant difference in survival rates.

In this analysis, the measures of region, race, age, gender, educational level, and median family income were included as predictors of the number of survival months. Since the data on the total number of survival months were found to be strongly positively skewed, a negative binomial regression was used for this analysis. Specifically, the predictors noted above included a dummy variable representing regional status, dummy variables representing blacks as well as individuals of other race and individuals whose race was unknown, a dummy variable representing females, along with age, the percentage of individuals with less than a high school education, the percentage with at least a bachelor's degree, as well as median family income measured in $10,000s, which were all included as continuous measures.

The results of the analysis found statistical significance with respect to the effects of regional status, age, gender, and median family income. Significantly longer survival time was associated with urban status, female patients, and higher median family income. Additionally, greater age was associated with significantly reduced survival time. This overall regression model was found to achieve statistical significance, with a pseudo R^2 of .0302. Therefore, the null hypothesis is rejected. See Table 21.

Table 21

Negative Binomial Regression Results When Controlling for Region, Race, Age, Gender, Education, and Family Income

Variable	Coefficient	*SE*	*z*	*p*
Urban Region	.058	.020	2.85	0.004
Race: Black	- .050	.026	-1.88	0.060
Race: Other	.043	.029	1.46	0.143
Race: Unknown	.095	.140	0.68	0.500
Age	- .189	.002	-83.65	0.000
Female	.076	.012	6.35	0.000
% Less than High School	.001	.001	1.14	0.254
% At Least BA	- .001	.001	-0.67	0.501
Median Family Income	.035	.007	5.28	0.000
Constant	3.692	.048	76.31	0.000

Note. $N = 33175$; LR $\chi^2(9) = 7005.49$, $p < .0001$; Pseudo $R^2 = 0.0302$; Log likelihood = -112567.38; Likelihood-ratio test of $\alpha = 0$: $\chi^2(1) = 3.1E5$, $p >= \chi^2 < .001$.

Summary and Transition

This study examined if there were differences in tumor size, treatment options, and survival rates between rural and urban residents diagnosed with GBM. With regard to tumor size, the results of this study indicated a significant difference in tumor size at diagnosis between rural and urban GBM cases; that is, rural GBM patients presented with significantly larger tumors at diagnosis. Therefore, the null hypothesis was rejected. Treatment options of patients undergoing surgical resection, radiation therapy, and chemotherapy were explored. There were no significant differences observed in rural and urban GBM patients undergoing surgical resections. Therefore, the null hypothesis was accepted. On the other hand, there were significant differences in urban GBM patients undergoing radiation therapy compared to their rural counterparts. Therefore, the null hypothesis was rejected. It was also noted that the chemotherapy variable could not

be measured as it was removed from the SEER 18 database. The survival rate of GBM patients in rural and urban areas was found to be statistically significant; that is, GBM patients in rural areas have a poorer survival rate than GBM patients in urban areas. Therefore the null hypothesis was rejected. In the final analysis, the survival rate was examined in relationship to region, race, age, gender, educational level, and median family income. Significantly longer survival times were noted with living in urban regions, being female, and higher median family income. Additionally, greater age was associated with significantly reduced survival time. The overall regression model was found to be statistically significant. Thus, the null hypothesis was rejected.

Chapter 4 included the results of this quantitative, retrospective study that examined the differences in tumor size, treatment options, and survival rate in rural and urban patients diagnosed with GBM. Chapter 5 will include a further discussion on the results by providing an interpretation of the observed findings, and how the findings relate to current literature and within the context of the proposed theoretical foundation. In Chapter 5, I will also outline the strengths and limitations of this study, as well as provide recommendations for future research. Finally, in Chapter 5, I will discuss the potential impact for making positive social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

The purpose of this quantitative, retrospective study was to determine if there were differences in tumor size, treatment options, and survival rates between rural and urban residents diagnosed with GBM. Patients who receive a GBM diagnosis barely survive a year beyond the original diagnosis. Studies have not identified any consistent links between possible risk factors and the development of GBM despite the rising incidence of GBM (Bondy et al., 2008; Connelly & Malkin, 2007; Gomes et al., 2011). While there is a plethora of research specific to GBM from environmental and genetic influences, very little research has examined GBM from a regional perspective. This project is unique in that examining patients diagnosed with GBM from an urban-rural perspective has never been done before, highlighting a significant gap in the literature.

