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The Hidden Morbidity of Cancer:
An Exploratory Study of Burden in Caregivers of Cancer Patients with Brain Metastases

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Nursing

by

Marlon Garzo Saria

2016

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ABSTRACT OF THE DISSERTATION

The Hidden Morbidity of Cancer:
An Exploratory Study of Burden in Caregivers of Cancer Patients
with Brain Metastases

by

Marlon Garzo Saria
Doctor of Philosophy in Nursing
University of California, Los Angeles, 2016
Professor Sally Louise Maliski, Chair

Caregiving is a highly individualized experience. While numerous papers have been published on caregiver burden in the context of a variety of diagnoses and conditions, this paper presents the unique features of caregiving in cancer patients with brain metastases. Improved long-term survival of patients, concerns about disease recurrence or progression, the mileposts of the cancer experience (initial diagnosis, treatment, survivorship, recurrence, progression, and end of life), and the increasing complexity of cancer treatments add to the demands placed upon the caregiver of patients with brain metastases.

The aim of this dissertation was to explore the antecedents and outcomes of caregiver burden within the context of brain metastases using the Comprehensive Health Seeking and Coping Paradigm as a framework to describe the highly interactive

relationship among the variables. The first paper derived from this dissertation is a literature review that describes the challenges of caring for a patient with brain metastases and highlights the implications for healthcare professionals. The second paper presents the analysis of the relationships between caregiver burden and the affective disorders anxiety and depression. It describes the higher risk of screening positive for anxiety and depression for caregivers who report increased schedule burden. The third paper examines the impact of the patient's cognitive impairment on caregiver resilience and caregiver coping strategies. This paper reports the significant correlation found between the coping strategy acceptance and the two dimensions of the patient's cognitive/behavioral status, i.e., patient's memory problems and disruptive behavior.

Caregivers of patients with brain metastases are the hidden morbidity of cancer. While the healthcare industry has consistently recognized the contributions of caregivers, we have fallen behind in identifying and managing their needs. Healthcare providers need to continue to be perceptive of caregiver burden and be ready to administer the appropriate interventions that must be as unique and individualized as their experiences.

The dissertation of Marlon Garzo Saria is approved.

Adeline M. Nyamathi

Linda R. Phillips

Annette Louise Stanton

Sally Louise Maliski, Committee Chair

University of California, Los Angeles

2016

DEDICATION

This dissertation is gratefully dedicated

To my parents, Mario Santiago Saria and Marlyn Garzo Saria
for encouraging me to explore the world, discover my passion,
and overcome my fear of making mistakes,
for showing me that integrity and kindness are important virtues, and
for making me realize that I need to live for something bigger than myself;

To my mentor, Dr. Santosh Kesari
who believed in me (and convinced other people to believe in me),
whose fingerprint is all over this dissertation,
who kept me employed while I was finishing this dissertation; and
who has the brilliance, conviction, and determination to find the cure for cancer

To my late grandparents, Apolinar delaRea Saria, Aurora Santiago Saria,
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for being my homing beacon, always guiding me back to what is really important.

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ACKNOWLEDGEMENTS

And whatever you do, whether in word or deed, do it all in the name of the Lord Jesus, giving thanks to God the Father through him (Colossians 3:17).

If you are grateful, I will give you more (Ibrahim, 14:7).

He that gives should never remember,
he that receives should never forget (The Talmud).

Your work is to discover your work and then, with all your heart,
to give yourself to it (Buddha).

Put your heart, mind, and soul into even your smallest acts.
This is the secret of success (Swami Sivananda).

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My heartfelt thanks to all!

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CHAPTER I: INTRODUCTION

Brain metastases are diagnosed in 10% to 40% of all cancer patients and the incidence continues to rise due to the increasing number of long-term survivors (Lorger & Felding-Habermann, 2010). Brain metastases are the most common intracranial tumors, and reportedly, the annual incidence of brain metastases is more than ten times greater than that of primary brain tumors, which totals more than 170,000 cases in the United States (U.S.) every year (Al-Shamy & Sawaya, 2009; Santarelli, Sarkissian, Hou, Veeravagu, & Tse, 2007). While the consequences of brain metastases on the patients' quality of life (QOL) have been well documented (Levy & Cashman, 2007), less is known about the consequences for caregivers caring for patients who have been diagnosed with this disabling condition. Often, the needs of caregivers, those who provide care for another individual, are neglected in a patient-centered care environment. Therefore, this study will focus on the needs of the caregivers of cancer patients with brain metastases.

Family caregivers provide long-term care and are often the primary source of physical, social, and emotional support for patients. Depending on the responsibility assigned, caregivers have been classified as primary caregivers if they are mainly responsible for providing and/or assisting with the care recipients' activities of daily living or secondary caregivers if they assist in caregiving or provide support to a care recipient but are not primarily responsible for the day-to-day care or decisions regarding that care. It is important to note that secondary caregivers are critical to the network of support for primary caregivers (Ryba, 2012). Caregivers of patients with brain metastases represent a unique and increasing population of cancer caregivers. They

provide care to patients with a diagnosis that often heralds the start of the terminal phase of an advanced disease that can be manifested by worsening functional, cognitive, and neuropsychological impairment. Empirical research building from early anecdotal reports and clinical observations of the effects of caregiving in the general population has shown an association between caregiving and negative health outcomes for the caregiver (e.g. cellular and immunologic changes, physical symptoms, neuro-cognitive/psychological symptoms and even death) (Rohleder, Marin, Ma, & Miller, 2009; Schulz & Sherwood, 2008). In the past three decades, studies have documented negative caregiver outcomes in the context of the stress response that arise from the introduction of new care demands or escalation of existing demands (Sherwood et al., 2004; Sherwood, Given, Given, & von Eye, 2005). Caregiver outcomes have been examined within the context of providing care to individuals with increasing physical disabilities as seen in cancer and/or deteriorating cognitive function (e.g., dementia) (Sherwood et al., 2004). Caregivers of patients with brain metastases not only acquire new care demands in addition to increasing intensity of existing demands, but also deal with both physical and cognitive deterioration of these patients. Unfortunately, despite decades of research showing the negative emotional and physical responses that result from the caregiving role in the context of chronic illnesses (e.g. cancer and dementia), little has been done in the field of neuro-oncology (Sherwood & Baer, 2011).

What makes the experience of caregivers of patients with brain metastasis unique is that caregivers are forced to deal not only with the emotional sequelae of a metastatic cancer diagnosis but also with the physical and cognitive consequences that accompany the brain metastasis (Khalili, 2007). Sherwood and colleagues (2005)

described the relationship between the burden experienced by the caregiver and the cognitive dysfunction exhibited by the patient as being worsened by “the unpredictable and multidimensional nature of the care demands along with the loss of personhood by someone intimate to the caregiver” (p.129). The relationship between the patients’ cognitive function and caregiver burden, often defined as a negative appraisal and perceived stress resulting from caring for an individual, warrants further investigation because literature in this area is scant. In addition, the dynamic and multidimensional nature of caregiver burden requires the analysis of variables that may affect the caregivers’ appraisal of the burden brought about by the patients’ cognitive dysfunction. These variables include social support, an external resource available to caregivers, resilience, an inherent personality characteristic that can be developed throughout the caregiving trajectory, and coping, the caregivers’ response to burden.

To my knowledge, no individual study has investigated the combination of cognitive dysfunction, social support, resilience, cognitive appraisal, coping behavior, caregiver burden, anxiety, and depression as it relates to caregivers of patients with brain metastasis; however, several studies have investigated these variables separately within this context.

The Context: Cancer Patients with Brain Metastases

Brain metastases are associated with a myriad of symptoms, including but not limited to neurological dysfunction and functional decline; both of which are very difficult to manage (Lorger & Felding-Habermann, 2010) and distressing for caregivers.

Consequently, these symptoms contribute to increased morbidity and mortality, as well as to diminished QOL (Levy & Cashman, 2007) of patients and their caregivers.

The symptoms of brain metastases are similar to those of primary brain tumors and are related to the tumor location within the brain (American Brain Tumor Association, 2010). The functional geography of the brain often indicates the deficits that can be expected with a growing mass, e.g., left temporal lobe tumors can cause a disturbance of auditory sensation and perception, disturbance of selective attention of auditory and visual input, disorders of visual perception, impaired organization and categorization of verbal stimuli, disturbance of language comprehension, impaired long-term memory, altered personality and affective behavior, and altered sexual behavior (Klein, Engelberts, et al., 2003). In addition, physical symptoms, such as headaches and seizures, two of the most common symptoms regardless of tumor location, can significantly reduce the patient's QOL (American Brain Tumor Association, 2010). These consequences of brain metastases are thought to have an effect that extends beyond that of the patient with cancer, affecting the person providing the care- the caregiver.

Caregiver Burden among Caregivers of Patients with Brain Metastases

Caring for another person during an episode of acute or chronic illness has existed within the family structure for centuries, although formal research did not begin until the 1960's (Hoffmann & Mitchell, 1998). Since then, the majority of conditions for which caregiving issues have been explored are illnesses with deteriorating courses. A caregiver is an unpaid individual who provides direct care to relatives or friends who are

unable to provide for themselves while burden is an “oppressive or worrisome load” (Hunt, 2003, p. 28). Therefore, caregiver burden, has been defined as the worrisome load borne by people providing care for another individual (Hunt, 2003). The concept has also been defined as the physical, psychological or emotional, social, and financial problems experienced by caregivers resulting from changes in cognition and behavior of the patient and the patient’s subsequent need for care and supervision (Braithwaite, 1992). In addition to the multidimensional nature of caregiver burden, it has also been described as dynamic in that it responds to fluctuations in demands and the contextual variations during the caregiving experience (Chou, 2000; Perlick, Clarkin, & Sirey, 1995). Therefore, for the current study, caregiver burden will be defined as the cognitive appraisal of the multidimensional response to demands and their consequences within the context of an evolving caregiving experience (Hoffmann & Mitchell, 1998; Pereyra et al., 2010).

Cognitive Dysfunction in Cancer Patients with Brain Metastases

Cognitive dysfunction has been identified as an independent variable that can negatively affect caregiver burden (Sherwood et al., 2004). In patients with brain metastases, cognitive dysfunction ranges from subtle changes in cognitive domains to severe deficits that may impair their ability to speak, remember, or act appropriately (Farace & Melikyan, 2008). While cognition and behavior are expected to decline at some point during the cancer trajectory, the pattern of decline for patients with brain metastases has been described as variable and unpredictable, owing to the complex nature of the predisposing factors that can affect a person’s abilities. The type of

cognitive dysfunction depends on tumor size, location, and type, and can be further complicated by surgery, chemotherapy, radiation therapy and individual patient characteristics (Lee, 2010).

It has long been acknowledged that cognitive impairment is a sequela of primary or metastatic brain tumors and can be induced by cancer treatment, specifically chemotherapeutic regimens. Cognitive impairment is one of the symptoms found prior to initiation of treatment in a significant percentage of patients with various types of cancer (i.e. hematologic and neurologic cancers) and is aggravated by aggressive treatment (Meyers, Albitar, & Estey, 2005). Mounting research has begun to shed light on cognitive impairment in terms of epidemiology, patient-specific outcomes, and underlying mechanisms (Miller, Ancoli-Israel, Bower, Capuron, & Irwin, 2008) but few studies have considered its effects on the patient's entire family and social network. There is a paucity of studies that evaluate the long-term effects of functional and cognitive rehabilitation programs in patients with brain tumors (Salander, 2010) let alone those with metastatic disease, and even fewer studies that include caregiver outcomes.

Resilience of Caregivers

Another personal resource that has been associated with caregiver outcomes is resilience (Hooker, Frazier, & Monahan, 1994). Resilience has been defined as a psychological phenomenon that may result within any person from the operation of basic human adaptive processes (Wilks & Croom, 2008). A more modern conceptualization of resilience refers to effective adaptation and coping: an adaptational success that suggests overcoming the odds, adapting to adversity, and recovery (Wilks,

2008). It is linked with an individual's capacity to have hope and to find comfort and encouragement amid distress. Despite the focus on resilience in caregivers of neurocognitively-impaired individuals (Foster, 2010; Harmell, Chattillion, Roepke, & Mausbach, 2011; O'Rourke et al., 2010; Wilks, 2008; Wilks & Croom, 2008; Wilks, Little, Gough, & Spurlock, 2011; Zauszniewski, Bekhet, & Suresky, 2010), an extensive literature search on resilience in caregivers of patients with cancer yielded few studies.

Resilience may affect the variability in caregiver burden, decreasing the likelihood of experiencing distress from caring for a cognitively-impaired individual or increasing the benefits derived from social support. While exposure to severe forms of physical and emotional burden has been linked to the development of psychological distress (Anda et al., 2006; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Repetti, Taylor, & Seeman, 2002; Turner & Lloyd, 2003), a far less researched, but equally important contention is that caregiver burden may not result in vulnerability but instead enhanced resilience (Harmell et al., 2011).

Social Support for Caregivers

While cognitive dysfunction can increase caregiver burden, social support is theoretically believed to have the potential to account for variability in perceived caregiver burden. Social support is comprised of emotional and instrumental support and has been defined as "an advocative interpersonal process that involves the reciprocal exchange of information, is context specific, and results in improved mental health" (Finfgeld-Connett, 2005, p. 8). Social support is a personal resource of the caregiver and has been related to less burden and higher life satisfaction in caregivers

who report more informal support when compared to those who have received less informal support (Chappell & Dujela, 2008). Social support reduces the psychological burden of caregiving in patients with Alzheimer's disease (Colerick & George, 1986; Drentea, Clay, Roth, & Mittelman, 2006; Haley, Levine, Brown, & Bartolucci, 1987; Morycz, 1985; Stewart et al., 2006; Vitaliano, Maturo, Ochs, & Russo, 1989; Zarit, Reever, & Bach-Peterson, 1980), a diagnosis that shares some of the cognitive features seen in patients with brain metastasis. Literature on cancer and other chronic conditions have established the benefits of social support on caregiver outcomes, including a link between the nature and degree of social support received and the individuals' health conditions and emotional states (Cohen & Syme, 1985). Despite the lack of consistency in the measurement of social support, this variable is often operationalized as the level of satisfaction an individual has with their sources of support and the quality of support rather than the amount of support they receive (Sarason, Levine, Basham, & Sarason, 1983).

While positive social support has been found to alleviate caregiver burden, adverse social contacts have been associated with increased burden (Chappell & Dujela, 2008). Among caregivers of patients with dementia, lower levels of negative social interactions have been associated with better caregiver adjustment (Haley, LaMonde, Han, Burton, & Schonwetter, 2003). In addition, O'Rourke and Tuokko (2000) found that the perception of satisfaction with social support is more important than the amount of social support. A variety of social support attributes (e.g., emotional support, instrumental support, informational support, and appraisal support) and antecedents (e.g. social network, social embeddedness, and social climate) have been investigated

as potential protective factors and have been observed to significantly moderate the effects of caregiver burden (Murray, 2000; Wilks & Croom, 2008).

Theoretically, supportive social interactions can buffer the negative impact of burden from caring for a cognitively-impaired individual. To date, however, few studies have investigated the impact of the patients' cognitive impairment and the caregivers' satisfaction with social support in patients with cancer. Furthermore, the variables have not been studied relative to the caregivers' personal characteristic (i.e. resilience).

Cognitive Appraisal among Caregivers

Cognitive appraisal is one of the proposed predictors of an individual's response to highly stressful situations (Harvey, Nathens, Bandiera, & Leblanc, 2010). The cognitive appraisal process is initiated by a situation that threatens an important goal. An individual subjectively evaluates the demands of the environment (primary appraisal) and subsequently analyzes the available resources that can be applied to a particular situation. For caregivers of patients with brain metastases, their appraisal of the difficult challenges of caregiving has implications to their emotional response, coping capacity, and, consequently, their adaptation to stressful events.

Coping: Managing Caregiver Burden

Coping is a broad concept that pertains to an individual's efforts to manage stressful demands regardless of outcome. While coping is most commonly operationalized as an adaptive or successful method of managing stressful situations, it is important to recognize coping strategies that are otherwise maladaptive and

ineffective also exist. Lazarus and Folkman (1984) defined coping as *"constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (p.141).*

Coping strategies used by caregivers are important variables to consider within the context of this study. The coping strategies employed by caregivers ultimately determine the impact of perceived caregiver burden on immediate and long-term caregiver health outcomes and can eventually affect the caregiver's relationship with the patient as well as patient outcomes. Coping can be considered effective to the extent that caregiver burden is reduced.

Anxiety and Depression among Caregivers

Anxiety and depression have been studied in caregivers of patients with cancer. However, few studies focused on a subset of caregivers of patients with brain metastases. Caregivers of patients with advanced cancer have been reported to experience emotional stress, depression and increased anxiety related to their caregiving activities (Mystakidou et al., 2012). Caregivers of patients with brain tumors have also been reported to live with higher levels of anxiety and depression symptoms when compared with the general population (Finocchiaro et al., 2012). It has been suggested that affective symptoms of caregivers of patients with cancer vary along the illness continuum and could be affected by factors related to the patient's deteriorating condition (Song et al., 2011). Therefore, it can be expected that anxiety and depression

among caregivers of patients with brain metastases would be different from those caring for early stage disease or those with different pathologies.

Goals and Specific Aims

The goal of this study is to explore caregiver burden and the coping behavior of caregivers of patients with brain metastasis. It has been documented that non-professional caregivers and long-term care providers to patients with cancer receive little preparation, information, or support to perform their vital role (Northouse, Katapodi, Song, Zhang, & Mood, 2010). Through this study, we will identify the relationship between the patient's cognitive dysfunction as perceived by the caregiver, and caregiver's resilience, social support, cognitive appraisal, coping behavior, burden, anxiety, and depression within the context of brain metastases. The findings of this study will direct future intervention studies to reduce caregiver burden and improve outcomes for the many individuals caring for family members with brain metastases.

Specific aims

The specific aims of this descriptive, exploratory study are as follows.

1. Evaluate caregiver burden among caregivers of patients with brain metastases
    a. Explore the relationship between the patients' cognitive dysfunction and perceived burden of caregivers of patients with brain metastases;
    b. Describe the relationship between resilience and caregivers' perceived burden;

c. Describe the relationship between social support and caregivers' perceived burden;
d. Describe the relationship between coping behavior and perceived burden of caregivers.

2. Identify the associations of caregivers' demographic characteristics, patients' cognitive function, and caregiver resilience, social support, cognitive appraisal, and coping behavior as it relates to caregiver perceived burden.
3. Identify predictors of increased anxiety and depression in caregivers of patients with brain metastases.