Using the SEER 18 database covering the years 1973 to 2011, this study used secondary data sets of GBM cases reported between 1988 and 2011. Tumor size was measured in millimeters, treatment was evaluated by ascertaining the number of GBM patients who experienced surgical resection of their tumors and adjuvant therapies of radiation and chemotherapy, and survival rate was evaluated using Kaplan-Meier curves and Cox Regression analysis. With a sample size of 33,202 cases, data were obtained and examined using descriptive and multivariable analyses of data with SPSS. Using the Mann-Whitney *U* test and the independent samples *t* test, results showed statistically significant differences in tumor size at diagnosis in rural patients compared to urban patients ($p = 0.0085$; $p = 0.018$); that is, rural GBM patients had significantly larger

tumor size at diagnosis compared to urban GBM patients. Furthermore, more urban GBM patients were treated with radiation compared to their rural counterparts ($p < 0.001$). Additionally, rural GBM patients had poorer survival rates than urban GBM patients ($p < 0.001$). Finally, when controlling for region, race, age, gender, educational level, and median family income, a negative binomial regression analysis showed significantly longer survival time was associated with urban status, female patients, and higher median family income (Pseudo $R^2 = 0.0302$; $p < 0.0001$). Moreover, greater age was associated with significantly reduced survival time (Pseudo $R^2 = 0.0302$; $p < 0.0001$).

Interpretation of the Findings

When comparing the results of this study to previous findings identified in the Literature Review found in Chapter 2, the descriptive data appear to confirm prior research. However, as noted previously, this study was unique in that examining patients diagnosed with GBM from an urban-rural perspective has never been done before. Therefore, this study's results provide new knowledge in the GBM arena outlined below.

Descriptive Data

As discussed previously, while primary malignant brain tumors are rare in the United States compared to other types of cancer (American Cancer Society, 2012a), there is an increasing incidence of brain cancer reported for the last 3 decades (Deorah et al., 2006). Figure 9 in Chapter 4 showed an increase in GBM incidence from 1988 to 2011. Furthermore, while Aldape et al. (2003) found that GBMs are 1.6 times more common in men than women, this study found GBMs are 1.7 times more common in men than

women. Additionally, as in the study by Ohgaki and Kleihues (2005), this study confirmed that glioblastomas are significantly higher among Whites as compared to Blacks, American Indians and Alaskan natives, and Asian-Pacific Islanders race groups. As in other peer-reviewed studies, the results of this study confirm that glioblastomas are more common in older adults, and increase with age with primary occurrence in adults from 45 to 70 years old (National Cancer Institute, 2012). Finally, with regard to survival, the median survival time for a newly diagnosed GBM patient is approximately 1 year (Aldape et al., 2003) compared to slightly less than 1 year in this study.

Research Question 1: Tumor Size

In this study, I tested the hypotheses associated with the following research question: When comparing urban and rural patients with GBM, is there a significant difference in GBM tumor size at diagnosis?

$H_0$1: When comparing urban and rural patients with GBM, there is no significant difference in GBM tumor size.

$H_1$1: When comparing urban and rural patients with GBM, there is a significant difference in GBM tumor size.

In order to test this first research question, initially, measures of skewness and kurtosis indicated strong nonnormality with respect to tumor size. However, the very large sample size present in this data set would make nonnormality less important with respect to an independent samples *t* test; for this reason, both a *t* test as well as a Mann-Whitney *U* test were conducted in order to test this research question. In these analyses, tumor size at the time of diagnosis was analyzed as the outcome measure of interest, with

regional status included as the dichotomous predictor variable. Both tests showed statistically significant differences in tumor size in rural GBM patients compared to urban GBM patients (Mann-Whitney, p= 0.0085; independent samples t test, p= 0.018); that is, rural patients presented with larger GBM tumors than urban GBM patients. This resulted in the rejection of the null hypothesis. To date, no other studies have explored GBM tumor size from this urban-rural perspective. Several studies have suggested that rurality is a risk factor in presenting with larger tumor size in other cancers including breast, lung, cervical, and prostate cancers (Obertova, Brown, Holmes, & Lawrenson, 2011; Smaliyte & Kurtinaitis, 2008; Westeel et al., 2007, Zhang, Bu, & Gao, 2013).

Research Question 2: Surgical Resection

This study tested the hypotheses associated with the following research question: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced surgical resections?

$H_0$2: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced surgical resections.

$H_1$2: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced surgical resections.

Initially, a new measure was created which consisted of a dummy measure of whether or not respondents had a surgical resection. In the overall sample of 33,202 patients, 24,493 (73.8%) had a surgical resection, while 8,709 did not (26.2%). A chi-square analysis was then conducted in order to determine whether a significant association existed between these two measures. The chi-square analysis conducted in

relation to this hypothesis failed to achieve statistical significance, $\chi 2$ (1) = .5707, p = .450. Therefore, the null hypothesis was accepted; that is, there is no significant difference in the number of GBM patients who experienced surgical resection. These findings are new and add to the current body of knowledge. Research from the Glioma Outcomes Project demonstrated that patient age, functional status, and complete resection of the tumor were statistically significant prognostic indicators for patient survival (Laws et al., 2003). However, complete surgical resection of the GBM tumor is impossible because of the hyper-vascularity and invasiveness of the tumor. Therefore, near-total resection is done to decrease the tumor size, relieve intracranial pressure, and improve survival (Chandana et al., 2008).

Research Question 3: Treatment Options

This study tested the hypotheses associated with the following research question: When comparing urban and rural patients with GBM, is there a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy?

$H_0 3$: When comparing urban and rural patients with GBM, there is no significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

$H_1 3$: When comparing urban and rural patients with GBM, there is a significant difference in the number of patients who experienced the adjuvant therapies of radiation treatment and chemotherapy.

It should be noted that data for the SEER database are routinely collected on cancer patients who undergo radiation treatments and chemotherapy administration. SEER has a rigorous methodology for ensuring the quality and accuracy of collected data. Over the last decade, SEER database administrators have ascertained that data associated with chemotherapy administration are significantly under-reported. For this reason, chemotherapy data were not included in the SEER database made available to the public. Consequently, for this current study, the chemotherapy variable was not measured.

Continuing with radiation treatments, for this research question, a new variable was constructed that consisted of a dummy variable measuring whether patients received radiation treatment. This measure was coded 1 for patients who received any kind of radiation therapy including the categories of beam radiation, combination of beam with implants or isotopes, radiation NOS method or source not specified, radioactive implants, and radioisotopes, and was coded 0 in cases of no radiation, and missing if responses to this question were refused. Out of this sample of 32,366 patients, it was found that 24,333 patients received radiation therapy (75.2%) while 8,033 (24.8%) patients did not receive radiation therapy. As shown in Table 18, the use of radiation was slightly more common among patients residing in urban regions compared to rural areas. The chi-square analysis conducted was found to achieve statistical significance, $\chi 2\ (1) = 18.3962$, $p < .001$. Therefore, the null hypothesis was rejected; that is, when comparing urban and rural patients, there is a significant difference in the number of GBM patients who experienced the adjuvant therapy of radiation treatments. In other words, more urban

GBM patients undergo radiation therapy compared to their rural counterparts. These findings are new and add to the current body of knowledge. Prior to 2005, the standard of care for newly diagnosed GBM patients was surgical removal of the tumor (surgical resection) followed by radiation therapy (adjuvant radiotherapy). The benefit of chemotherapy had not been well established. However, in 2005, a landmark randomized trial demonstrated the overall survival benefit of adding chemotherapy identified as temozolomide with radiation following maximal surgical resection of the tumor (Stupp et al., 2005). As a result of this landmark study, and given the dismal prognosis associated with GBM diagnosis, multimodal aggressive therapy consisting of surgical resection of the tumor, local radiotherapy, and systemic chemotherapy is done in an attempt to prolong survival time.

Research Question 4: Survival

This study tested the hypotheses associated with the following research question: When comparing urban and rural patients with GBM, is there a significant difference in survival rates?

$H_0$4: When comparing urban and rural patients with GBM, there is no significant difference with survival rates.