Significance of the Study

The number of people of all ages in the U.S. who have cancer is projected to grow from 11.8 million in 2005 to 18.2 million in 2020, a 55% increase (Warren, Mariotto, Meekins, Topor, & Brown, 2008). This number consequently expands the population at risk for developing brain metastasis, currently with a reported annual incidence estimated between 98,000 and 170,000 (Hutter, Schwetye, Bierhals, & McKinstry, 2003; Levin, Leibel, & Gutin, 2001; National Cancer Institute, 2010). More than 80% of the care provided to the patients during the initial (first year) and all treatment phases, and close to 60% during the last year of life (Warren et al., 2008), falls upon families. Studies have shown the negative emotional (e.g., depression and anxiety) and physical (e.g., altered immune function, hypertension, poor overall physical health) consequences of providing care (Sherwood et al., 2008). Additionally, studies

have documented a reduction in caregiver QOL with increased responsibilities (Munoz et al., 2008).

While there is a wealth of literature on a variety of predictors of caregiver burden in cancer, more information is needed on the contributions of the demands of caregiving (care recipients' cognitive deterioration) and protective factors (social support as a surrogate for external resources and resilience as a surrogate for internal resources) on caregiver burden. Moreover, there is an even greater paucity of research that explores the effects of cognitive appraisal and coping behavior on perceived burden, anxiety and depression.

In contrast to published studies on caregiver burden in different patient populations, this study will focus on the caregiver's appraisal of the multiple predictors of caregiver burden including the patients' cognitive function. Assessment of patients' cognitive functioning can help determine the differential contributions of the neurocognitive effects of brain metastasis on caregiver burden (Farace, 2008). In a study of patients with high-grade gliomas, alterations in cognitive function was shown to reflect the severity of the underlying disease, which was not always apparent in measurements of functional or performance status such as the Karnofsky or Barthel scores (Klein, Postma, et al., 2003). In patients with primary brain tumors, cognitive dysfunction has been identified as a leading cause of disability and the single greatest cause of patient distress (Locke et al., 2008) that potentially contributes to increased caregiver burden.

The role of the caregiver can be overwhelming and is often a physically challenging and emotionally exhausting experience (Northfield & Nebauer, 2010). It is

therefore important that caregivers be supported to meet the escalating demands of the caregiving experience with as little impact on their emotional and physical well-being as possible.

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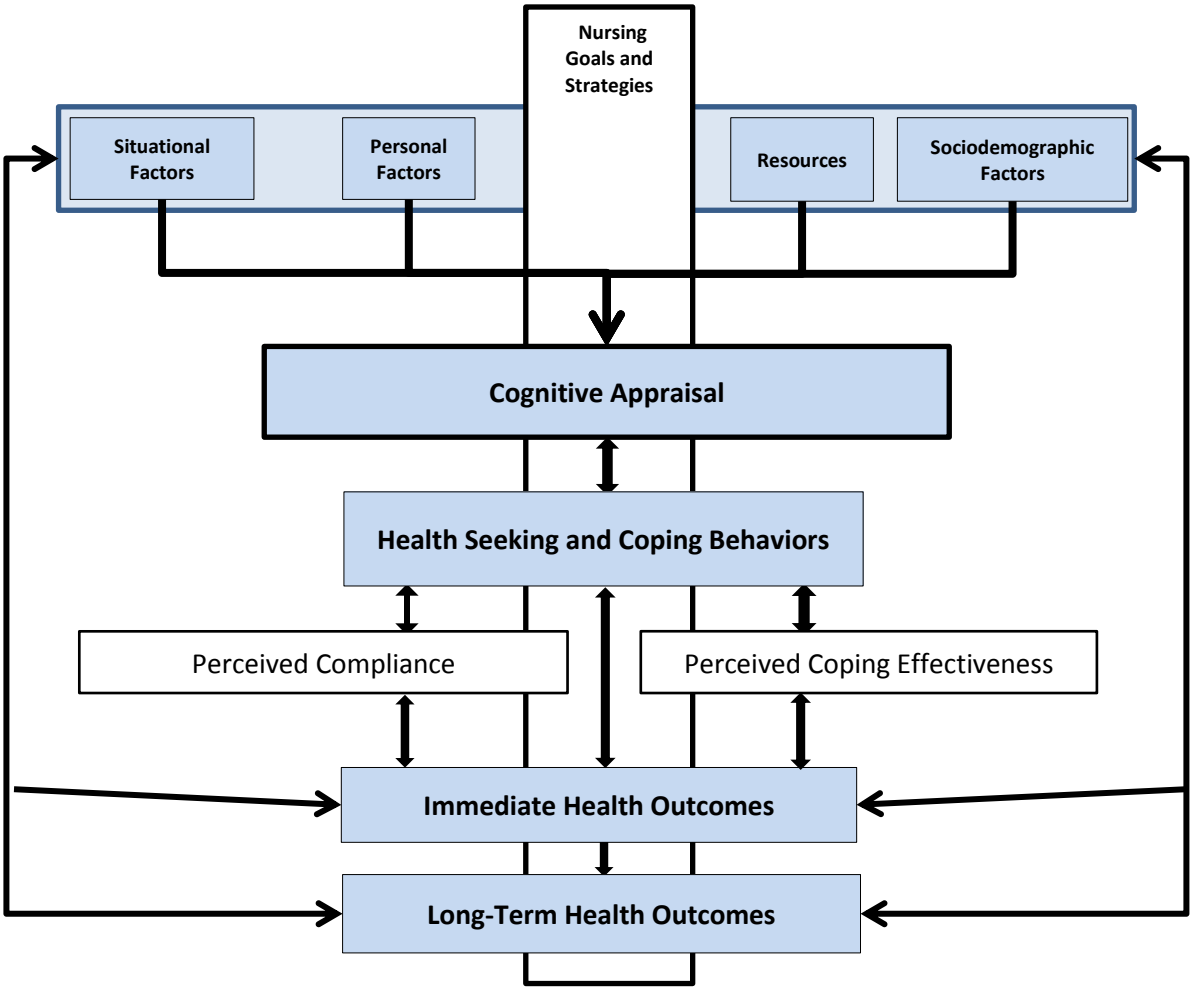
CHAPTER II: CONCEPTUAL FRAMEWORK

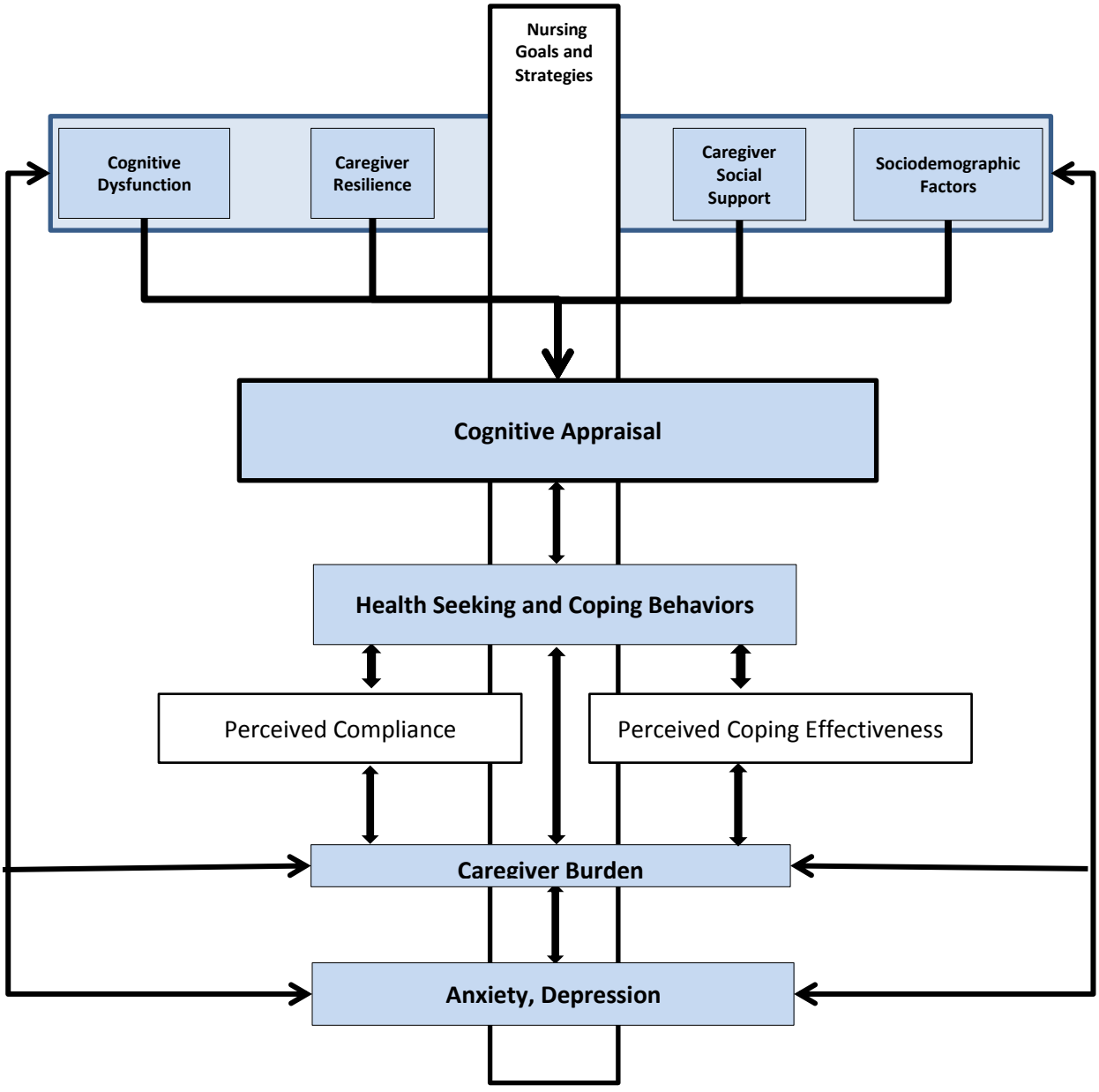
Caregiving research has become a fluorishing enterprise that is driven by several disciplinary perspectives and theoretical orientations (Pearlin, Mullan, Semple, & Skaff, 1990). There are, however, overlapping variables of interest and one that is arguably the most common approach to caregiver research is from the perspective of the stress process. Pearlin, et al. (1990) acknowledged that "*there is more than one way to think about the issues we address and more than one way to measure constructs*" and that theoretical models "*should be regarded as an heuristic device rather than as a literal reflection of realities and pathways that join them, many of which are still unclear*" (p.591). With that being said, while the Lazarus Schema of Coping and Adaptation (Lazarus & Folkman, 1984) and the Caregiver Stress Process Model (Pearlin et al., 1990) have been consistently adapted as the theoretical model for caregiving research, the Comprehensive Health Seeking and Coping Paradigm (CHSCP) (Nyamathi, 1989) (Figure 2-1) was adapted for this study to emphasize the perspective from the discipline of nursing and guide future intervention studies that can be applied in all the variables included in the study.

Figure 2-1. Comprehensive Health Seeking and Coping Paradigm



The CHSCP is built upon a number of antecedent, mediating, and dependent variables and has been applied in intervention research designed to reduce the risks associated with drug and alcohol use, tuberculosis, hepatitis, homelessness and HIV among vulnerable populations (Berg, Nyamathi, Christiani, Morisky, & Leake, 2005; Nyamathi, Berg, Jones, & Leake, 2005; Nyamathi, Branson, et al., 2012; Nyamathi, Hanson, et al., 2012; Nyamathi, Marlow, Branson, Marfisee, & Nandy, 2012; Nyamathi, Sinha, Greengold, Cohen, & Marfisee, 2010; Washington, Moxley, & Taylor, 2009). For this study, the following factors will be examined either directly or through proxy variables: situational (patient's cognitive dysfunction), personal (caregiver resilience), resources (caregiver social support), sociodemographic (gender, age, kinship, ethnicity, religious affiliation, educational level, marital status, number and location of children, employment status, family income, comprehensive health insurance, and financial strain), cognitive appraisal, and coping behaviors in relation to immediate (caregiver burden) and long-term (anxiety and depression) health outcomes (Figure 2-2).

Figure 2-2. Conceptual Framework



The CHSCP provides for the development of appropriate interventions that can modify the complex network of variables that influence the health-seeking and coping behaviors of caregivers to assist them to better deal with burden. It provides a theoretical basis for the proposed study that examines how social support and resilience mediates the effects of cognitive dysfunction in patients with brain metastasis on caregiver burden.

Nyamathi (1989) constructed the CHSCP to reflect an integration of the Lazarus Theoretical Schema of Coping and Adaptation (Lazarus & Folkman, 1984) and the Schlotfeldt Paradigm of Health Seeking Behaviors (Schlotfeldt, 1981) to accurately reflect the perspective of the discipline of nursing in overcoming threats to optimal health and functioning (Al-Shamy & Sawaya, 2009; Nyamathi, 1989). Stress and coping models in caregiver research can guide our understanding of the individual response to specific external or internal demands that are appraised as exceeding the resources of the person (Nyamathi, 1989). Health--seeking behavior models serve as catalogues of relevant variables and allow for the appraisal of the relative impact of different factors in health behavior. The goal is to determine areas of concern in order to intervene with specific health system strategies (Hausmann-Muela, Ribera, & Nyamongo, 2003).

The CHSCP is based on the premises that (1) all individuals variably utilize the process of health-seeking and coping; (2) the relationship between the individual and the environment influences health-seeking and coping; (3) health-seeking and coping involves problem- and emotion-focused behaviors; (4) guided-learning enhances innate individual capabilities; (5) nurses impact the complex network of variables that influence health seeking, coping behaviors and health outcomes; and (6) nursing aims to restore

individuals to optimal health and function (Nyamathi, 1989). The CHSCP is a complex, multi-dimensional framework that depicts a highly interactive relationship among its 12 components: situational factors, personal factors, resources, sociodemographic factors, cognitive appraisal, health goals of the client, health seeking and coping behavior, nursing goals and strategies, perceived coping effectiveness, perceived compliance, immediate health outcome and long-term health outcome (Berg et al., 2005; Nyamathi, 1989; Nyamathi, Stein, & Bayley, 2000; Nyamathi et al., 2010; Washington et al., 2009).

Nyamathi (1989) defined **situational factors** as variables that characterize the individual's environment which include constraints, duration of the stressor, past experience with the illness, and the timing of the event. It is important to indicate that this critical component of nursing assessment influences all other components of the model, and thus strenghtens the contribution of the discipline of nursing in advancing the science on caregiver burden. In a study examining the predictors of mental distress and poor physical health among homeless women, situation factors was defined as negative environmental exposures and included both the parent and the client abuse history (Nyamathi et al., 2000). In this caregiver study, situational factors include the care recipients' physical condition and **cognitive function** as factors that may increase caregiver burden and influence coping behaviors. These variables directly affect the caregivers' appraisal of the severity of the patient's condition (cognitive appraisal) which can significantly influence their health-seeking and coping behaviors. The length of time that patients may be physically or cognitively-impaired can also be associated with coping behaviors. Much of what is known about caregiving is framed within the context of providing care to patients who experience deficits in physical function, impaired

cognition, or both (Given et al., 2006). In patients with chronic disease, these deficits increase over time as the condition deteriorates during the course of illness. In a patient population that has been extensively studied for the effects of functional and cognitive decline on caregiver burden, functional decline and dependence were most predictive of caregiver burden in the early stages of Alzheimer's disease, while impairments in cognitive function were more burdensome in patients with moderate-to-severe disease. It is therefore more critical to manage impaired cognitive functioning as disease progresses (Gallagher et al., 2011).

Personal factors is a comprehensive term that encompasses individual characteristics that can affect coping behavior. Nyamathi (1989) includes mood and personality (e.g., anxiety, depression, and fear), perceived seriousness of event, stimulus ambiguity, perceived self-esteem, perceived self-control, and hardiness as the elements of this component. Washington, et al., (2009) described personal factors to include perceived needs related to health conditions, e.g., individual's beliefs, values, and commitments, that affect well-being on a cognitive, emotional, and physical level. In another study that utilized the theoretical constructs of the CHSCP, Nyamathi, et al. (2010) defined the construct in terms of inner strength (Nyamathi et al., 2010).

Resilience has been defined as adapational success that suggests overcoming the odds and recovering from adversity (Wilks & Croom, 2008). It is considered as a psychological resource that has been shown to account for variances in caregiver outcomes by moderating the negative effects of stress (i.e. burden) and promoting adaptation (i.e. coping)(Ahern, Kiehl, Sole, & Byers, 2006). Therefore, in a given

population that is vulnerable to consistent adversity, there is considerable merit in including resilience as a variable (Wilks, 2008).

The major variables that Nyamathi (1989) considered as **resources** are physical and mental health, financial and spiritual security, and social support. **Social support** is considered as a protective factor that increases resistance to the negative effects of stressful situations; in this case, perceived burden from caregiving. It is generally assumed that social support has a favorable impact on health maintenance and coping (Schwarzer & Leppin, 1991). Similar to the CHSCP, another conceptual model, the Stress Process Model, proposes that psychosocial resource factors that include social support may mediate the effects of caregiver burden and account for variations in caregiver health outcomes (Goode, Haley, Roth, & Ford, 1998; Ho, Weitzman, Cui, & Levkoff, 2000).

The relationship between social support and burden has been described by several studies in different populations, among them a 2008 study that suggested that low levels of satisfaction with social support can be an indicator of negative health outcomes in a group of dementia caregivers (Clay, Roth, Wadley, & Haley, 2008). In a population of homeless adults, it has been shown that positive outcomes such as higher levels of self-esteem, life satisfaction, and problem-focused coping can result from receiving social support from positive sources while negative outcomes such as poor health-promoting behaviors have resulted from receiving social support from deviant sources (Berg et al., 2005; Nyamathi et al., 2000). The role of positive social support in reducing caregiver burden has been widely acknowledged but further research is

needed concerning the protective impact of perceived social support on caregivers' health (Moller-Leimkuhler & Wiesheu, 2011).

Sociodemographic variables including age, gender, educational status, and marital status have been reported to affect self-reported caregivers' physical and psychological health (Grov & Valeberg, 2012; Kitrungroter & Cohen, 2006; Vrettos et al., 2012; Yee & Schulz, 2000). Sociodemographic characteristics that include age, gender, ethnicity, education, and employment have been associated with depression, i.e., depression in the general population has been found to be more prevalent among ethnic minorities, young adults and females while higher education is associated with a lower risk of depression in homeless populations (Berg et al., 2005). In a caregiver study, male gender and higher education has been linked with higher health-related quality of life (Vrettos et al., 2012). By considering these individual characteristics as antecedent and mediating variables, individuals who have a higher risk for negative health outcomes may be identified earlier and appropriate health promoting interventions applied sooner.