$H_1$4: When comparing urban and rural patients with GBM, there is a significant difference in survival rates.

Of the overall sample of 33,176 patients, 4,056 (12.2%) rural patients survived 10.3 months while 29,120 (87.8%) urban patients survived 12.04 months. Survival data are commonly depicted with a Kaplan-Meier curve (refer to Figure 10). To further

explore this fourth research question, a Cox regression was conducted in which region was used to predict survival time. This analysis again incorporated a total of 33,176 cases with the same number of failures and a total time at risk of 392,283 months. Urban region was found to achieve statistical significance, with a hazard ratio of .882 (robust SE = .015), $p < .001$, 95% CI = [.853, .913]. Additionally, this regression model was found to achieve statistical significance, Wald $\chi 2$ (1) = 52.94, $p < .001$. Therefore, the null hypothesis was rejected; that is, GBM patients who live in urban regions survive longer than GBM patients in rural areas. This study is unique in that it is the first to demonstrate a significant relationship between poorer survival for rural GBM patients compared to their urban counterparts. However, the prognosis for patients diagnosed with GBM remains poor despite ongoing therapeutic advancements (Stupp et al., 2005; Yuile et al., 2006; Yabroff et al., 2012). Median survival from initial diagnosis is, at best, approximately 1 year.

Research Question 5: Survival With Controlled Variables

This study tested the hypotheses associated with the following research question: In the study population of GBM patients, is there a significant difference in survival rates when controlling for region, race, age, sex, educational level, and median family income?

$H_0 5$: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is no significant difference in survival rates.

$H_1$5: In the study population of GBM patients, when controlling for region, race, age, sex, educational level, and median family income, there is a significant difference in survival rates.

In this analysis, the measures of region, race, age, gender, educational level, and median family income were included as predictors of the number of survival months. Since the data on the total number of survival months were found to be strongly positively skewed and overly dispersed, a negative binomial regression was used for this analysis. Skewness refers to the asymmetry of the data's distribution. When data are symmetrically distributed, data are not skewed, and the mean, median, and mode are the same. Positively skewed data means that their distribution are asymmetric and the "mean" of the data is pulled towards larger numbers. Since the data in this study are described as strongly positively skewed, the mean is pulled in the direction of extreme scores that are significantly large, and the mean is greater than the median and mode. Overdispersion of data means there is greater variability in a data set than would otherwise be expected; that is, the variance is larger than the mean.

When using negative binomial regression, dummy variables are created (Gerstman, 2008, p. 337). For this study, the predictors noted above included a dummy variable representing regional status, dummy variables representing Blacks as well as individuals of other races and individuals whose race was unknown, a dummy variable representing females, along with age, the percentage of individuals with less than a high school education, the percentage with at least a bachelor's degree as well as median family income measured in $10,000s, which were all included as continuous measures.

The results of the analysis found statistical significance with respect to the effects of regional status, age, gender, and median family income. Significantly longer survival time was associated with urban status, female patients, and higher median family income. Additionally, greater age was associated with significantly reduced survival time. This overall regression model was found to achieve statistical significance, with a pseudo R^2 = 0 .0302. Therefore, the null hypothesis was rejected. Again, this study is unique in that it is the first to show a statistically significant relationship between survival and GBM patients living in urban versus rural regions, gender, family income, and age. There have been studies that have examined significant prognostic factors for survival in primary brain tumors. Results of these studies demonstrated that age is the single most significant prognostic factor for survival in patients diagnosed with primary brain tumors, especially when age is younger than 60 years (Chandana et al., 2008; Mineo et al., 2007).

Theoretical Framework of the Study

The theoretical framework used for this study is based on the behavioral model of health services developed by Andersen (1995). This framework has been applied in access to healthcare, determination of quality, and outcomes (Blustein & Weitzman, 1995; Fryer et al., 1999; Love & Lundquist, 1995; Phillips et al., 2000). Andersen's framework is based on the assertion that late access to cancer diagnostic services for patients experiencing GBM may potentially lead to increased tumor size, decreased treatment options, and decreased survival rates. Concerned with inequalities to medical care access, Andersen initiated studies on the concepts of access in 1968. Andersen's model suggests that people's use of healthcare relies on their general predisposition

concerning health services, issues that enable or block utilization of services, and their inherent need to seek health care. Andersen (1995) noted that the purpose of the initial measures of access was to identify situations that either promote access to health care services, or obstruct access to services. By 1995, Andersen revised the original focus on access to a behavioral approach of health services use, recognizing that the use of health services should maintain and/or improve the health status of the population, both perceived by the population and/or evaluated by health professionals (Andersen, Davidson, & Ganz, 1994).

Placing this study within the context of the theoretical foundation, study results suggest the following: (1) Significant predisposing characteristics are age, gender, and race; (2) Significant enabling resources are geographic regions of urban versus rural locations, location and availability of healthcare resources, and income level; (3) The individual need to access healthcare due to the sudden illness of GBM impacts the actual use of health services. Given the preponderance of these factors suggest that delays in accessing healthcare resources result in larger tumor size, fewer treatment options, and poorer survival rates for rural GBM patients.

Limitations of the Study

First, this study explored a cohort of patients diagnosed with GBM obtained from the SEER 18 database (National Cancer Institute, n.d.). Since this study focused only on the subpopulation of adult patients diagnosed with GBM, there is an inherent sample bias. Second, the potential presence of confounding conditions certainly posed a threat to internal validity of the study. Internal validity is decreased if the observed effect is caused

by uncontrolled conditions. Third, since GBMs are most common in the elderly who have complex health issues, survival could be affected by potential confounding conditions other than the GBM itself. Fourth, the SEER database reports only on cancer information and incidence. It does not address lifestyle factors or causes of cancer. Fifth, since the database covered a 23-year timeframe from 1988 to 2011, the migration of patients lost to follow-up could result in an overestimate or underestimate of study results. With the GBM population, survival is usually 12 to 15 months or less from time of diagnosis. Since SEER does follow all patients until death, and the survival rate for GBM patients is poor, the likelihood of losing patients to follow-up should be minimal. Sixth, while there are numerous definitions of rural and urban areas, this particular study was based exclusively on the SEER definitions of urban (metropolitan) and rural (nonmetropolitan regions) which ultimately affect the generalizability of results. There is no single, universally accepted definition of rural. However, counties are the most commonly used geographic component of rural definitions. The advantages of using "counties" to describe urban from rural areas are that they are simple to understand and their boundaries are very stable over time. Additionally, many national health data sets use counties as a core geographic unit. Finally, the SEER Extent of Disease was used to characterize tumor size, and treatment options of surgery, radiation therapy, and chemotherapy. These definitions need to be considered when comparing to other studies that use other definitions of measurements. Additionally, SEER database administrators ascertained that data associated with chemotherapy administration is significantly under-

reported. For this reason, chemotherapy data was not included in the SEER database made available to the public. Unfortunately, this variable could not be evaluated.

Recommendations

GBM is a lethal brain tumor with a terrible prognosis barely surviving a year beyond the original diagnosis (Holland, 2000). While the results of this study provide new information that certainly adds to the current body of knowledge, additional areas of exploration are warranted. Since the SEER 18 database contain registry data representing 28% of the population in the United States, additional research should focus on other areas of the U.S. to further explore the relationship of urban versus rural residence and associated outcomes. Future studies could also focus on study outcomes categorized by the different types of urban and rural regions utilized for this study. Additional studies could also focus on survival of GBM patients and their proximity to cancer centers and/or large, regional hospital. Finally, knowing the overall median survival of GBM patients of 12 to 15 months from diagnosis, perhaps future research should focus on long-term survivors and the associated factors that differentiate them from the majority.

Implications for Social Change

GBMs are a major public health problem with more than 10,000 new cases reported annually in the U.S. (Clarke, Butowski, & Chang, 2011; Wen & Kesari, 2008). Despite recent advances in the standard of care, GBM prognosis remains grim. Essentially, GBM is an incurable disease that ultimately leads to death within one year from diagnosis. This study can significantly impact social change by identifying geographical variables associated with health outcomes of GBM patients thereby leading

to earlier detection and improved survival rates of individuals and populations. This study also provides valuable information to lawmakers responsible for the creation of healthcare policy and the allocation of healthcare resources.