Cognitive appraisal is the mediating process between the antecedent and the dependent variables. Cognitive appraisal is a process through which an individual evaluates the relevance of a particular encounter to one's well-being and is considered as one of the critical mediators of immediate and long-term health outcomes resulting from stressful events (Folkman, Lazarus, Dunkel-Schetter, DeLongis, & Gruen, 1986). An individual responds to an initial or ongoing episode of a stressful encounter through mental operations of thinking and reasoning. The response, influenced by the characteristics of the individual and the contextual factors surrounding the encounter,

directs the continuous reappraisal and exchanges between the individual and the environment (Kessler, 1998).

Two kinds of cognitive appraisals occur simultaneously during stressful encounters: primary and secondary appraisal. Primary appraisal is an assessment of the importance of an encounter and classifies it as irrelevant, benign-positive (beneficial), or stressful; and among those classified as stressful, primary appraisal further distinguishes each encounter into harm/loss, threat, and challenge (Peacock & Wong, 1990). Secondary appraisal is mainly concerned with actions that can be taken during the encounter and involves a thorough assessment of coping options (Peacock & Wong, 1990). Folkman et al. (1986) reported that an individual's assessment of the importance of an encounter (primary appraisal) and what they view as the options for coping partially explains variability in coping. Similarly, Hudek-Knezevic & Kardum (2000) underscored the importance of cognitive appraisals on adaptational outcomes, situational coping efforts and highlighted their mediating role between some coping resources (i.e., perceived social support and preferred coping styles) and adaptational outcomes.

The concept of **coping** has a rich history and widespread popularity outside of the health sciences and is as much a colloquial term as a scientific one (Lazarus & Folkman, 1984, p. 117). Coping is integral not only within the tradition of human psychology where it is rooted but in disciplines that belong to the collective biomedical sciences, including nursing. A myriad of psychotherapies and educational programs are directed at the development of coping skills (Lazarus & Folkman). Within this study, coping is conceptualized as an effort made by the caregiver to manage the burden of

caregiving regardless of the outcome. The goal of studying coping behaviors is to examine the different types of coping responses people have in stressful situations and to explore the possible relations between coping behaviors and psychological distress and well-being. Coping is defined as a voluntary response to perceived threat, harm, loss, or stress. It is a broad concept that has a very complex history. A number of distinctions and dimensions of coping have been identified by researchers. Some of the most important taxonomies that have been commonly used in research are discussed hereafter.

Problem-focused coping is directed at the source of stress while emotion-focused coping is directed at the effects of the stressor (Carver & Connor-Smith, 2010). While the first type of coping is aimed at eliminating or ameliorating stress or diminishing the impact, the second type of coping may become operative through minimizing the distress triggered by the stressors. Among caregivers of patients with metastatic cancers, examples of problem-focused coping would include obtaining home health aides or taking advantage of respite care and examples of emotion-focused coping would be taking part in caregiver support groups and participating in stress-reduction exercises (i.e., yoga, progressive relaxation, visual imagery).

Engagement or approach coping is aimed at facing the stressor while disengagement coping seeks to avoid or escape the threat (Carver & Connor-Smith, 2010). Activities that fall under engagement coping include seeking support and cognitive restructuring while disengagement coping include responses such as avoidance, denial, and wishful thinking. Among cancer patients and caregivers, attending support group meetings to learn how to live with the diagnosis is an example

of engagement coping while watching a movie to escape the distress brought on by the diagnosis would be disengagement coping. With disengagement coping, while the individual is given a temporary respite from the stressful situation, the threat remains and eventually must be confronted.

Accommodative or secondary-control coping is an attempt to adapt or adjust to the stressor, in contrast to an attempt to control the stressor itself as occurs with primary-control coping. Primary- and secondary-control coping are both elements of engagement coping (Carver & Connor-Smith, 2010). Meaning-focused coping, on the other hand, involves attempts to find or be reminded of the benefits gained from stressful experiences. Activities may include reordering life priorities and infusing ordinary events with positive meaning (Carver & Connor-Smith, 2010). The belief that positive thought can influence outcomes and an emphasis on positive changes that occur with every stressful situation, however, is often an acknowledgment of the constraints within the situation. It is therefore not uncommon for individuals to utilize meaning-focused coping when the stressful situation becomes uncontrollable or gets worse (Carver & Connor-Smith). Proactive coping involves anticipating an emerging threat and engaging in activities that will prevent the stressful situation from happening or that removes the individual from the situation (Carver & Connor-Smith, 2010). By assessing the coping behaviors utilized by caregivers in this study, interventions can be designed to enhance effective coping and acknowledge ineffective strategies to mediate immediate and long-term health outcomes.

Burden is a concept frequently used in caregiving research, either as a dependent or independent variable and is often operationalized as stress, distress or

strain (Chou, 2000). In this model, caregiver burden is the immediate health outcome of interest. While systematic generation and organization of the body of nursing knowledge on the concept of burden continues to thrive since it was first introduced in the literature in 1966 (Chou, 2000); the theoretical frameworks and conceptualizations used to guide investigations have often been borrowed from other disciplines. For example, research that focuses on the cognitive and behavioral responses to stress is frequently grounded in a cognitive appraisal theory while biologic responses to stress are framed within a physiologic model (Sherwood et al., 2008). The use of stress and coping framework for caregiving reseach in psychology has gained the favor of caregiving researchers from across multiple disciplines, including nursing. This may be explained by the proposition that the degree to which caregivers perceive burden is influenced in part by their coping behaviors (Chou, 2000).

Caregiver burden has been identified through the reports or experiences of the caregivers and maybe conceptually defined as “the physical, psychological or emotional, social, and financial problems that can be experienced by family members caring for impaired older adults” (Braithwaite, 1992; George & Gwyther, 1986, p. 253). In addition, caregiver burden has also been defined as “the impact of the changes in cognition and behavior of the Alzheimer patient on the family, and the patient’s subsequent need for care and supervision” (Ory et al., 1985, p. 631), a destinction that reflects the expectations of researchers and highlights a less experiential perspective (Braithwaite, 1992). While these definitions were utilized for caregivers of patients with Alzheimer Disease, it would be important to point out that caregivers of patients with metastatic brain tumors share with caregivers of Alzheimer patients the experience of

dealing with the patients' cognitive dysfunction as one of the antecedent variables for caregiver burden.

Anxiety and Depression. Cancer caregiving has been shown to increase burden, alter mental and physical health status, and reduce the QOL of caregivers. QOL is a multidimensional construct that has received significant attention and among the components, psychological distress has been most studied (Kim, Spillers, & Hall, 2012). Research reports have consistently described the high prevalence of anxiety and depression among cancer caregivers (Fridriksdottir et al., 2011) and that these symptoms can vary along the illness trajectory (Song et al., 2011), i.e., low QOL and higher anxiety and depression scores have been reported among caregivers during the palliative versus curative phase of cancer treatment even as scores for patient symptom burden were similar (Valeberg & Grov, 2012). Furthermore, studies have supported that the psychological distress of cancer caregiving not only varies during the illness trajectory but by diagnosis as well (Song et al., 2011). While it seems that considerable attention has been given to caregiver anxiety and depression, gaps in literature remain and warrant additional studies, including extending the scope beyond that of caregivers of men with prostate cancer or women with breast cancer and describing the prevalence of the caregiver symptoms across the cancer continuum (Lambert, Girgis, Lecathelinais, & Stacey, 2012).

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CHAPTER III: MANUSCRIPT 1

The Hidden Morbidity of Cancer: Burden in Caregivers of Patients with Brain Metastases

Abstract

Caregiving is a highly individualized experience. While numerous papers have been published on caregiver burden in the context of a variety of diagnoses and conditions, this paper presents the unique features of caregiving in patients with brain metastases. Improved long-term survival of patients, concerns about disease recurrence or progression, the mileposts of the cancer experience (initial diagnosis, treatment, survivorship, recurrence, progression, and end of life), and the increasing complexity of cancer treatments add to the demands placed upon the caregiver of patients with brain metastases. Healthcare professionals need to identify caregiver burden and administer the appropriate interventions that must be as unique and individualized as the caregivers' experiences.

Key Points

The cancer caregiving experience can be distinguished from caregiving for other chronic conditions by the rapid and unpredictable deterioration of the health of the patient with cancer.

Caregivers of persons with brain metastases find themselves in an overwhelming and unpredictable role that is primarily influenced by the patient's cognitive and functional decline and aggravated by household, occupational, or societal demands.

While many of studies established the negative effects associated with caregiving, it is equally as important to consider the reported positive effects of caregiving, as well as effects not directly related to the caregiver.

Introduction

Despite remarkable milestones in cancer prevention, early detection, and treatment, many still encounter the catastrophic experience of a cancer diagnosis. After diagnosis, patients and caregivers are thrust on a journey where they encounter the cognitive, psychosocial, emotional, physical and practical consequences of the disease and its treatment. While the diagnosis of cancer, in and of itself, can lead to significant changes in all aspects of patients' and caregivers' lives, the subsequent diagnosis of brain metastases can be even more devastating. Brain metastasis has an annual incidence estimated between 98,000 and 170,000 (Hutter, Schwetye, Bierhals, & McKinstry, 2003; Levin, Leibel, & Gutin, 2001; National Cancer Institute, 2010). It can elicit rapid deterioration in quality of life brought on by progressive neurologic deficits which can be daunting challenges for family caregivers (Saria et al., 2015). In addition, median survival between 2 to 25 months despite treatment suggests that brain metastases indicate poor prognosis and is associated with increased mortality and morbidity (Leone & Leone, 2015). Recently, novel therapeutic discoveries have been shown to improve survival in a subset of patients, however for the majority of patients with brain metastases, palliation of symptoms, preservation of function, and maintenance of QOL are still considered to be the primary goals of treatment (Saria et al., 2015).

While there is a wealth of literature on the caregiving challenges associated with cancer, much less is written about the caregiving challenges associated with brain metastases. This paper focuses on describing some of these challenges and identifying implications of these challenges for health care professionals. Given the scant

research-base about caregiving in this area, the discussion relies heavily on research about caregiving in general with a particular focus on caregiving for individuals who have diagnoses associated with similar progressive neurologic deficits (e.g., dementia).

Caregiving Burden and the Experience of Caring for Persons with Brain Metastasis

The cancer caregiving experience can be distinguished from caregiving for other chronic conditions by the rapid and unpredictable deterioration of the health of the patient with cancer. Cancer is unique in that the clinical course can be marked by active disease, followed by prolonged remission that may be abruptly interrupted by recurrence, metastases, or a new primary disease. In addition, cancer caregivers have been reported to spend more time in caregiving, provide higher acuity care within a shorter time frame, and are predisposed to higher financial burden than the caregivers of persons with other diseases (Kent et al., 2016). From the first publications that introduced and explicated the concept to the current state of the science, caregiver burden has remained as one of the most commonly studied variables in caregiving research (Dionne-Odom et al., 2016; Etters, Goodall, & Harrison, 2008; Francis, Worthington, Kypriotakis, & Rose, 2010; Grunfeld et al., 2004; Mausbach, Harmell, Moore, & Chattillion, 2011; McLennon, Habermann, & Rice, 2011; Moller-Leimkuhler & Wiesheu, 2011; Poulshock & Deimling, 1984; Rafiyah & Sutharangsee, 2011; Rha, Park, Song, Lee, & Lee, 2015; van Ryn et al., 2011; Zarit, Reever, & Bach-Peterson, 1980). Caregiver burden is operationally defined as the cognitive appraisal of the multidimensional response to demands and their consequences within the context of an

evolving caregiving experience (Chou, 2000; Hoffmann & Mitchell, 1998; Pereyra et al., 2010). The critical attributes of caregiver burden include subjective perception, multidimensional phenomena, dynamic change, and overload.

Subjective perception. Consistent with Lazarus and Folkman's (1984) assertion that the degree and kind of reaction to the stress produced by environmental demands vary among individuals, studies have shown that even after controlling for patient characteristics and the type of stressors, the perception of caregiver burden varies among individuals (Connell, Janevic, & Gallant, 2001; Luchetti et al., 2009; Moller-Leimkuhler & Wiesheu, 2011; Nguyen, 2009; Stinson et al., 2014). These findings can be linked to the varied sensitivity and vulnerability of individual caregivers to certain types of experiences, as well as to the differences in caregivers' interpretations and reactions (Lazarus & Folkman).

Some research suggests that the dynamics of caregiving may differ by diagnosis (Harding et al., 2015; Kim & Schulz, 2008; Whisenant, 2011), but study results are equivocal. For example, a comparative study of caregiver burden in psychiatric and chronic medical illness (N=100) showed significantly higher caregiver burden scores (p<0.0001) for caregivers of psychiatric patients, a finding that confirmed results from a previous study (Ampalam, Gunturu, & Padma, 2012). On the other hand, a comparison of caregivers (N=179) of older adults with advanced cancer, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) showed that caregivers of patients with CHF reported higher burden at baseline, but the difference was not statistically significant (Garlo, O'Leary, Van Ness, & Fried, 2010). Another study in the same populations (N=139) also showed only a few differences in caregiver burden by

diagnosis. The authors concluded that caregiver resources, not patient diagnosis or illness severity, were the primary correlates of caregiver burden (Burton et al., 2012; Sautter et al., 2014).

These studies are relevant to caregiving for persons with brain metastases because they suggest that findings from research on general caregiving population also apply to caregivers of those with brain metastases. In addition, they underscore the importance of individual difference. As Ankri and colleagues (2005) noted, even when using a valid and reliable measure, a global score may not provide a complete and accurate assessment as caregivers with identical scores may be affected by different aspects of burden, i.e., while one caregiver may be overwhelmed with the physical demands of caregiving, another may suffer from emotional stress or feel socially marginalized because of the situation.

Multidimensional phenomena. Chou (2000) describes the multidimensional characteristics of burden in terms of outcomes, i.e., caregiver burden can affect the physical, psychological, social, and spiritual domains of the caregiver. In addition to the downstream effects of caregiver burden, the multidimensional nature of the antecedents of burden has also been explored. In cancer caregiving, variables that have been shown to affect caregiver burden include caregiver age, gender, relationship to the care recipient, length of time providing care, and care recipient tumor type (Jeong, Jeong, Kim, & Kim, 2015; Sherwood et al., 2006). In a sample of community-based caregivers (N=92), the strongest predictors of caregiver burden were related to the health-related needs of the care receiver which included their behavioral and mental health problems (p=0.01). In addition, two personal resources of caregivers, i.e., having less resilience

and using negative emotion-focused coping, were found to be significantly, but less strongly, correlated to caregiver burden (Chappell & Dujela, 2008).

The relationships of the multiple variables in the caregiving situation to caregiver burden have been well described in literature (Lou et al., 2015; Sherwood et al., 2008) for many conditions. These studies provide an insight into complexity of caregiver burden, in particular, for the caregivers of persons with brain metastases, a diagnoses that often implies significant physical and psychosocial burden.

Dynamic change. From the time of the initial cancer diagnosis and throughout the illness trajectory, caregivers face many challenges (Khalili, 2007). Throughout this trajectory, caregivers are subject to multiple transitions as they adapt to new demands brought on by disease progression, changes in physical and cognitive function, or acquisition of new debilities. As a result, situations that may have contributed significantly to caregiver burden at one point may not be as stressful as the caregiver learns to adapt and cope, or may be increased by new problems or crisis situations (Chou).

Among caregivers of persons with cancer, Kim and Given (2008) reported that quality of life (QOL) varied along the illness trajectory. For example, in a population of caregivers of women with advanced breast cancer, more caregivers were depressed (30% vs. 9%, p=0.02) and experienced higher levels of burden (mean score 26.2 vs. 19.4, p=0.02) at the start of the terminal period (n=84) than at the start of the palliative period (n=15) (Grunfeld et al., 2004). In another study of caregivers of patients with dementia, while most caregivers experienced problems, 98.9% experienced problems in the initial stage of dementia, 99.1% experienced problems within 1-4 years, and 98%

experienced problems beyond 4 years (chi-square test, $p>0.01$) (Zwaanswijk, Peeters, van Beek, Meerveld, & Francke, 2013). The types of problems reported by the caregivers also varied based on the stage of dementia. For example, caregivers of persons in later stages of dementia (49.1%) experienced more problems in their social networks than caregivers of people in the initial stage of dementia (25.6%). In contrast, another study found no significant differences in mental health and health-related QOL, a concept associated with caregiver burden, for caregivers of cancer patients (N=167) in the palliative and the curative phases, respectively (Grov & Valeberg, 2012). In caregivers of persons with a guarded prognosis such as brain metastases, usually identified after a sudden event (i.e., severe headaches, focal weakness, gait disturbances, seizures, nausea and vomiting) (Saria et al., 2015), the impact of dynamic changes can be profound.

Overload. The caregiver's response to the caregiving experience can range from low to high stress and results from an imbalance of care demand relative to caregiver's resources; i.e., knowledge or training, personal time, social roles, physical and emotional states, financial resources, and formal care resources (Sherwood et al., 2004; van Ryn et al., 2011). Demands may come from the patient, other family members, employment, or society, while resources may be internal or external (Chou, 2000). The caregiving experience can create physical and psychological strain over extended periods of time and is usually accompanied by high levels of unpredictability and loss of control (Schulz & Sherwood, 2008). These life stressors and demands increase the risk for caregiver burden by exacerbating role conflict and disruption.

Many caregivers are responsible for tasks from managing the household and finances to assisting with medical and personal care, and for persons with brain metastases, it can be assumed that their caregivers have been playing that role for some time. Caregivers of persons with brain metastases face the plural challenges of living their own lives, in addition to providing physical care, extending emotional support, while also coping for the anticipated decline of the patient's health.

These critical attributes, subjective perception, multidimensional phenomena, dynamic change, and overload, when experienced in combination, can be stressful to caregivers and the stress is sometimes severe enough to result in serious consequences and outcomes.

Demands of caregiving.

The caregiver role is associated with many demands. For many caregivers, these demands result in caregiving burden (an incongruity between demands and the caregiver's ability to cope) and negative biopsychosocial effects (Hunt, 2003; Kruithof, Post, & Visser-Meily, 2015). Caregiving demands can be broadly classified into primary and secondary.

Primary demands of caregiving. Primary demands are dictated by the health-related needs of the care receiver. They include both the cognitive deficits associated with the diagnosis of brain metastases and the functional impairment observed in patients with cancer.

Cognitive dysfunction of care-receivers. Patients with brain cancers often endure a variety of neurological, cognitive, and emotional problems which, even with the

slightest impairment can significantly alter QOL (Davis & Stoiber, 2011). In the past years, these problems have not been adequately addressed due to the dismal outcome associated with the diagnosis. Recently, however, in the milieu of improved survival with the accompanying neurorehabilitative potential of the patient, recognition of cancer- and cancer therapy-related neurological outcomes has become an indispensable step that precedes therapy selection.

Assessment and interpretation of neurocognitive function in patients with brain cancer is confounded by multiple variables that include neurotoxic effects of anti-cancer therapies and supportive care agents and the presence of mood disorders. In clinical trials, neurocognitive function has now been proposed as a secondary endpoint that can provide significant information otherwise not observed in traditional endpoints that include overall survival, progression-free survival, and radiographic changes. It is viewed as more than just a surrogate marker of disease response to therapy (Wefel et al., 2011; Weller, 2011). Neurocognitive assessment includes measures of general intellectual functioning (i.e., IQ), language, memory, attention, information processing speed, motor speed and dexterity, and executive functioning. In addition, self-reported measures of mood may be obtained in order to estimate the influence of depression on cognitive performances (Witgert & Meyers, 2011).

Cognitive deficits create care demands for the caregivers and increase the number of tasks with which the caregiver must render assistance. Cognitive dysfunction has been identified as a leading cause of disability and the single greatest cause of burden in patients with primary brain tumors (Davis & Stoiber, 2011; Sherwood et al., 2006). Among patients with brain metastases, the vast majority suffer from some

degree of neurocognitive impairment which may even be more common than functional impairment (Khuntia, Mathew, Meyers, Johnson, & Mehta, 2008). Mechanisms of cognitive dysfunction in brain cancers are diverse and may include direct damage due to cancer, indirect effects of cancer (paraneoplastic syndrome), and effects of cancer treatment on the brain (Khuntia et al., 2008; Schagen et al., 2014; Shen et al., 2012). These etiologies are in addition to pre-existing neurological and psychiatric disorders that alter the patient's cognition and mood.

It is important to highlight findings from studies that distinguish between the characteristics and outcomes of caregivers of individuals that have cognitive symptoms caused by different etiologies or whose symptoms occur during different time points during the disease trajectory. One study found that depressive symptoms were more commonly reported by caregivers of patients with dementia compared to caregivers of patients with non-dementia related cognitive impairment (Fisher et al., 2011). Another study reported divergence in caregiver burden in patients with amnesic mild cognitive impairment (AMCI) and mild Alzheimer's disease (AD), where burden was more severe in patients with mild AD (Ikeda et al., 2015). These studies highlight the findings that multiple factors contribute to caregiver burden at different stages of the disease.

Many other studies explored the relationship between the patient's cognitive impairment and caregiver burden in a variety of diagnoses. One study reported that caregiver burden is directly associated with an increase in patients' comorbidities, independent of behavioral, functional status and cognitive impairment (Dauphinot et al., 2016). Another study reported that when compared with functional status, cognitive status has been found to be a much stronger predictor of caregiver burden in caregivers

of patients with dementia according to a meta-analysis of 228 studies of the relationship between caregiving stressors, caregiver burden, and depression (Pinquart & Sorensen, 2003) which was supported by a study in patients with Alzheimer's disease (Germain et al., 2009).

In a study of burden and depressive symptoms in caregivers of geriatric patients, the care recipients' mental status was almost twice as powerful in predicting caregiver burden as the care recipients' functional status (Sherwood, Given, Given, & von Eye, 2005). However, in several studies of the relationship between cognitive abilities of patients with dementia and their caregivers' burden, there were either no or weak relationships between the variables. Findings from one study indicated that cognitive impairment did not contribute significantly to caregiver burden (Rosdinom, Zarina, Zanariah, Marhani, & Suzaily, 2013). However, Etters and colleagues postulate that it may be the patients' behavioral disturbances associated with cognitive impairment that predicts caregiving burden rather than the cognitive impairment itself (Etters et al., 2008).

Functional impairment of care-receivers. Functional status is defined as an individual's ability to perform a task. Patients with brain cancer may not be able to carry out activities of daily living due to neurologic disorders such as paralysis, paresis, sensory loss, blindness, decreased level of consciousness, ataxia, and headaches. These problems may be complicated by treatment-related toxicities, comorbidities and mood disorders (Sherwood et al., 2006).

In caregivers of patients with cancer, care recipients' functional status has been consistently reported as a common predictor of negative caregiver outcomes. However,

while caring for someone with functional limitations added to burden, functional status was not as strong a predictor of burden as was the care recipients' cognitive and neuropsychiatric status. In a convenience sample of 488 family caregivers of patients with diverse diagnoses (e.g., cerebrovascular, circulatory, musculoskeletal, or pulmonary disorders; fractures of hip or major limb; and cancer), the care recipient's mental status was almost twice as powerful (standardized path coefficient of –.37) in predicting caregiver burden as was the care recipient's functional status (standardized path coefficient of .23 (Sherwood et al., 2005). Similar outcomes were reported in a study involving caregivers of patients with amyotrophic lateral sclerosis (N=140), i.e., behavioral changes have greater impact on caregiver burden (odds ratio of 1.4) than the level and pattern of physical disability (Lillo, Mioshi, & Hodges, 2012).

In the area of oncology caregiving, there is a lack of information on caregiver outcomes when multiple variables, i.e., alterations in functional, cognitive, and neuropsychiatric status, are examined together (Russell et al., 2014). In a study of 95 caregivers of patients with primary malignant brain tumors, the patient's functional status as measured by activities of daily living (eating, bathing dressing, toileting, walking inside the house and getting out of bed) and instrumental activities of daily living (transportation, laundry, shopping, housework, meal preparation) affected a subscale of caregiver burden but the patient's cognitive status was not associated with caregiver burden while neuropsychiatric status consistently affected every subscale of caregiver burden. However, the authors suggested that the lack of a significant relationship between the patients' cognitive status and caregiver burden might have been due to lack of an objective measure of cognitive status (Sherwood et al., 2006).

Caregivers are key participants in the care of persons with brain metastases and are compelled to take more important roles compared to many other clinical situations. The additional tasks of managing the functional and cognitive deficits of the patient increases the demands on caregivers who must deal with the changes that accompany a diagnosis that is the most common neurological complication of cancer.

Secondary demands of caregiving. Family, work, and/or society contribute to the secondary demands on caregivers. These demands come from outside the caregiving relationship between the patient with metastatic brain tumor and the caregiver.

Family. Caregiver burden has been reported to be specifically related to multiple roles assumed by the caregiver. Family roles of caregivers directly impact their ability to take on new responsibilities and adjust to living with constant uncertainty (Northfield & Nebauer, 2010). The presence of young children in the household and single-parent families with a female head-of-household are but some of the family structures that have been reported as significant predictors of caregiver burden (Chou, 2000).

Work. The impact of the caregiver's employment on caregiver burden is not clear. While it is intuitive to reason that work outside the caregiving relationship is a competing priority for the caregiver that adds to perceived caregiver burden, several studies have reported that employment or other roles outside of the family may in fact be the key to caregiver well-being (Given & Given, 1991). In 205 family caregivers of hospitalized patients with cardiovascular disease who participated in a family intervention trial, time demands (38%) and work adjustments (25%) were among the most commonly reported causes of burden (Mochari-Greenberger & Mosca, 2012).

In contrast, a cross-sectional household survey conducted among 2,458 adult residents having at least one close relative with any chronic physical and/or mental illness revealed that employment did not significantly contribute to caregiver burden (67.1% of the 1,720 who were employed full time did not perceive burden, *p*=0.0747) (Vaingankar, Subramaniam, Abdin, He, & Chong, 2012). Another study looking at caregivers of seven geographically and institutionally defined cohorts of newly diagnosed colorectal and lung cancer patients (N=677), 21% (n=142) cared for at least one other individual, 49% (n=312) were employed (including 2/3 full time), and 28% (n=86) of the respondents who were working either full or part time reported having difficulty balancing work and caregiving demands. In the same study, 67% (n=453) of caregivers faced at least one, and 19% (n=131) faced two or more of these additional demands with one in five reported suffering from 'poor' to 'fair' health (van Ryn et al., 2011).

Society. Several studies confirmed that a number of family caregivers suffer from financial difficulties related to lost wages from reduced work hours (Northfield & Nebauer, 2010). Surprisingly, another study revealed that very few caregivers reported financial burden and even fewer caregivers had to give up employment to continue to care for a family member (Abernethy, Burns, Wheeler, & Currow, 2009). The differences were attributed to differing health policies between the countries where the studies were conducted.

Caregivers of persons with brain metastases find themselves in an overwhelming and unpredictable role that is primarily influenced by the patient's cognitive and functional decline and aggravated by household, occupational, or societal demands.

The caregiving experience presents a situation where multiple concurrent stressful demands compete for the caregiver's attention. It is therefore important that caregivers be supported to meet the escalating demands of the caregiving experience with as little impact on their emotional and physical well-being as possible.

Consequences and outcomes of caregiver burden.

The caregiving experience is commonly perceived as chronically stressful and can imminently lead to negative outcomes. In caregivers of patients with brain metastases, that experience begins with the diagnosis of the primary cancer and is relived with the diagnosis of brain metastases.

While the nature and magnitude of caregiver burden may vary in the context of different clinical and medical diagnoses, many studies have established the negative effects associated with caregiving (Connell et al., 2001; Moller-Leimkuhler & Wiesheu, 2011; Rodriguez-Sanchez et al., 2011; Stenberg, Ruland, & Miaskowski, 2010). Although not as well documented, it is equally as important to consider the reported positive effects of caregiving (Beattie & Lebel, 2011; Given & Given, 1991; Guetin et al., 2009; S. Picot, 1995; S. J. Picot, 1991; S. J. Picot, Youngblut, & Zeller, 1997; Schulz & Sherwood, 2008), as well as effects not directly related to the caregiver. Some of the indirect effects include clinical outcomes of patients (care recipients), effects on the other members of the household, and impact on the healthcare system in general.

Consequences to caregivers. The high incidence of brain metastases resulting from improved therapy for systemic disease is contributing to the increase in the number of cancer caregivers. Historically, caregiving was considered a stressor that

leads to implications, usually negative, for the caregivers' well-being. More recently however, research in this tradition has evolved from an emphasis on the role-specific negative outcome of burden (e.g., caretaker role fatigue, spousal burnout, and role engulfment) to more general well-being considerations, including positive psychological well-being (e.g., improved relationships, and improved self-satisfaction, gratification, self-efficacy and self-respect), negative psychological well-being (e.g., depression, anxiety), and physical health and immune functioning (Dias et al., 2015; Given & Given, 1991; Hoffmann & Mitchell, 1998; Li & Loke, 2013; Marks & Lambert, 1997; Sherwood, Cwiklik, & Donovan, 2016; Sherwood, Price, et al., 2016).

Results of a systematic review to identify the types of problems and burdens faced by family caregivers of cancer patients reported that 97 of the 164 research-based studies described the physical, social, and/or emotional problems related to caregiving (Stenberg et al., 2010). In one study, investigators assessing the caregivers of newly diagnosed colorectal and lung cancer patients (N=677) reported that the relationship between objective burden and caregiver mental-health and physical-health outcomes varied by caregiver resources. More specifically, caregivers with significant coping, social, and material resources were less likely to suffer deleterious consequences as a result of caregiving demands, while those with few resources were at elevated risk (van Ryn et al., 2011). In a sample of family caregivers of patients with prostate cancer who were to begin radiation therapy (N=60), 12.2% had clinically meaningful levels of depression, 40.7% anxiety, 15.0% pain, 36.7% sleep disturbance, 33.3% morning fatigue, and 30.0% evening fatigue. In addition, those who were older and who had lower levels of state anxiety and higher levels of depression, morning

fatigue, and pain reported significantly poorer functional status (R^2=38.7%). Moreover, those who were younger, had more years of education, were working, and had higher levels of depression, morning fatigue, sleep disturbance, and lower levels of evening fatigue reported significantly lower QOL scores (R^2=70.1%) (Fletcher et al., 2008).

Physical/physiological/biological implications to caregivers. The increase in the length of time providing care and the corresponding burden perceived by family caregivers of patients with brain cancers have been shown to negatively affect the physical well-being of the caregiver (Sherwood, Price, et al., 2016). Caregivers can develop their own health problems from their caregiving responsibilities (Table 3-1).

Table 3-1. Most common aspects of caregiver health that have deteriorated as a result of caregiving.

Symptom	**Frequency (n=528)**
Energy and sleep	87%
Stress and/or panic attacks	70%
Pain, aching	60%
Depression	52%
Headaches	41%
Weight gain/loss	38%

Adapted from (National Alliance for Caregiving, 2006).

Caregivers have been reported to be less likely to engage in preventive health activities and are at a high risk of contracting serious illnesses (Collins & Swartz, 2011). Approximately 50% of caregivers report at least one chronic condition, 20% describe their health as fair or poor, and 17% believe that their health has deteriorated as a result

of caregiving (Aldrich; Collins & Swartz, 2011; Family Caregiver Alliance, 2007). In one study of older spousal caregivers, those who reported caregiver stress had a 63% higher mortality rate than non-caregivers of the same age (Schulz & Beach, 1999). Additionally, data obtained from salivary biomarkers of caregivers of patients with cancer has shown marked changes in neurohormonal and inflammatory processes within the year of the cancer diagnosis (Rohleder, Marin, Ma, & Miller, 2009) while a more recent study found higher levels of pro-inflammatory cytokines in male caregivers with anxiety, obese caregivers who reported higher burden from disrupted schedules, and in younger caregivers with lower self-esteem (Sherwood, Price, et al., 2016).

Psychological/emotional implications to caregivers. The confounding problems including fear, uncertainty, and lack of hope that accompany the diagnosis of cancer continue to surround the patient and the caregiver throughout the continuum of care (Khalili, 2007). These psychological responses may be heightened upon receiving a diagnosis of brain metastases. On the grounds that cancer caregiving has the features of a chronic stress experience (Schulz & Sherwood, 2008), it can be expected that the most common and severe health effects of caregiving are found within the psychological and emotional domains.

In a sample of 116 caregivers of individuals with schizophrenia, the psychological impact of traumatic experiences from the patient's violent behavior was significantly associated with caregiver burden ($p<0.05$) (Hanzawa et al., 2013). A systematic review of 164 research-based studies of family caregivers of cancer patients identified more than 200 problems and burdens related to caregiving responsibilities, with social and emotional implications as the most frequently studied categories (Stenberg et al., 2010).

The National Alliance for Caregiving reported a link between caregiving and higher rates of insomnia and depression, with rates reported as high as 91% for depression; of which 60% was rated as moderate or severe (National Alliance for Caregiving, 2006). In addition, a high prevalence of psychological distress in caregivers has been documented in a study involving 152 caregivers of cancer patients in Italy; more than half scored positive in screening for mood disorders, more than 10% experienced severe levels of post-traumatic stress disorder, and 37% scored positive for clinically-relevant emotional disturbance (Mazzotti, Sebastiani, Antonini Cappellini, & Marchetti, 2013).

Results from a cross-sectional, descriptive, and correlational study involving 410 caregivers recruited from the community indicate a high level of burden and depression among all caregivers. Significant differences ($p<0.001$, $F=26.11$) between the 3 caregiving groups (Alzheimer's disease, cancer, schizophrenia) were detected in terms of burden, with the highest reported for Alzheimer's disease caregivers. One-way analysis of variance showed significant differences ($p=0.008$, $F=4.85$) between the 3 caregiving groups in terms of depression, with the highest depression levels being for cancer caregivers (Papastavrou, Charalambous, Tsangari, & Karayiannis, 2012).

A longitudinal study of 193 family caregivers of terminally ill cancer patients in Taiwan demonstrated the dynamic change and multidimensional attributes that can also be observed with the consequences of caregiver burden. In that study, caregivers' depressive symptoms increased as the patient's death approached. Adult children or spousal caregivers suffered more depressive symptoms if they self-identified as lacking social support and confidence in offering substantial assistance for younger terminally ill

cancer patients with higher levels of symptom distress. Likewise, the study reported that caregivers were susceptible to higher levels of depressive symptoms if they were heavily burdened by caregiving, that is, experienced more disruptions in schedules, greater health deterioration, stronger sense of family abandonment, and lower caregiver esteem (Tang et al., 2012).

Social implications to caregivers. The cancer experience can significantly impact the social well-being of caregivers. For caregivers of patients with brain metastases, the uncertain disease trajectory riddled with a variety of distressing events present a unique challenge. Caregivers have trouble balancing their work and family responsibilities and many have to adjust their work schedules, take leaves of absence, or reduce work hours as a result of care responsibilities (Family Caregiver Alliance, 2009). Caregivers may have to spend their own money to take care of their sick family member. The average out-of-pocket expense for caregivers in 2007 was $5,531, approximately 10 percent of the annual household income for more than 40 percent of caregivers in the U.S. The cost did not include the loss of salary, benefits, and the reduction in retirement savings and social security benefits (Collins & Swartz, 2011).

A 2012 study of caregivers of patients with lung cancer (N=74) reported that close to three fourths (74%) had one or more adverse economic or social changes, i.e., disengagement from most of their regular social and leisure activities and hours of work lost due to the illness. The investigators further reported that 16 was the average number of hours of work lost each week due to the illness (SD=13, range=1–50). Additionally, 28% of caregivers (n=21) reported that their family lost their major source of income or made a major change in plans that included delaying medical care for

another family member or altering educational plans (22%) because of the high cost of the illness.

Nearly one fifth (18%) of caregivers reported losing most or all of the family savings and another 18% indicated that a family member made a major life change (e.g., quit work) to care for the patient (Mosher et al., 2013). In a similar study looking at 70 caregivers of patients in palliative care, Mazanec, Daly, Douglas, and Lipson (2011) reported that the overall work productivity loss in their sample was 22.9% which was slightly higher than the number (20.1%) previously reported by Giovannetti, Wolff, Frick, and Boult (2009). This study also found associations between greater work productivity loss and higher levels of depression and anxiety, and greater perceived caregiver burden related to financial problems, disrupted schedule, and health problems (Mazanec et al., 2011).

Consequences to care-receivers. While most studies on cancer caregiving focus on either patient or caregiver outcomes, addressing each as separate individuals, a few studies explored caregiver-patient dyads and dyadic outcomes (Kent et al., 2016). This is of particular importance to caregivers of patients with brain metastases because of the multiple assaults to the physical and mental health of both the patient and the caregiver. Despite their good intentions and hard work, caregivers can place their family members at risk if they lack the knowledge and skills to perform their work or if they engage in harmful behaviors, intentional or unintentional, because of their lack of capacity to provide the level of care that is needed (Reinhard, Given, Petlick, & Bemis, 2008). Studies in non-cancer caregiver-care receiver dyads have documented that depressed caregivers are more likely to engage in neglect or abusive behaviors (Beach

et al., 2005). In a systematic review of risk factors for elder abuse among community dwelling elders, caregiver burden was found to be a risk factor in three studies of elders requiring assistance with daily activities and in four studies of elders with dementia (Johannesen & Logiudice, 2013). Studies have also linked cognitive behavioral problems of care receivers with an increased risk for abusive behaviors by the caregivers (Fulmer et al., 2005; Heath, Kobylarz, Brown, & Castano, 2005; 2004).