Conclusion

GBM is a malignant brain neoplasm characterized by its destructive ability to invade healthy brain tissue at an accelerated rate (Holland, 2000). Due to its lethality, patients diagnosed with GBM have a dismal prognosis, barely surviving a year beyond the original diagnosis. For this reason, Holland has referred to GBM as "the terminator" (p. 6242). Since the vast majority of patients with GBM die of their disease within a year, and very few have long-term survival, these particular tumors have drawn significant attention in the research world. There is a plethora of research seeking to identify risk factors, genetic connections, immunological explanations, viral vectors, and novel therapeutic approaches focused on tricking the GBM tumor into submission and thereby improving survival.

This quantitative, retrospective study collected data on all adult GBM patients diagnosed from 1988 to 2011, and the ultimate purpose was to determine if differences in tumor size, treatment options, and survival rate occurred in urban and rural GBM patients in the United States. Results showed statistically significant differences in tumor size at diagnosis and radiation treatments in rural patients compared to urban patients, and rural GBM patients had poorer survival rates than urban GBM patients. Finally, when controlling for region, race, age, gender, educational level, and median family income,

significantly longer survival time was associated with urban status, female patients, younger patients, and higher median family income.

Every research attempt in the GBM field should be with guarded optimism in that we get one step closer to successfully treating this devastating disease. For those patients and families who have faced this terminal condition, the hope is to live long enough until a cure is available. Until that time comes, the research imperative in the GBM arena takes on a sense of urgency.

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Appendix A

Last Name: Nohelty
SEER ID: 11142-Nov2013
Request Type: Internet Access

SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM
Data-Use Agreement for the SEER 1973-2011 Research Data File

It is of utmost importance to protect the identities of cancer patients. Every effort has been made to exclude identifying information on individual patients from the computer files. Certain demographic information - such as sex, race, etc. - has been included for research purposes. All research results must be presented or published in a manner that ensures that no individual can be identified. In addition, there must be no attempt either to identify individuals from any computer file or to link with a computer file containing patient identifiers.

In order for the Surveillance, Epidemiology, and End Results Program to provide access to its Research Data File to you, it is necessary that you agree to the following provisions.

1. I will not use - or permit others to use - the data in any way other than for statistical reporting and analysis for research purposes. I must notify the SEER Program if I discover that there has been any other use of the data.
2. I will not present or publish data in which an individual patient can be identified. I will not publish any information on an individual patient, including any information generated on an individual case by the case listing session of SEER*Stat. In addition, I will avoid publication of statistics for very small groups.
3. I will not attempt either to link - or permit others to link - the data with individually identified records in another database.
4. I will not attempt to learn the identity of any patient whose cancer data is contained in the supplied file(s).
5. If I inadvertently discover the identity of any patient, then (a) I will make no use of this knowledge, (b) I will notify the SEER Program of the incident, and (c) I will inform no one else of the discovered identity.
6. I will not either release - or permit others to release - the data - in full or in part - to any person except with the written approval of the SEER Program. In particular, all members of a research team who have access to the data must sign this data-use agreement.
7. I will use appropriate safeguards to prevent use or disclosure of the information other than as provided for by this data-use agreement. If accessing the data from a centralized location on a time sharing computer system or LAN with SEER*Stat or another statistical package, I will not share my logon name or password with any other individuals. I will also not allow any other individuals to use my computer account after I have logged on with my logon name and password.
8. For all software provided by the SEER Program, I will not copy it, distribute it, reverse engineer it, profit from its sale or use, or incorporate it in any other software system.
9. I will cite the source of information in all publications. The appropriate citation is associated with the data file used. (Please see either Suggested Citations on the SEER*Stat Help menu or the Readme.txt associated with the ASCII text version of the SEER data.)

My signature indicates that I agree to comply with the above stated provisions.