The stressful work associated with caregiving can increase the risk of the caregiver engaging in harmful behaviors toward the care recipients. Additionally, caregiver burden can impact patient outcomes. The National Alliance for Caregiving reported that one-half of caregivers believed that the decline in their own health compromised their ability to provide care for the care recipient (Aldrich; Collins & Swartz, 2011).

In an editorial in the Journal of Clinical Oncology, Lutgendorf and Laudenslager (2009), commented on an article on the dysregulation of pro- and anti-inflammatory signaling pathways in caregivers of patients with cancer. The authors of said article reported that caregivers of patients with cancer showed a profound linear increase in systemic inflammation (Rohleder et al., 2009). Lutgendorf and Laudenslager called for more research to determine the extent and reversibility of biologic changes in the caregiver that may accompany the ultimate improvement, stabilization, or death of the patient. Further, they proposed that the dyadic interaction between caregiver well-being and patient outcomes be tested in well designed randomized controlled trials.

Consequences to the family. Cancer significantly affects the entire family and is not an isolated experience for one individual (Otis-Green & Juarez, 2012). The stress

of caring for a relative with cancer can create new conflicts or can bring long-standing unresolved family issues to the surface. Conflicts arise when patients and caregivers avoid discussion of sensitive issues surrounding the cancer diagnosis and its treatments. Barriers to communication and negotiation of family roles hinder the caregivers' and the patients' abilities to support one another, decrease spousal intimacy, or have a detrimental effect on marital and family relationships (Northouse, Katapodi, Song, Zhang, & Mood, 2010).

Family caregivers assume more load when they assume the responsibilities of the sick family member in addition to their own. It has been reported that primary caregivers not only need the assistance of family members but their expressed encouragement and appreciation as well (Etters et al., 2008). Family conflicts have also been found to be predictors of caregiver depression but on a positive note, prior good family dynamics have been associated with significantly less caregiver burden (Etters et al.). It may be that positive family support can be an important resource to the caregiver in mitigating some of their perceived burden.

Consequences to the health care system. Brain metastases are 10 times more common that primary brain tumors and have been reported in as many as 40% of patients with systemic cancer (Chamberlain, 2010; Lorger & Felding-Habermann, 2010; Saria et al., 2015). With the rise in the number of patients with brain metastases comes a corresponding increase in the number of caregivers. While the role of caregivers has been well recognized, most healthcare systems have yet to develop a formal process to integrate caregiver health into their structures. Caregiver burden has been associated with the caregiver's own poor health status, a decrease in health maintenance

behaviors, and increase in health-risk behaviors and prescription drug use (Collins & Swartz, 2011; Reinhard et al., 2008). In terms of utilization of acute care services, investigators studying caregivers of patients with Alzheimer's Dementia reported that 24% of the caregivers (N=153) had at least one emergency room visit or hospitalization in the six months prior to study enrollment (Schubert et al., 2008). In addition, caregivers who reported higher levels of burden had a higher Framingham Stroke Risk and an increased all-cause mortality risk (Collins & Swartz).

Family caregivers constitute the foundation of long-term care system and while many studies have reported on the negative impact of caregiver burden on the healthcare system, family caregiving can also have a positive impact on health care expenditure. Family caregiving saves billions of dollars that would otherwise be required for long-term hospitalization and care (Chou, 2000). The Association of American Retired Persons (AARP) estimated that the economic value of unpaid contributions of family caregivers was approximately $450 billion in 2009 (Feinberg, Reinhard, Houser, & Choula, 2011).

Caregiving at the end-of-life (EOL). While a subset of patients benefit from novel treatments, cure remains to be an unrealistic expectation for most patients with brain metastases (Saria et al., 2015). Multiple prognostic models predicting the overall survival of patients with brain metastases reiteratively report a median survival of 2 to 7 months (Stavas, Arneson, Friedman, & Misra, 2014), and because of this, the diagnosis of metastatic disease is often considered an eligibility criteria for admission to hospice [University of Texas Health Sciences Center San Antonio (http://geriatrics.uthscsa.edu/tools/Hospice_elegibility_card__Ross_and_Sanchez_Reill

y_2008.pdf), Hospice and Palliative Care of Greensboro (https://www.hospicegso.org/wp-content/uploads/2013/07/AdmissionCriteriaBooklet-8-2013.pdf) , Optum (https://campaign.optum.com/hospice/clinical-professionals/hospice-eligibility.html), Hospice of the Valley (https://www.hov.org/hospice-eligibility-guidelines)]. In contrast to the traditional healthcare delivery model that is centered on the patient's individual needs, hospice provides support with the patient and the family as the unit of care (Oliver, Demiris, Washington, Clark, & Thomas-Jones, 2016). However, referral to hospice typically occurs very late in the dying process and whether patients and caregivers receive hospice support depends on many things, including patients', caregivers, and healthcare providers' preferences for aggressive treatment (Wright et al., 2016). Hence, these individuals often deal with EOL issues before hospice care is even offered as an option.

When caregivers of patients with brain metastases transition from *usual care* provided in hospitals and ambulatory care setting to the specialized *end-of-life care*, they receive minimal preparation and limited information from healthcare providers (Guo, Phillips, & Reed, 2010; Phillips & Reed, 2010). The lack of preparation and limited information are reflected in the themes that emerged from a qualitative study exploring caregivers' perspectives in providing end-of-life care. In the study, caregivers described end-of-life care as unpredictable, intense, and complex, but at the same time, profoundly moving and affirming (Phillips & Reed, 2009).

Implications for Practice

It is worth noting that caregivers have regular interactions with the healthcare system and yet may not receive the attention they need (Adelman et al., 2014). Caregivers who continue to suffer in silence as they juggle the tasks and prioritize the needs of the patients and those who knowingly suppress their needs so as not to contribute to the cancer patient's guilt or remorse over being the cause of burden can be helped by comprehensive and holistic care provided by those same healthcare systems. Stakeholders need to develop a plan to integrate the care of caregivers into formal healthcare systems in cancer care. Clinicians and researchers need to work together to create an infrastructure for more comprehensive caregiver surveillance at national and/or state levels.

While routine interactions between patients and providers that are focused on an integrated care is the cornerstone of a quality comprehensive care, the well-being assessment of family caregivers is currently not considered standard of care. In the age of precision medicine, the care of the caregiver is several years behind the powerful advances in the diagnosis and treatment of cancer. We need to identify the factors that cause burden, relationship conflicts in the patient-caregiver dyad and among other members of the household, and financial toxicity, in caregivers of patients with cancer. More importantly, we need to provide an individualized plan of care for caregivers, including respite for caregivers, supplemental services, interventions to reduce burden and improve health (Adelman et al., 2014).

Summary

Caregiving is a highly individualized experience as demonstrated in caregivers of patients with brain metastases. Whether expressed or implied, the responsibilities they take on upon assuming the caregiving role place additional demands that the caregivers must adapt to and cope with. While some demands of caregiving are more likely to increase caregiver burden, every caregiver has a different threshold and the variation in responses are as diverse as the characteristics of caregivers.

What is unique about the features of caregiving in patients with brain metastases that would warrant the development of a program of research that does not duplicate the work already done with other caregiver populations? As described in previous chapters, improving long-term survival of patients has corresponded with an increased incidence of brain metastases. This sequence of events in the trajectory of patients with cancer has extended the length of the caregiving experience. In addition, the universal concerns about disease recurrence or progression that are unique to cancer predisposes the patient and the caregiver to uncertainty and stress. Likewise, the diagnosis of cancer takes the patient and their caregiver through a journey that winds through unique mileposts (i.e., initial diagnosis, treatment, survivorship, recurrence, progression, and end of life). The route that the patient with cancer and the caregiver take can take them through a direct path to remission or end-of-life, but can also maneuver them in a path that circles through these mileposts. Lastly, developments in cancer research has increased the complexity of cancer treatment as new therapies, devices, and clinical trials are now available to patients when only a years ago, options

for further treatment would not have existed. All these contribute to the demands placed upon the patient and their caregivers.

This paper described the challenges of caregiving in brain metastases. In this paper, we reviewed the critical attributes of caregiver burden: subjective perception, multidimensional phenomena, dynamic change, and overload. These attributes have been examined in many caregiver studies within a variety of diagnoses and health conditions. Here, we also described the demands of caregiving, classifying them into primary and secondary demands, where primary demands are dictated by direct health-related needs of the care receiver and secondary demands are determined by factors outside the environment of the caregiver-patient dyad, i.e., family, work and society. Lastly, we presented the consequences and outcomes of caregiver burden. While the paper mostly describes the negative consequences of caregiving, it acknowledges the growing body of work highlighting positive outcomes and more general well-being considerations for the individual in the caregiving role.

Caregiver burden is an important component of comprehensive and holistic clinical care. It is a consequence of a process that involves a number of interrelated conditions within the caregiving experience. As healthcare providers prepare to care for an aging population, whereas advancing age is a known risk factor for cancer, it becomes increasingly important to address the needs of the caregiver, and the “other patient” who is at an increased risk for various psychological, physical, financial, and social problems.

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CHAPTER IV: MANUSCRIPT 2

Anxiety and Depression Associated with Caregiver Burden in Caregivers of Patients with Brain Metastases

Abstract

Background. Caregivers of patients with brain metastases represent a unique and increasing population of cancer caregivers. It has been suggested that affective symptoms of caregivers vary along the illness continuum and could be affected influenced by factors related to the patient's deteriorating condition.

Objectives. To describe and examine the relationship between caregiver burden, and the affective disorders anxiety and depression, in caregivers of patients with brain metastases.

Design. Cross-sectional, descriptive/correlational.

Setting. A comprehensive cancer center.

Sample. 56 family caregivers of patients with brain metastases.

Methods. Self-administered survey.

Main Research Variables. Caregiver burden, anxiety, and depression.

Findings. In our sample, we found that with the exception of caregiver esteem, there were statistically significant relationships between schedule burden, a dimension of caregiver burden and screening positive for affective disorders.

Conclusions. Findings from our study supported previous reports indicating that the odds of having anxiety as well as depressive symptoms are higher in family caregivers who report higher levels of caregiver burden.

Implications for Nursing. The identification and management of caregiver burden is an important consideration for a comprehensive cancer care program. It becomes increasingly important to address the needs of the caregiver, the “other patient” who is at an increased risk for various psychological, physical, financial, and social problems.

Introduction

Brain metastases are diagnosed in 10% to 40% of all cancer patients and the incidence continues to rise due to the increasing number of long-term survivors (Lorger & Felding-Habermann, 2010). Brain metastases are the most common intracranial tumors, and reportedly, the annual incidence of brain metastases is more than ten times greater than that of primary brain tumors. These figures total more than 170,000 new cases in the United States (U.S.) every year (Al-Shamy & Sawaya, 2009; Santarelli, Sarkissian, Hou, Veeravagu, & Tse, 2007).

Family caregivers provide long-term care and are often the primary source of physical, social, and emotional support for patients. A caregiver is an unpaid individual who provides direct care to relatives or friends who are unable to provide for themselves (Hunt, 2003). Depending on their responsibilities, caregivers have been classified as primary caregivers if they mainly provide and/or assist with care recipients' activities of daily living. Caregivers are classified as secondary caregivers if they assist someone else with caregiving or provide support to care recipients but are not primarily responsible for the day-to-day care or decisions regarding the care (Penrod, Kane, Kane, & Finch, 1995; Ryba, 2012).

Caregivers of Patients with Brain Metastases

Caregivers of patients with brain metastases represent a unique and increasing population of cancer caregivers. They provide care to patients with a diagnosis that often heralds the start of the terminal phase of an advanced disease that can be manifested through worsening functional, cognitive, and neuropsychological impairment. Caregivers of patients with brain metastases not only acquire new care

demands in addition to increasing intensity of existing demands, but also deal with both physical and cognitive deterioration of their loved ones (Gerstenecker et al., 2014; Vaughan, 2012). Unfortunately, despite decades of research showing the negative emotional and physical responses of caregivers in the context of chronic illnesses (e.g. cancer and dementia), little caregiving research has been done in the field of neuro-oncology (Sherwood & Baer, 2011).

Caregiver Burden

Caregiver burden, a negative response that has been studied extensively, is defined as the worrisome load borne by people providing care for another individual (Hunt, 2003). Caregiver burden has also been described as the physical, psychological or emotional, social, and financial problems experienced by caregivers resulting from changes in cognition and behavior of the patient and the patient's subsequent need for care and supervision (Braithwaite, 1992). Caregiver burden is multidimensional and dynamic in that it responds to fluctuations in demands and the contextual variations during the caregiving experience (Chou, 2000; Perlick, Clarkin, & Sirey, 1995).

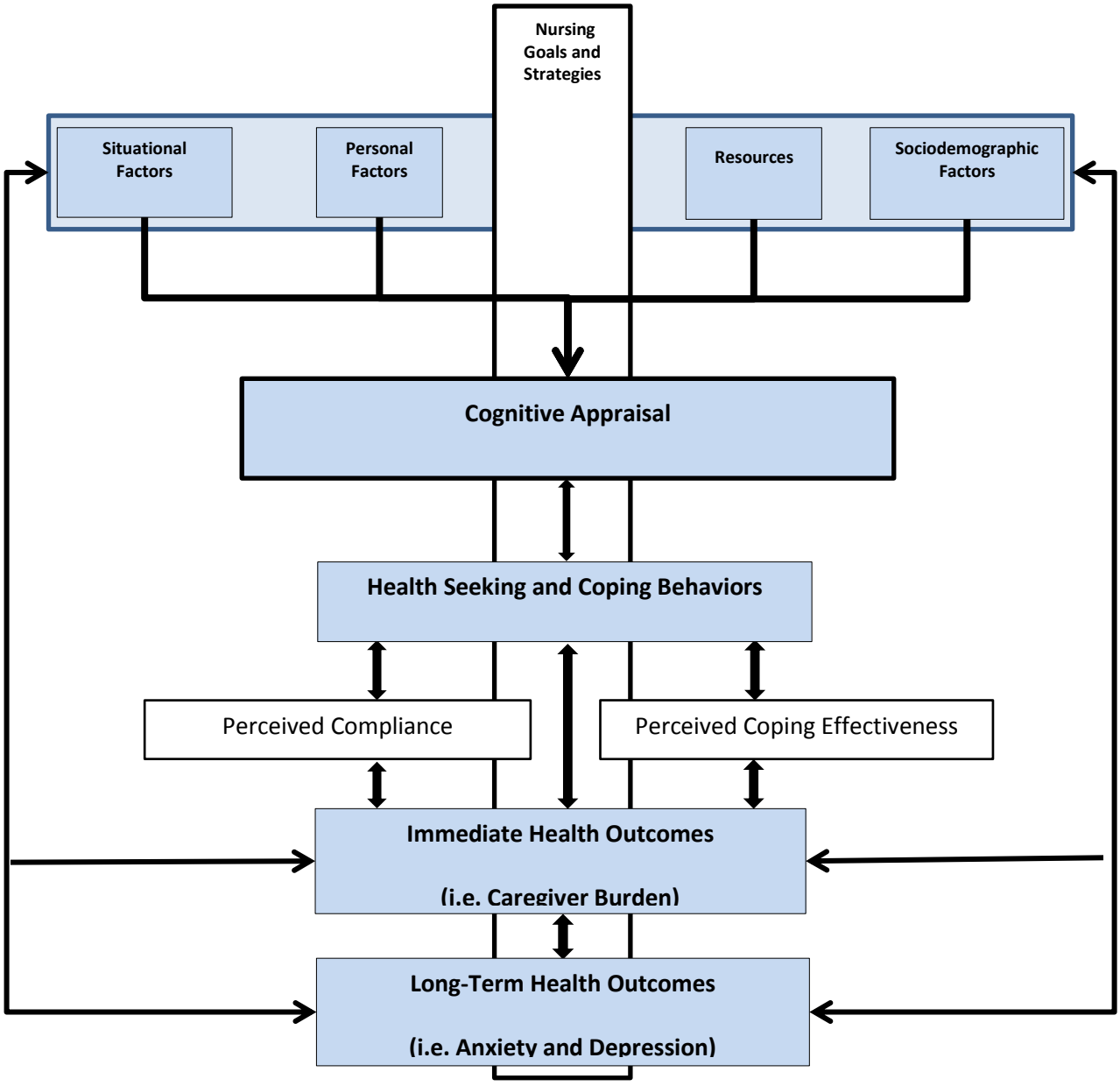
Caregiver Anxiety and Depression

Anxiety and depression, other negative responses, have been studied in caregivers of patients with cancer (Lambert, Girgis, Lecathelinais, & Stacey, 2012; Lee et al., 2013; Sklenarova et al., 2015). However, few studies focused on a subset of caregivers of patients with brain metastases. Caregivers of patients with advanced cancer have been reported to experience emotional stress, depression and increased anxiety related to their caregiving activities (Mystakidou et al., 2012). Caregivers of patients with brain tumors have also been reported to live with higher levels of anxiety

and depressive symptoms when compared with the general population (Finocchiaro et al., 2012). It has been suggested that affective symptoms of caregivers of patients with cancer vary along the illness continuum and could be influenced by factors related to the patient's deteriorating condition (Song et al., 2011). It can be expected that anxiety and depression among caregivers of patients with brain metastases would be different from those caring for early stage disease or those with different primary sites.

The Comprehensive Health Seeking and Coping Paradigm (CHSCP) (Nyamathi, 1989) was adapted as the conceptual framework for this study to describe the relationship between antecedent, mediating, and dependent variables that influence caregivers' perception of and behavior towards caregiver burden. It is a complex multi-dimensional framework that depicts highly interactive relationships among its 12 components (Berg, Nyamathi, Christiani, Morisky, & Leake, 2005; Nyamathi, 1989; Nyamathi, Stein, & Bayley, 2000; Nyamathi et al., 2010; Washington, Moxley, & Taylor, 2009). For this study, caregiver burden was conceptualized as an immediate health outcome that could lead to long-term health outcomes that include anxiety and depression (Figure 4-1).

Figure 4-1. Comprehensive Health Seeking and Coping Paradigm



The aim of this study was to describe anxiety, depression, and caregiver burden among caregivers of patients with brain metastases, an area that has not previously been studied. An additional aim was to examine the relationships between caregiver burden, and anxiety and depression in caregivers of patients with brain metastases. We hypothesized that, similar to the findings in other patient and caregiver populations, increased caregiver burden was associated with increased anxiety and depression.

Methods

Design

This study used a descriptive, cross-sectional design. Data for this study were obtained through a self-administered survey (approximately 90 minutes in length) completed by family caregivers of patients diagnosed with brain metastases. The survey packet had undergone pilot testing to identify potential problems with the questionnaire that might lead to biased answers. This multi-campus affiliated study was approved by the University of California (UC) Institutional Review Board (IRB) Reliance Registry, with UC Los Angeles (academic affiliation) serving as the reviewing IRB and UC San Diego (study accrual site) as the relying IRB.

Sample

Convenience sampling was used to enroll eligible caregivers from UC San Diego, a National Cancer Institute-Designated Cancer Center in Southern California. Participant eligibility criteria included: (a) age ≥ 18 years; (b) self-identified primary caregiver of patients diagnosed with brain metastasis, (c) able to speak, read, and understand English, (d) willing and able to complete a survey, (e) co-residence with the

patient with brain metastasis, and (f) providing a minimum of 4 hours of direct care for at least 3 days per week. We did not limit eligibility by relationship (i.e., spouse, parent, child, sibling, or friend), length of the caregiving relationship, or intensity of care provided.

Of the 104 caregivers of patients with brain metastases who consented to participate, 56 completed the survey. The response rate was 53.8%, which was similar to most mail-in surveys but lower compared to what has been reported in studies using similar approaches (Hanly, Maguire, Hyland, & Sharp, 2015; Hartnett, Thom, & Kline, 2016). Since the survey was anonymous, we were precluded from analyzing the reasons for non-participation.

Procedure

Because patients with brain metastases meet the definition of human subjects, they were considered secondary subjects in this study. A waiver of informed consent for the secondary subjects was granted by the IRB as the study met the requirements outlined in 45 CFR 46.116(d). The caregivers of patients with brain metastases were recruited using flyers that described the study and included the criteria for enrollment and contact information of the study team. The flyers were distributed to physicians and staff in medical oncology offices, infusion center and radiation oncology. Potential participants were identified by physicians and staff. Those who gave permission to receive more information were subsequently approached by a member of the study team. The participants who consented were provided with a survey packet and cover letter stating the purpose of the study. The survey was self-administered and upon completion, was either mailed using a self-addressed stamped envelope or handed to a

study team member on site. A $5.00 gift card was included in the packet as a small token of appreciation for taking part in the study.

Outcome Measures

Caregiver Data Form. The caregiver data form was developed from a literature review of cancer caregiving studies. The questions included caregiver and patient demographics, social and economic characteristics, description of relationship with the patient, and caregiver health status. Information about the patient, including the history of present illness, date of initial diagnosis, date of diagnosis of brain metastases, cancer treatment received and co-morbidities were also obtained.

Caregiver Burden. Caregiver burden was measured using the Caregiver Reaction Assessment (CRA), an instrument that reflects the reactions of family members as they care for patients with cancer (Given et al., 1992). The instrument was designed as a questionnaire with Likert-type responses ranging from strongly agree (1) to strongly disagree (5). The 24 items form 5 distinct unidimensional subscales that include: family burden (lack of family support; 5 items), financial burden (struggle with bills; 3 items), health burden (caregivers' health decline; 4 items), schedule burden (disruption of daily tasks; 5 items), and caregiving esteem (7 items), a positive subscale that measures enjoyment and importance of caregiving (Sautter et al., 2014). A higher score on the caregiver's esteem subscale indicates a more positive effect of caregiving while higher scores on the other subscales indicate greater negative effects of caregiving in those domains (Given et al., 1992).

Internal consistency of the subscales was calculated using Cronbach's alpha, the findings ranged from .80 to .90. Construct validity of the CRA was explored by

correlating the five subscales with the number of patient dependencies in activities of daily living (ADL) and caregiver's level of depression. These two external variables were selected because of the way they relate with indicators of burden in conceptual models explaining the impact of caring on family members, i.e., number of dependencies in ADLs is commonly viewed as an indicator of stressful demands of care leading to caregiver burden and caregiver depression is often viewed as an outcome. For construct validity, the CRA yielded a coefficient alpha of 0.91 using the Center for Epidemiologic Studies Depression Scale and a coefficient alpha of 0.83 using the ADL Dependency Scale (Given et al., 1992).

Anxiety and Depression. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), a 14-item scale that yields subscale scores that categorize individuals as having normal, borderline, or clinical anxiety or depression (Zigmond & Snaith, 1983). Each item is scored from 0-3; total subscale scores range from 0 and 21 for either anxiety or depression; scores of 8 and above for both subscales indicate emotional distress. A recent literature review reported that correlations between the anxiety and depression subscales of the HADS varied from 0.40 to 0.74 (mean 0.56) with Cronbach's alpha for the anxiety subscale ranging from 0.68 to 0.93 (mean 0.83) and from 0.67 to 0.90 (mean 0.82) for the depression subscale (Bjelland, Dahl, Haug, & Neckelmann, 2002). In addition, the investigators of the review paper found that the correlations between HADS and other commonly used questionnaires ranged from 0.49 to 0.83.

The HADS was used in a population of caregivers of patients with brain tumors and showed a mean anxiety score of 10.94 (SD= 4.06), and a mean depression score

of 7.25 (SD= 3.99). One-sample *t*-test showed significant differences between caregivers and control group for anxiety ($p<0.001$) and depression ($p<0.001$). Using a higher threshold (≥ 11) for anxiety and depression, 52% and 19% of caregivers demonstrated clinically relevant levels of anxiety and depression, respectively (Finocchiaro et al., 2012).

Statistical Analysis

All data were coded and placed into an SPSS version 21 file (SPSS Inc., Chicago, IL., USA). Continuous variables were summarized with means and standard deviations while categorical variables were expressed as frequencies and percentages. Specific items on the CRA and HADS subscales that were negatively worded were reversed coded so that a higher score indicated higher burden, heightened anxiety, or worse depression.

In scoring instruments, items missing within a subscale were imputed as the average of non-missing items in the subscale, assuming that data were missing at random. Logistic regression models were run in SPSS 21.0 (SPSS Inc., Chicago, IL, USA) to predict anxiety and depression as a function of each of the caregiver burden subscales (disrupted schedule, financial problems, lack of family support, health problems, and caregiver esteem). In addition, a multivariable logistic regression was run for anxiety and for depression with the set of five caregiver burden subscale scores as predictors.

The variables were dichotomized using published scoring interpretation for the CRA and HADS subscales. The scores were added for each of the CRA subscale items and were dichotomized as high (4 to 5, indicating agreement with statements and higher

perceived burden) or low (1 to 3, indicating disagreement with statements or lower perceived burden) (Sautter et al., 2014). For the HADS subscales, a score of 0 to 7 indicates absence of the condition while a score of ≥ 8 indicated the presence of the condition (i.e., anxiety or depression) (Bjelland et al., 2002). A p value of less than .05 was considered indicative of statistical significance, and 95% confidence intervals (CIs) were calculated.

Results

Sample description

Between February 2014 and August 2015, we received 56 completed surveys from the 104 caregivers of patients with brain metastases, yielding a response rate of 53.8%. The average caregiver age was 56.3 years (SD = 14.9). A majority of the caregivers were women (69.6%, n = 39). Seventy-one percent self-identified as Caucasian/White (n = 40) followed by Asian (16.1%, n = 9). Eighty-six percent of the caregivers had a spouse or partner (n = 48). Sixty-eight percent reported they were spouses or significant others of the care recipients (n = 38), with 16.1%% (n = 9) reporting that they were children of the care recipients (Table 4-1).

Table 4-1. Demographics of caregivers of patients with brain metastasis.

Characteristics	Caregivers (N = 56) [mean ± SD or n (%)]
Age (years)	56.3 ± 14.9
Gender	
Female	39 (69.6)
Male	17 (30.4)
Education	
College grad	19 (33.9)
Some college	18 (32.1)
Graduate degree	16 (28.6)
Grade school	1 (1.8)
High School	1 (1.8)
Left blank	1 (1.8)
Ethnicity	
Not Hispanic or Latino	24 (42.88)
Left blank	22 (39.3)
Hispanic or Latino	9 (16.1)
Other	1 (1.8)
Race	
White	40 (71.4)
Asian	9 (16.1)
Left blank	5 (8.9)
Black/African-American	2 (3.6)
Marital Status	
With spouse or partner	48 (85.7)
Without spouse or partner	6 (10.7)
Left blank	2 (3.6)
Income	
> $75,000	30 (53.6)
$40,001 to $75,000	10 (17.9)
< $20,000	6 (10.7)
$20,001 to $40,000	5 (8.9)
Left blank	5 (8.9)
Religion	
Christian	37 (66.1)
Unaffiliated	12 (21.4)
Other	5 (8.9)
Left blank	2 (3.6)
Covered by Health Insurance	
Yes	53 (94.6)
No	3 (5.4)
Self-assessment of Health	
Good	29 (51.8)
Excellent	19 (33.9)
Fair	7 (12.5)
Poor	1 (1.8)
Current Health	
Same	45 (80.4)
Worse	8 (14.3)
Better	3 (5.4)
Relationship	
Spouse / Significant Other	38 (67.9)
Son / Daughter	9 (16.1)
Parent	3 (5.4)
Left Blank	3 (5.4)
Brother / Sister	2 (3.6)
Son-in-law / Daughter-in-law	1(1.8)

Characteristics	Caregivers (N = 56) [mean ± SD or n (%)]
Length of time caring for patient	
> 24 months	24 (42.9)
<6 months	14 (25.0)
13-23 months	10 (17.9)
7-12 months	7 (12.5)
Left blank	1 (1.8)
Primary caregiver for others	
Yes	15 (26.8)

Note. Values are mean ± SD or (%). Data presented in order of most frequently chosen response.

Caregiver Burden, Anxiety and Depression

Table 4-2 the mean scores of the respondents on the 5 CRA dimensions and the number of caregivers crossing the threshold for burden. Table 4-3 presents the number of caregivers reporting severity of anxiety or depressive symptoms and the number of caregivers that meet criteria for either anxiety or depression. Using the thresholds for screening for the two subscales, 60.71% scored 8 or higher on the HADS anxiety subscale and 51.79% scored 8 or higher on the HADS depression subscale.

Table 4-2. Caregiver burden in caregivers of patients with brain metastases (N=56).

Dimensions of Caregiver Burden	Score Range	mean ± SD or n (%)	Burden Threshold [n (%)]
Schedule burden	5-25	17.57 ± 4.40	<20 = 39 (69.64) ≥20 = 17 (30.36)
Financial burden	3-15	7.69 ± 3.31	≥12 = 9 (16.07) <12 = 47 (83.93)
Family burden	5-25	10.43 ± 3.68	<20 = 55 (98.21) ≥20 = 1 (1.79)
Health burden	4-20	9.07 ± 3.32	<16 = 54 (96.43) ≥16 = 2 (3.57)
Caregiver esteem*	7-35	28.95 ± 4.06	<28 = 21 (37.5) ≥28 = 35 (62.5)

NOTE. Values are mean ± SD or n (%).
*Higher scores indicate increased caregiver burden except in caregiver esteem.

Table 4-3. Anxiety and depression in caregivers of patients with brain metastases (N=56)

HADS Subscales	Score Range	n (%)	HADS Screening Threshold (≥ 8)
HADS Anxiety			
Normal	0-7	22 (39.29)	
Mild	8-10	18 (32.14)	
Moderate	11-14	10 (17.86)	34 (60.71)
Severe	15-21	6 (10.71)	
HADS Depression			
Normal	0-7	27 (48.21)	
Mild	8-10	22 (39.29)	
Moderate	11-14	7 (12.50)	29 (51.79)
Severe	15-21	0 (0)	

Schedule burden as predictor of anxiety and depression

Schedule burden was a statistically significant predictor of anxiety and depression (Table 4-4). The odds of having mild to severe anxiety was 7.90 times higher (95% CI, 1.588 to 39.238; P=0.005) in caregivers who reported schedule burden as a result of their caregiving compared to caregivers who did not report schedule burden. Likewise, the odds of having mild to moderate depression was higher in caregivers who reported schedule burden compared to those who did not report schedule burden (OR=13.39; 95% CI, 2.666 to 67.268; P=<0.001).

Table 4-4. Burden, Anxiety, and Depression Odds Ratio and 95% CI

	Anxiety		Depression	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Schedule burden	7.895 (1.588-39.238)	0.005	13.393 (2.666-67.268)	<0.001
Financial burden	1.357 (0.302-6.103)	0.690	2.087 (0.466-9.346)	0.329
Family burden*	Undefined		Undefined	
Health burden*	Undefined		Undefined	
Caregiver esteem**	0.300 (.097-0.932)	0.034	0.766 (0.259-2.264)	0.629

*No cases with negative outcome in the no burden group.
**High caregiver esteem was considered as the control (no burden).

Financial burden, family burden, and health burden as predictors of anxiety and depression

Financial burden was not a significant predictor of anxiety and depression in caregivers (Table 4-4). For family burden and health burden, there were no cases with negative outcomes observed in the control (no burden) group.

Caregiver esteem as predictor of anxiety and depression

Low caregiver esteem was a statistically significant predictor of anxiety (OR=0.30, 95% CI 0.097 to 0.932; P=0.034) but not a statistically significant predictor of depression (OR=0.766, 95% CI 0.259 to 2.264; P=0.629) (Table 4-4).

Discussion

Distinctive characteristics of brain metastasis shape the nature of the caregiving experience. It symbolizes the beginning of the terminal phase of cancer, often marked by progressive focal neurological deficits and the presence of symptoms that lead to profound psychosocial distress for both the care recipient and the caregiver (Argyriou et al., 2006; Dhandapani et al., 2015; Saria et al., 2015). Cancer caregiving has been shown to increase burden, a concept frequently used in caregiving research, either as a dependent or independent variable that is often operationalized as stress, distress or strain (Chou, 2000).

Increased caregiver burden has been associated with high rates of psychological distress in advanced stage cancer and other chronic diseases (Finocchiaro et al., 2012; Papastavrou, Charalambous, Tsangari, & Karayiannis, 2012; Rumpold et al., 2015). For

this paper, we hypothesized that, similar to the findings in caregiver populations, higher caregiver burden would be associated with increased anxiety and depression.

In this study, we used the CRA for its ability to discriminate between the different dimensions of caregiver burden. In a study exploring the association between hope and burden reported by caregivers of patients with advanced cancer, the mean scores for each of the negative domains of the CRA subscales ranged from 1.8 (SD=0.6) on “lack of family support” to 2.7 (SD=0.9) on “disrupted schedule, with the score on the esteem subscale being 4.1 (SD=0.6) (Utne, Miaskowski, Paul, & Rustoen, 2013). We found slightly higher but almost similar results in our sample with mean scores for the negative domains ranging from 2.1 (SD=0.7) for “lack of family support” to 3.5 (SD=0.9) for “disrupted schedule” and 4.1 (SD=0.6) for “caregiver esteem”. Consistent with findings from other studies utilizing the CRA to measure caregiver burden (Sautter et al., 2014; Utne et al., 2013), our study indicated “disrupted schedule” as the most frequently perceived domain of burden experienced by caregivers of patients with advanced cancer.

Research reports have consistently described the high prevalence of anxiety and depression among cancer caregivers (Fridriksdottir et al., 2011) and that these symptoms can vary along the illness trajectory (Song et al., 2011). Higher anxiety and depression scores have been reported among caregivers during the palliative versus curative phase of cancer treatment even as scores for patient symptom burden were similar (Valeberg & Grov, 2012). Furthermore, studies have supported that the psychological distress of cancer caregiving not only varies during the illness trajectory but by diagnosis as well (Song et al., 2011).

For a closer comparison, data from a study involving 100 caregivers of patients with brain tumors suggest that caregivers of patients with brain tumors live with a clinically significant reduction in their quality of life and a higher level of anxiety. Using HADS, the study reported a mean score of 10.94 (SD=4.06) for anxiety and a mean score of 7.25 (SD=3.99) for depression, which were relatively higher when compared with normative data from a large population (mean score of 6.14, SD=3.76 and 3.68, SD=3.07 for anxiety and depression respectively) (Finocchiaro et al., 2012). In our study, we found that more than half of our sample screened positive for depression and about two-thirds screened positive for anxiety. Our findings are consistent with published literature that suggests a higher rate of psychological distress exists among caregivers of patients with cancer, with anxiety being the most prevalent (Rumpold et al., 2015).

A comprehensive literature review of sixteen quantitative and three qualitative research articles describing the experience of caregivers of hematological cancer patients undergoing a hematopoietic stem cell transplant found significant rates of caregiver distress (conceptualized as depression and anxiety) and reported that high levels of subjective burden were the most common predictors (Beattie & Lebel, 2011). The relationship between caregiver burden and psychological distress has been documented in conditions outside of oncology caregiving as well.

In an example involving caregivers of patients with stroke (N=150), a more acute condition than metastatic cancer, path analysis showed a direct, significant association between caregiver burden and the caregiver's emotional states (Jaracz, Grabowska-Fudala, & Kozubski, 2012). In 43 primary caregivers of children/adolescents with

meningomyelocele, significantly higher levels of anxiety and depressive symptoms were reported in subjects with higher burden than lower burden (Valenca, de Menezes, Calado, & de Aguiar Cavalcanti, 2012). The results of our study revealed that the odds of screening positive for an affective disorder were higher in caregivers of patients with brain metastasis who reported higher levels of schedule burden.

We can attribute the significant impact of caregiving on the caregivers' daily schedule to the complexity of cancer care. From initial diagnosis, cancer patients and their caregivers face the daunting task of navigating the healthcare system that has often been described as fragmented and inaccessible (Cantril & Haylock, 2013). The patients and their caregivers find themselves in labyrinthine pathways within a health system, a visual metaphor for the journey that they unwillingly began immediately after hearing the words "you have cancer". In addition to managing their day-to-day responsibilities, these caregivers are asked to manage the patients' medical needs that include, among other things, frequent encounters with healthcare professionals.

Enhancing the patient and caregiver experience can help reduce schedule burden. Improving communication and collaboration within the interdisciplinary healthcare team promotes a more efficient healthcare delivery system. In addition, oncology nurse navigators, experienced cancer nurses with disease-specific knowledge, can facilitate the implementation of patient and family-centered care throughout the continuum of cancer care and impact patient and caregiver outcomes (McMullen, 2013).