Susan R. Nohelty
Signature

5/27/14
Date

Please print, sign, and date the agreement. Send the form to The SEER Program:

- **By fax to 301-680-9571**
- **Or, e-mail a scanned form to seerfax@imsweb.com**

Last Name: Nohelty | SEER ID: 11142-Nov2013 | Request Type: Internet Access

Appendix B

Permission for Use of Andersen Model

From: Ron Andersen <randerse@ucla.edu>
To: Nohelty, Susan <snohelty@cayugamed.org>
Cc: 'susan.nohelty@waldenu.edu' <susan.nohelty@waldenu.edu>; Susan Nohelty (susan.nohelty@aol.com)
(susan.nohelty@aol.com) <susan.nohelty@aol.com>
Subject: Re: Permission granted!

Date: Wed, Feb 4, 2015 5:01 pm

Dear Susan,
I don't know either but you are more than welcome to cite and use material from the article as far as I am concerned. Just FYI, I am attaching a book chapter that describes the latest version 6 of the model. It is in Koiminski, ed. Changing the US Health Care System, 4th ed. San Francisco: Jossey Bass, 2014. Not relevant to your dissertation or its defense. Everybody has to stop somewhere.

Best wishes for your successful defense and bountiful research career.
Ron Andersen

Curriculum Vitae

Susan R. Nohelty, RN, MSN

Education

- Doctoral Candidate: Public Health/Epidemiology
  Walden University (Minneapolis, Minnesota)

- 2009-2014: Doctoral Dissertation
  Glioblastoma Multiforme: Geographic Variations in Tumor Size, Treatment Options, and Survival Rate

- Masters of Science in Nursing, Critical Care Nursing
  Georgetown University (Washington, DC)
  1993

- Bachelor of Science in Nursing
  Columbia Union College (Takoma Park, Maryland)
  1988

- Associate Degree in Nursing
  Montgomery College (Takoma Park, Maryland
  982

Career History

Cayuga Medical Center (Ithaca, New York)
April 2007 – Present
Vice President of Patient Services

Lock Haven Hospital (Lock Haven, Pennsylvania)
July 2005 – November 2006
Chief Nursing Officer

Northwest Hospital (Randallstown, Maryland)
April 2003 – July 2005
Director of Nursing/Perioperative Services

Kaiser Permanente (Silver Spring, Maryland)
November 2001 – April 2003
Medical Center Administrator (CEO)

Kaiser Permanente (Kensington, Maryland)

October 2000 - November 2001
Clinic Coordinator (Director)

Suburban Hospital (Bethesda, Maryland)
August 1998 - April 2003
Nurse Administrator

Inova Fair Oaks Hospital (Fairfax, Virginia)
April 1997 - July 1998
Director/Medical-Surgical-Orthopedics

Medstar – Georgetown University Health System
May 1990 - April 1997
Georgetown University Hospital (Washington, DC)
April 1996 - April 1997
Clinical Educator/ Perioperative Services

Georgetown University Medical Center (Washington, DC)
April 1994 – April 1996
Clinical Administrator

Georgetown University Hospital (Washington, DC)
May 1990 - April 1994
Staff Nurse

Suburban Hospital
March 1988 - April 1990
Patient Care Manager, CCU/ICU

Shady Grove Adventist Hospital (Gaithersburg, Maryland)
March 1986 - March 1988
Head Nurse, Coronary Care Unit

Prince Georges General Hospital (Largo, Maryland)
July 1985 - March 1986
Assistant Head Nurse, CCU

Suburban Hospital (Bethesda, Maryland)
June 1982 - July 1985
Staff Nurse

Concurrent Employment

Sibley Memorial Hospital (Washington, DC)
April 2001 – April 2003
Patient Care Coordinator

Georgetown University Medical Center (Washington, DC)
April 1997 – April 2003
Clinical Administrator

Georgetown University (Washington, DC)
August 1994 - June 1996
Clinical Instructor, School Of Nursing

- Hospital-Based Clinical Instructor for Medical-Surgical Nursing, Junior and Senior Levels.
- Participated In Course Planning, Curriculum Development And Review.
- Curriculum Development And Course Coordinator For Perioperative Clinical
- Elective For Senior Nursing Students.

Marymount University (Arlington, Virginia)
August 1993 - August 1994
Clinical Instructor, School of Nursing

- Hospital-based clinical instructor for fundamental and medical-surgical nursing students.
- Instruction in mathematical concepts for drug calculations.
- Participation in course planning, curriculum development and review.
- Advisor for 20 nursing students in various phases of the nursing curriculum.