Data from published literature provides information that caregiver burden can be differentially expressed among caregivers. Caregiving involvement and caregiving

outcomes differed among four different types of caregivers (cancer, dementia, diabetes, and frail elderly); that is, cancer and dementia caregivers reported greater levels of physical burden and psychological distress than other caregivers (Kim & Schulz, 2008). One of the unwritten assumptions of this study was that caregiving for the patient with brain metastases is somewhat similar to dementia or Alzheimer's caregiving, which are generally viewed as the most burdensome caregiving experience faced by family members (Kim & Schulz, 2008). Findings from our study supported previous reports indicating that the odds of having anxiety as well as depressive symptoms are higher in family caregivers who reported who reported higher levels of caregiver burden.

Limitations

This study is limited by its small sample which allowed for a cursory analysis but not a more in-depth exploration of the relationships between the variables, including our lack of ability to control for covariates. The cross-sectional design of the study precluded us from measuring changes in variables that are likely to change over time and while our measure of caregiver burden (CRA) allowed us to investigate the multidimensional nature of caregiver burden, it limited us from comparing our results with other measures of overall caregiver burden. Another limitation of the study is that our sample was not demographically diverse (ethnicity, income, relationship to care receiver). There is growing evidence that demographic variables and caregiver-care receiver relationship can differentially impact the caregiving experience. Additionally, our study design does not allow interpretation of the direction of causality. While our data show that schedule burden can be a predictor of anxiety, we are unable to verify a direct causal relationship

between the two variables. One can argue that anxiety can precede the caregiving role and that the presence of anxiety and/or depression influenced the perception of burden. A future longitudinal study will help establish causality amongst the variables. In consideration of these limitations, we caution the readers to interpret our conclusions as exploratory.

Summary

Cancer caregivers represent the hidden morbidity of cancer. The identification and management of caregiver burden, a consequence of a number of interrelated conditions within the caregiving experience, is an important consideration for a comprehensive cancer care program. As healthcare providers prepare to see an increase in cases of brain metastases, it becomes increasingly significant to address the needs of the caregiver, the “other patient” who is at an increased risk for various psychological, physical, financial, and social problems.

Published research on caregiver burden has examined selected populations, with primarily caregivers of patients with dementia and patients at the end of life as two of the most studied groups. Results across studies examining single populations suggest that there may be differences in caregiver burden with different diseases. However, in the absence of direct comparisons within a single study, it is difficult to know whether these are true differences or whether they result from differences in methods across the individual studies (Garlo et al., 2010).

Within neuro-oncology, caregiving research has focused on caregivers of patients with primary brain tumors and has remained relatively silent on the burden of

caregivers of patients with brain metastases. In addition, there has been a limited examination of caregiver versus patient characteristics associated with burden. Findings from this study contributed a more accurate description of caregiver characteristics within the context of caregiving for a loved one with brain metastases. These findings will support and direct future research efforts with the ultimate aim of improving the care of cancer caregivers.

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CHAPTER V: MANUSCRIPT 3

Cognitive Dysfunction in Patients with Brain Metastases: Influences on Caregiver Resilience and Coping

Abstract

Neurologic deficits that may be manifested as cognitive impairment may contribute to the challenges faced by caregivers of patients with brain metastases. The dynamic and multidimensional nature of caregiver burden requires the analysis of variables that may affect the caregivers' appraisal of the burden brought about by their perception of the patients' cognitive impairment. For this paper, we explored the relationships between the patients' cognitive impairment, caregiver resilience, and caregiver coping strategies. The study is an analysis of a cross-sectional self-reported data among caregivers of patients with brain metastases. For data analysis, Spearman's rho was used to examine correlations between the patients' cognitive impairment and caregivers' coping and resilience. In our sample, we found a significant correlation between the coping strategy "acceptance" with two dimensions of the patient's cognitive and behavioral status. Additionally, we found that the coping strategy "focus and venting of emotions" correlated with disruptive behavior. Findings from this study are valuable for identifying coping strategies and individualizing interventions to enhance the coping skills of individual caregivers.

Introduction

The number of people of all ages in the U.S. who have cancer is projected to grow to 18.1 million in 2020, a 30% increase from 2010 (Mariotto, Yabroff, Shao, Feuer, & Brown, 2011). This number correspondingly expands the population at risk for developing brain metastases, with the reported annual incidence estimated between 98,000 and 170,000 (Hutter, Schwetye, Bierhals, & McKinstry, 2003; Levin, Leibel, & Gutin, 2001; National Cancer Institute, 2010). Brain metastases can elicit rapid deterioration in quality of life (QOL) brought on by progressive neurologic deficits which can be a daunting challenge for family caregivers (Saria et al., 2015). Neurologic deficits that may be manifested as cognitive impairment may contribute to the challenges faced by caregivers of patients with brain metastases. It is therefore important to examine how caregivers respond to these challenges and explore the relationship between the patient's cognitive impairment and caregiver resilience and coping.

It has been reported that greater than 80% of the care needed by patients during initial treatment phases, and close to 60% during the last year of life (Warren, Mariotto, Meekins, Topor, & Brown, 2008) are provided by family caregivers. While family caregiving can be regarded as rewarding and positive, studies have shown the negative emotional (e.g., depression and anxiety) and physical (e.g., altered immune function, hypertension, poor overall physical health) consequences of caregiving on the caregiver (Sherwood et al., 2008). Furthermore, studies have documented a reduction in caregiver QOL with increased responsibilities (Munoz et al., 2008).

Cognitive impairment

While there is a wealth of literature on caregiver burden in cancer, more information is needed on a variety of predictors of caregiver burden, including situational and personal factors, (e.g., patients' cognitive functioning and caregivers' coping and resilience). In patients with primary brain tumors, cognitive impairment has been identified as a leading cause of disability and the single greatest cause of patient distress (Locke et al., 2008) that potentially contributes to increased caregiver burden. In a study of patients with high-grade gliomas, alterations in cognitive function were shown to reflect the severity of the underlying disease, which was not always apparent in measurements of functional or performance status such as the Karnofsky or Barthel scores (Klein et al., 2003). Assessment of patients' cognitive functioning can help determine the differential contributions of the neurocognitive effects of brain metastases on caregiver burden (Farace, 2008).

What makes the experience of caregivers of patients with brain metastases unique is that caregivers are forced to deal not only with the emotional sequelae of a metastatic cancer diagnosis but also with the physical and cognitive consequences that accompany the brain metastases (Khalili, 2007). Sherwood and colleagues (2005) described the relationship between the burden experienced by the caregiver and the cognitive impairment exhibited by the patient as being worsened by "the unpredictable and multidimensional nature of the care demands along with the loss of personhood by someone intimate to the caregiver" (p.129). The relationship between the patients' cognitive function and caregiver burden, often defined as a negative appraisal and perceived stress resulting from caring for an individual, warrants further investigation

because literature in this area is scant. In addition, the dynamic and multidimensional nature of caregiver burden requires the analysis of variables that may affect the caregivers' appraisal of the burden brought about by the patients' cognitive impairment. These variables include resilience, an inherent personality characteristic that can be developed throughout the caregiving trajectory, and coping, the caregivers' response to burden.

Caregiver resilience and coping

Resilience may affect the variability in caregiver burden by decreasing the likelihood of experiencing distress from caring for a cognitively-impaired individual or increasing the benefits derived from social support. It is a variable that can influence the perception of caregiver burden and have a protective effect on various health outcomes in cancer caregivers.

Coping, described as voluntary internal psychological processes to address the demands created by stressful events, is recognized as a mediator of stress-related mental and physical health outcomes that carries a significant intervention potential (Taylor & Stanton, 2007). Interventions aimed at improving the coping skills of caregivers have shown positive results. They can easily be individualized to fit the needs of individual caregivers and have been shown to be effective in moderating the burden or distress associated with the caregiving experience (Chen, Huang, Yeh, Huang, & Chen, 2015). Coping can be considered effective to the extent that caregiver burden is reduced. One of the frequently used measures to assess the many different ways individuals respond to increased demands is the COPE inventory (Carver,

Scheier, & Weintraub, 1989). The COPE inventory measures 15 conceptually distinct aspects of coping. An additional two subscales measuring emotional processing and emotional expression were embedded in the COPE inventory to dispute the traditional conceptualization that emotional-approach coping is maladaptive (Stanton, Kirk, Cameron, & Danoff-Burg, 2000).

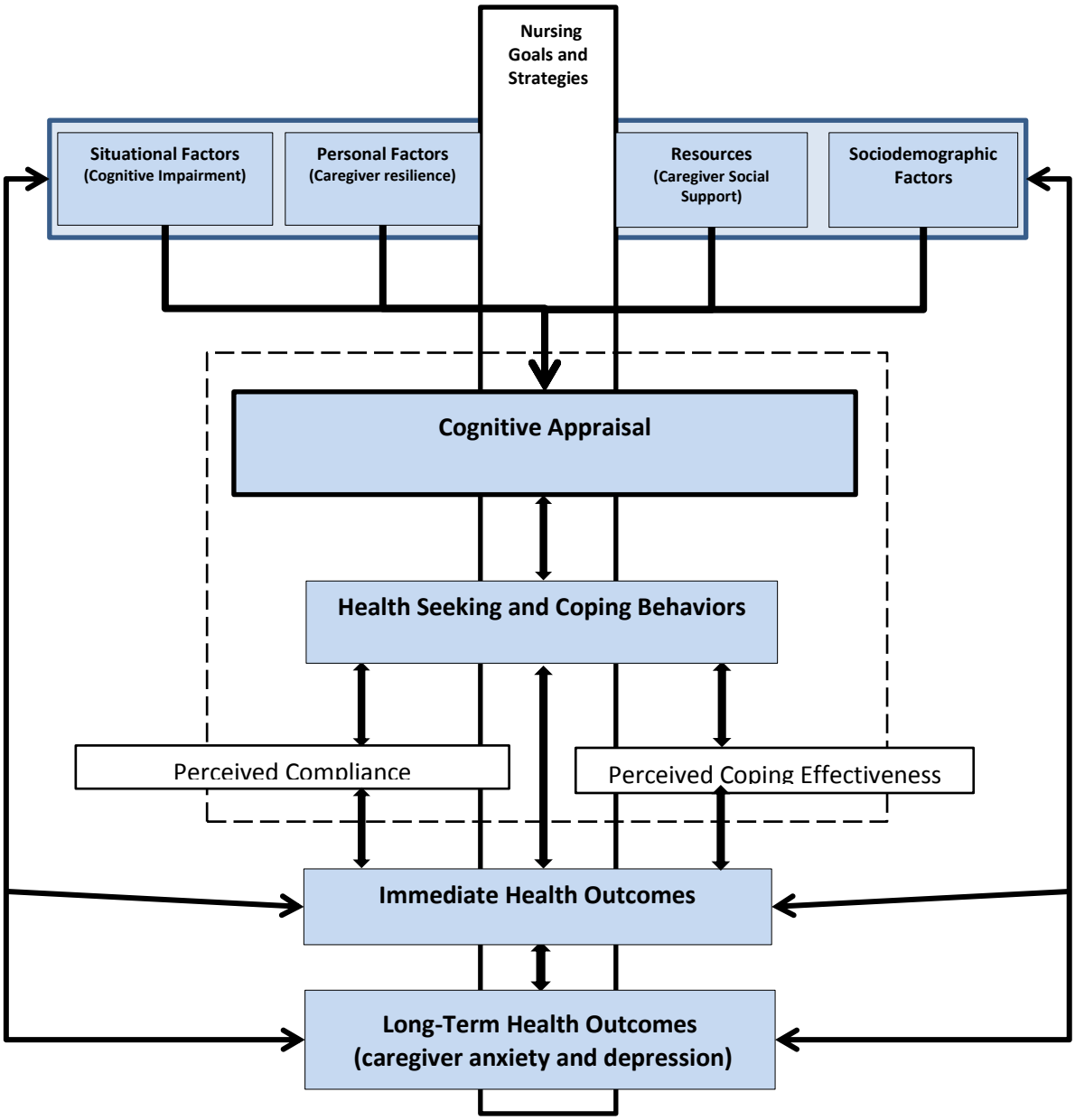
The Comprehensive Health Seeking and Coping Paradigm: A conceptual framework for caregiver research

Caregiving research is driven by multiple disciplinary perspectives and theoretical orientations (Pearlin, Mullan, Semple, & Skaff, 1990). One of the most common approaches used to guide caregiving research is from the perspective of the stress process. For this study, we adapted the Comprehensive Health Seeking and Coping Paradigm (CHSCP) (Nyamathi, 1989), a framework that merged components of the Schlotfeldt Paradigm of Health Seeking Behaviors and the Lazarus Theoretical Schema of Coping and Adaptation, to describe causal antecedents and mediating variables that influence long-range adaptational consequences guided by the nursing perspective on health seeking and coping (Lazarus & Folkman, 1984; Nyamathi, 1989; Schlotfeldt, 1975).

The CHSCP is a complex, multi-dimensional framework that depicts the highly interactive relationship among its 12 components (Berg, Nyamathi, Christiani, Morisky, & Leake, 2005; Nyamathi, 1989; Nyamathi, Stein, & Bayley, 2000; Nyamathi et al., 2010; Washington, Moxley, & Taylor, 2009). For this paper, we explored the relationships between the patients' cognitive impairment as a surrogate for CHSCP's

situational factors, caregivers' resilience as the measure for personal factors, and caregivers' coping strategies (Figure 5-1).

Figure 5-1. Conceptual Framework: The Comprehensive Health Seeking and Coping Paradigm



The purpose of this study was to examine the impact of the patients' cognitive impairment on caregiver resilience and caregiver coping strategies. The study was guided by the following research questions:

1. What is the level of observed cognitive impairment among patients with brain metastasis?
2. For caregivers, what is the frequency of utilization of the 15 conceptually-distinct aspects of coping and the 2 aspects of emotional-approach coping?
3. What is the extent of the caregiver's perceived resilience?
4. Is cognitive impairment negatively associated with caregiver resilience?
5. Is caregiver-perceived cognitive impairment associated with specific, caregiver coping strategies?

METHODS

Design

The study was registered with the Institutional Review Board (IRB) Reliance Registry of a University System. Upon the approval of the reviewing IRB of the academic institution and the Relying IRB at the study accrual site located on a different campus, we initiated the study using a cross-sectional analysis of self-reported data among caregivers of patients with brain metastases. Data were obtained using a survey instrument that had undergone pilot testing using a small group of cancer caregivers. Given that all but the demographics section of the survey were already tested for validity and reliability, pilot testing of the survey instrument was conducted to appraise possible trends in missing data, determine clarity of instructions, seek feedback on the formatting

and organization of the instruments, estimate time to completion, and desirability and ease of use.

Sample

The sample for the study consisted of family caregivers of patients with brain metastases. A waiver of informed consent was granted by the IRB for the patients with brain metastases who were acknowledged as secondary subjects based on Title 45 Code of Federal Regulations Part 46. Convenience sampling was used to enroll eligible caregivers at a National Cancer Institute-Designated Cancer Center in Southern California. Inclusion criteria were: (a) age ≥ 18 years; (b) self-identified primary caregiver of patients diagnosed with brain metastasis, (c) able to speak, read, and understand English, (d) willing to participate in completion of surveys, (e) co-resided with the patient with brain metastasis, and (f) provided a minimum of 4 hours of direct care for at least 3 days per week. Inclusion criteria were not limited by type of relationship such as spouse, parent, child, sibling, and friend, nor by the duration of caregiving role or the level of dependency.

Procedure

Recruitment of subjects involved the use of informational flyers and brochures that described the study and included the criteria for enrollment and contact information of the research team. Flyers were provided to physicians and staff in three departments (multispecialty cancer clinic, infusion center, and radiation oncology clinic) within an academic cancer center. Participants who granted permission to be contacted by the study team were approached and were offered more information about the study.

Eligible subjects who agreed to participate in the study and signed the consent form were given the option to mail or hand-deliver the completed survey. Those who opted to complete the survey by mail were provided with a survey packet that included a cover letter with a copy of the consent that described the rights of study participants, risks and benefits of participating, anticipated time to complete the survey and their right to withdraw at any time. The cover letter also explained the study requirements. The survey instrument and a self-addressed, stamped envelope for returning the documents were also included in the packet. Participants who agreed to participate were provided with a $5.00 gift card as a small token of appreciation.

The study team received 56 completed surveys from 104 caregivers, yielding a response rate of 53.8%. The response rate was within the range for mail-in surveys but lower when compared to similar cancer caregiving studies (Hanly, Maguire, Hyland, & Sharp, 2015; Hartnett, Thom, & Kline, 2016). Since demographic or identifying data were not collected during the screening and consenting process, we were not able to distinguish between responders and non-responders.

Instruments

Caregiver Data Form. An instrument was developed from the relevant literature to collect socio-demographic data, employment and financial status, educational status, and health condition. In addition, the caregivers were asked to recall the history of present illness, including the date of initial diagnosis of the primary cancer, date of diagnosis of the brain metastasis, cancer treatment modalities received, and other comorbidities.

Cognitive Dysfunction. The caregiver's perception of the patient's cognitive dysfunction was measured using a modified version of the Revised Memory and Behavior Problems Checklist (RMBC), a brief, conceptually, and psychometrically sound instrument for assessing behavioral problems (Roth et al., 2003; Teri et al., 1992). The modified RMBC (mRMBC) uses the same 24 stimulus phrases as the origin. The phrases represent observable behavioral problems. It provides one global score and 3 subscale scores for memory, depression, and disruptive behavior. The modification was to change from Likert-type scale responses indicating frequency of each problem (0 = never and 4 = daily or more often) to "yes" or "no" indicating if the problem had occurred during the past week (Roth et al., 2003). Behaviors that have occurred in the past week were then scored on caregiver reaction using a 5-point Likert scale where 0 = not at all bothersome or upsetting to 4 = extremely bothersome or upsetting. Cronbach's alpha for the mRMBC ranged from .55 to .78 for the number of problems subscales and .73 to .87 for the total reaction subscales. Spearman rank-order correlation between the mRMBC scores and the Center for Epidemiological Studies Depression (CES-D) Scale revealed moderate positive correlations (Roth et al., 2003).

Resilience. Caregiver resilience was measured using the Resilience Scale (RS-25) developed by Wagnild and Young (1993). Caregivers were asked to state the degree to which they agreed or disagreed with each of the 25 items on this scale that were scored on a 7-point scale, with 1=disagree and 7=agree. Possible scores ranged from 25 to 175 with higher scores reflecting higher resilience. The reported internal consistency was high with a coefficient alpha of 0.91 and item-to-total correlations

ranged from 0.37 to 0.75, with the majority falling between 0.50 and 0.70 ($p \leq .001$). Principal components factor analysis of the instrument indicated the presence of two factors (Personal Competence and Acceptance of Self and Life) indicated positive correlations with adaptational outcomes (i.e., life satisfaction, $r= 0.30$; morale, $r= 0.28$) and a negative correlation with depression ($r= -0.26$) supported concurrent validity of the RS-25.

Coping. The coping responses of the caregiver were measured by the COPE Inventory (Carver et al., 1989) and the Emotional-Approach Coping (EAC) Scale (Stanton et al., 2000). The COPE Inventory is a 60-item questionnaire that was developed to assess a broad range of coping responses, specifically to assess the different ways people respond to stress. The scale assessed 15 conceptually-distinct methods of coping and respondents were asked to rate the frequency with which they utilized each strategy based on a Likert-type scale, ranging from 1 (“I usually don’t do this at all”) to 4 (“I usually do this a lot”). Scores on each subscale range from 4 to 16, with higher scores indicating greater use of that coping strategy. Cronbach’s alpha reliability coefficients for the majority of scales ranged from $\alpha= 0.45$ to 0.92 with one scale falling below 0.6.

The EAC Scales, which are typically embedded in the COPE Inventory, has also, undergone psychometric testing that revealed high internal consistency, test-retest reliability, convergent and discriminant validity. The EAC includes 2 subscales (emotional processing and emotional expression) of 8 items for each. Similar to the COPE Inventory, respondents were asked to rate each item on a 4-point scale. Subsequent tests supported the predictive validity of the scales with regard to

adjustment to stressful encounters (Stanton et al., 2000). Cronbach's alpha for the 8-item scales ranged from 0.72 to 0.94, with correlations for test-retest reliabilities ranging from 0.63 to 0.89 (Stanton et al., 2000).

Data Analysis

IBM SPSS 21.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive data, including frequencies and percentages of demographic variables were used to describe the sample. Frequency scores for memory-related problems, affective distress, and disruptive behaviors were determined by adding the scores on items that had a frequency rating of 1 while reaction scores for the subscales were determined by adding the score for each of the items on the subscale.

The frequency of behavioral problems, the caregiver reaction to memory and behavioral problems of patients, and the utilization of coping strategies of caregivers were summarized as means and standard deviations. The scores for caregiver resilience were summed and categorized into 6 categories ranging from "very low" to "high" as recommended in instrument scoring instructions (Wagnild & Young, 1993) and summarized as frequencies and percentages. In scoring instruments, missing items missing were imputed as the average of non-missing items in the subscale, assuming that data were missing at random. Spearman's rho was used to examine correlations between the patients' cognitive impairment and caregivers' coping and resilience. Statistical significance was set at $p < .05$.

Results

Description of the sample population

The mean age, sex, education, race, marital status, employment status, household income, health insurance, perceived health, relationship to the care recipient, and caregiving responsibility (Table 5-1). Most caregivers were women (69.6%, n = 39) and white (71.4%, n = 40) with a mean age of 56.3 years. Caregivers were most often the spouses or the significant others of care recipients (67.9%, n = 38) and a subset of caregivers reported they were also the primary caregiver for at least one other individual in addition to the care recipient with brain metastasis (26.8%, n = 15).

Table 5-1. Demographics of caregivers of patients with brain metastasis. (N=56)

Characteristics	Mean ± SD or n (%)
Age (years)	56.3 ± 14.9
Gender	
Female	39 (69.6%)
Male	17 (30.4%)
Education	
College grad	19 (33.9)
Some college	18 (32.1)
Graduate degree	16 (28.6)
Grade school	1 (1.8%)
High School	1 (1.8%)
Missing data	1 (1.8%)
Ethnicity	
Not Hispanic or Latino	24 (42.9)
Hispanic or Latino	9 (16.1)
Other	1 (1.8)
Missing data	22 (39.3)
Race	
White	40 (71.4)
Asian	9 (16.1)
Black/African-American	2 (3.6)
Missing data	5 (8.9)
Marital Status	
With spouse or partner	48 (85.7)
Without spouse or partner	6 (10.7)
Missing data	2 (3.6)
Income	
> $75,000	30 (53.6)
$40,001 to $75,000	10 (17.9)
< $20,000	6 (10.7)
$20,001 to $40,000	5 (8.9)
Missing data	5 (8.9)

Characteristics	Mean ± SD or n (%)
Religion	
Christian	37 (66.1)
Unaffiliated	12 (21.4)
Other	5 (8.9)
Missing data	2 (3.6}
Covered by Health Insurance	
Yes	53 (94.6)
No	3 (5.4)
Self-assessment of Health	
Good	29 (51.8)
Excellent	19 (33.9)
Fair	7 (12.5)
Poor	1 (1.8)
Self-assessed health status compared to 6 months ago	
Same	45 (80.4)
Worse	8 (14.3)
Better	3 (5.4)
Relationship	
Spouse / Significant Other	38 (67.9)
Son / Daughter	9 (16.1)
Parent	3 (5.4)
Brother / Sister	2 (3.6)
Son-in-law / Daughter-in-law	1(1.8)
Missing data	3 (5.4)
Length of time caring for patient	
> 24 months	24 (42.9)
<6 months	14 (25.0)
13-23 months	10 (17.9)
7-12 months	7 (12.5)
Missing data	1 (1.8)
Primary caregiver for others	
Yes	15 (26.8)

Note. Values are mean ± SD or n (%).

What is the level of observed cognitive impairment among patients with brain metastasis?

The sample means on the mRMBC frequency subscales were 3.52 ± 2.42 for memory, 2.34 ± 2.12 for depression, 1.32 ± 1.63 for disruptive behavior, with a total mean of 2.39 ± 2.26. Caregivers reported that memory-related problems occurred more frequently compared to depression and disruptive behavior. The mRMBC reaction subscale means were 4.50 ± 5.63, 4.59 ± 5.74, 2.14 ± 3.57, and 3.74 ± 5.18 for memory, depression, disruptive behavior, and total reaction, respectively. Table 5-2 incudes the possible range for each of the subscales.

Table 5-2. Scores for the modified version of the Revised Memory and Behavior Problem Checklist

mRMBC Subscale	Behavior Frequency		Caregiver Reaction	
	Possible Range	Mean ± SD	Possible Range	Mean ± SD
Memory	0-7	3.52 ± 2.42	0-28	4.50 ± 5.63
Depression	0-9	2.34 ± 2.12	0-36	4.59 ± 5.74
Disruptive behavior	0-8	1.32 ± 1.63	0-32	2.14 ± 3.57
Total Score	0-24	2.39 ± 2.26	0-96	3.74 ± 5.18

What is the frequency of utilization of the 15 conceptually-distinct aspects of problem-and emotion-focused coping and the 2 aspects of emotional-approach coping?

The most frequently used coping strategies included acceptance, planning, positive reinterpretation and growth, active coping, and suppression of competing activities. The least frequently used strategies included substance use, denial, and behavioral disengagement. For the EAC scale, mean score for emotional processing was 2.61 ± 0.68 and the mean score for expression was 2.47 ± 0.69 (Table 5-3).

Table 5-3. Distinct aspects of coping using the COPE Inventory and the Emotional Approach Coping scales (N=56).

COPE Inventory (range 1 - 4)	Mean ± SD
Acceptance	3.28 ± 0.60
Planning*	3.08 ± 0.68
Positive reinterpretation and growth	2.95 ± 0.81
Active coping*	2.88 ± 0.61
Suppression of competing activities*	2.76 ± 0.72
Religious coping	2.69 ± 1.17
Use of emotional social support	2.57 ± 0.75
Use of instrumental social support*	2.45 ± 0.82
Restraint*	2.38 ± 0.52
Focus on and venting of emotion	2.29 ± 0.69
Mental disengagement	2.19 ± 0.48
Humor	1.83 ± 0.90
Behavioral disengagement	1.59 ± 0.58
Denial	1.45 ± 0.71
Substance use	1.31 ± 0.59
Emotional Approach Coping (range 8 to 32)	Mean ± SD
Emotional Processing	2.61 ± 0.68
Emotional Expression	2.47 ± 0.69

*Problem-focused coping strategies

What is the extent of the caregiver's resilience?

For resilience, the caregivers scored an overall mean of 146.36 ± 17.02 (range 25-175) on the RS-25. Most caregivers scored moderate to high on the scale (n=43, 77%) (Table 5-4).

Table 5-4. Resilience (N = 56)

Resilience Category	Possible Range	N (%)
Very low	25-100	0 (0)
Low	101-115	3 (5.36)
On the low end	116-130	10 (17.86)
Moderate	131-145	8 (14.29)
Moderately high	146-160	24 (42.86)
High	161-175	11 (19.64)

Is cognitive impairment associated with specific, caregiver coping strategies?

In our sample, the coping strategy *acceptance* correlated significantly with the *memory* and *disruptive behavior* subscales of the mRMBC, both for frequency of occurrence and strength of reaction (Table 5-5).

Table 5-5. Spearman's Rho Correlation for mRMBC and Coping/EAC (reporting only coping subscales with statistically significant results)

mRMBC		Positive Re-interpretation or Growth	Mental Dis-engagement	Active Coping	Denial	Religious Coping	Acceptance
Memory	Frequency	-0.07	0.13	0.08	-0.18	0.00	0.31*
	Reaction	-0.15	0.28*	0.07	-0.20	-0.25	0.28*
Disruptive behavior	Frequency	0.28*	0.11	0.20	-0.24	0.28*	0.42**
	Reaction	0.12	0.08	0.15	-0.14	0.03	0.33*
Depression	Frequency	0.01	-0.01	0.27*	0.07	-0.14	-0.04
	Reaction	-0.09	0.05	0.26	0.27*	-0.21	-0.08

*P<0.05
**P<0.01

Is cognitive impairment associated with caregiver resilience?

In our sample, only the frequency of memory problems measured by the mRMBC had a significant negative correlation with caregiver resilience. There was no

correlation between caregiver resilience and the mRMBC subscales for disruptive behavior and depressive symptoms (Table 5-6).

Table 5-6. Spearman's Rho Correlation for Resilience and mRMBC

	Memory		Disruption		Depression	
	Frequency	Reaction	Frequency	Reaction	Frequency	Reaction
Resilience	-0.30*	-0.24	0.005	0.03	-0.21	-0.11

*P<0.05

Discussion

Cognitive impairment among patients with brain metastasis

In this study, the mRMBC was used for caregivers to rate the frequency of behavioral problems of the patient with brain metastasis. A study measuring neurocognitive function in patients with brain metastasis found that despite a high functional status, most of the patients demonstrated memory impairment (Herman et al., 2003). In our sample, memory problems were the most frequently reported problem and the problem behavior that bothered caregivers the most. Our results were consistent with findings from a previous research study using the mRMBC in patients with dementia (Roth et al., 2003). In contrast, a study conducted among caregivers of patients with Alzheimer's disease revealed that memory problems were most frequently reported, but disruptive behaviors elicited the most negative reactions (Robinson, Adkisson, & Weinrich, 2001).

Cognitive deficits create care demands for the caregivers and increase the number of tasks with which the caregiver must render assistance. In patients with primary brain tumors, cognitive dysfunction has been consistently linked to increased caregiver demands (Sherwood et al., 2006) and when compared with functional status,

cognitive status was found to be a much stronger predictor of caregiver burden (Pinquart & Sorensen, 2003).

In addition to the impact of cognitive impairment on caregiver burden, in patients with intracranial tumors, cognitive function has now become an important marker to determine whether a positive neuroimaging response truly translates into a clinical benefit for the patient (Weller, 2011). However, congruence of caregiver assessment with clinical assessment by trained neuropsychologists or with the use of validated battery of standardized neurocognitive tests need to be further explored.

Coping among caregivers of patients with brain metastasis

Coping strategies used by caregivers are important variables to consider within the context of this study. Coping is conceptualized as an effort made by the caregiver to manage the burden of caregiving regardless of the outcome.

Our results revealed that the most frequently used coping strategies included acceptance, planning, positive reinterpretation/growth, active coping, and suppression of competing activities. The least frequently used strategies included substance use, denial, and behavioral disengagement. Interestingly, these clusters of coping strategies, made up of what theoretically can be classified as adaptive (frequently used strategies) and questionable (less frequently used strategies) coping strategies, have been found to be correlated, albeit weakly (Carver et al., 1989). Acceptance is a functional coping response that is particularly important in situations wherein the stressor is something that requires adaptation, in contrast to a stressor that can be altered.

Planning and active coping are problem-focused coping strategies that involve outlining and executing direct action; and suppression of competing activities relates to eliminating distraction to allow focus on the task at hand (Carver et al., 1989). For the EAC scale, emotional processing and expression were reported at similar levels. Use of emotional processing is an active attempt to acknowledge and understand emotions, while use of emotional expression is said to assist in regulating the individual's social environment (Stanton et al., 2000).

Resilience in caregivers of patients with brain metastasis

While numerous papers have been written about resilience in caregivers of neurocognitively-impaired individuals (Foster, 2010; Harmell, Chattillion, Roepke, & Mausbach, 2011; O'Rourke et al., 2010; Wilks, 2008; Wilks & Croom, 2008; Wilks, Little, Gough, & Spurlock, 2011; Zauszniewski, Bekhet, & Suresky, 2010), few studies examined resilience in caregivers of patients with cancer. Resilience may affect the variability in caregiver burden by decreasing the likelihood of experiencing distress from caring for a cognitively-impaired individual or increasing the benefits derived from resources that serve as protective factors (Harmell et al., 2011). Our sample's mean score RS-25 scale score were within the average range of RS-25 scores in multiple studies involving a variety of individuals of different ages, socioeconomic, and educational backgrounds (range 140-148) (Wagnild, 2009). Previously published studies have reported a positive correlation between higher resilience scores and positive factors, i.e., coping effectiveness and optimism, and an inverse relationship between resilience and perceived burden and depression (Wagnild & Collins, 2009).

Future research using RS-25 should include longitudinal studies to measure how resilience changes over time.

Cognitive impairment and caregiver coping strategies

In our sample, the caregiver coping strategy acceptance was found to be significantly correlated with care recipients' memory problems and disruptive behavior. Acceptance is an active coping strategy in situations where the stressor is not likely to change (Carver et al., 1989).

Very few studies have investigated the association between caregivers' coping and care recipients' cognitive impairment. One recent study in patients with dementia reported an association between higher care-recipient neuropsychiatric symptoms at baseline with less use of behavioral and mental disengagement strategies by caregivers (Snyder et al., 2015). Another study indicated that caregivers tend to fall back on emotion and avoidance style coping strategies as cognitive impairment increases (Wilks et al., 2011). One could assert that dysfunctional coping strategies utilized in highly stressful situations associated with cognitive impairment or neuropsychiatric symptoms aggravates perceived caregiver burden subsequently leading to poorer caregiver outcomes, i.e., depression, illness, and diminished QOL (Snyder et al., 2015).

Most literature exploring caregiver coping strategies emphasizes the moderating or mediating effect of coping on caregiver burden and/or long-term outcomes- in the patients who are the recipients of care or in the caregivers themselves (Snyder et al., 2015; Tschanz et al., 2013). One perspective that we wanted to highlight based on the results of our study is the causal relationship between variables. The results that we

have presented in this paper show a correlation between acceptance as a coping strategy and the caregivers' perception of the frequency and their reaction to the care recipients' memory problems and disruptive behavior; but correlation does not necessarily establish causation. We do not have an evidence for the relationship between acceptance as a coping strategy and memory problems and disruptive behavior. It can be argued that caregivers who have fewer resources and/or more perceived distress are coping more and therefore have higher coping scores.

Cognitive impairment and caregiver resilience

Consistent with a previously published study, our data shows that frequency of memory problems in patients with brain metastases had a significant negative correlation with caregiver resilience, that is, more frequent memory problems were associated with less resilience (Wilks et al., 2011). This finding is important in the context of evaluating caregiver coping strategies and care-receiver's cognitive impairment because caregivers who use problem-focused coping strategies generally perceive themselves as more resilient (Wilks et al., 2011). In addition, the observation that caregivers tend to fall back on emotion and avoidance-style coping strategies as cognitive problems increase has to be further studied. Resilient caregivers were found to have a better outlook, higher quality relationship with the care recipient, well-informed, adequately supported, and appropriate users of healthcare resources (Joling et al., 2015).

Limitations and Future Research

This study is not without its limitations. We have a small sample that precluded more complex analyses, such as regression analyses for each type of coping and resilience scores (not categories). We have already planned to conduct future replication studies with larger and more varied samples to confirm the generalizability of our findings. The cross-sectional design of our study also prevented us from capturing changes that may occur over time, an important concept to integrate in a patient population that may exhibit worsening cognitive function during their disease course. The lack of diversity in the demographic characteristics of our sample (ethnicity and income) and in the caregiver-care receiver relationship add to the limitations of our study. These variables have been shown to differentially impact the caregiving experience. In addition, the cross-sectional design restricted the analysis of causality and directional relationships among the variables. Another limitation is that cognitive impairment was measured using a proxy rating by the caregiver, however, it is important to note that the conceptual framework takes cognitive appraisal into consideration. The caregiver's perception of the patients' cognitive impairment may still be independent of the clinical assessment of the patients' cognitive functioning by a neuropsychologist or through a battery of neurocognitive assessment tests. A more comprehensive analysis of the relationship between the variables is warranted. Future studies need to examine the congruence among caregiver assessments, a battery of cognitive tests, and neurocognitive evaluations.

Conclusion

Patients with brain metastases often endure a variety of neurological, cognitive, and emotional problems which, even with the slightest impairment, can significantly alter QOL. In the past years, these problems have not been adequately addressed due to the dismal outcome associated with the diagnosis. Assessment and interpretation of neurocognitive function in patients with brain metastases is confounded by multiple variables that include neurotoxic effects of previous anti-cancer therapies and supportive care agents and the presence of mood disorders. Neurocognitive assessment includes measures of general intellectual functioning (i.e., IQ), language, memory, attention, information processing speed, motor speed and dexterity, and executive functioning (Witgert & Meyers, 2011).

In this study, we gained insight into the complex relationships between the patient's cognitive dysfunction and the caregiver's coping styles and resilience. Given the protective effect of problem-focused coping in resilience and the high likelihood for caregivers to utilize less effective coping strategies in instances of worsening cognitive dysfunction, nurses need to systematically assess the coping strategies of caregivers and deliver a more individualized, personalized approach to enhance effective coping among caregivers of patients with brain metastases.

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CHAPTER VI: CONCLUSION AND IMPLICATIONS

Conclusion

Caregiving is a highly individualized experience as demonstrated in caregivers of patients with brain metastases. Whether expressed or implied, the responsibilities they take on upon assuming the caregiving role place additional demands that the caregivers must adapt to and cope with. While some demands of caregiving are more likely to increase caregiver burden, every caregiver has a different threshold and the variation in responses are as diverse as the characteristics of caregivers.

What is unique about the features of caregiving in patients with brain metastases that would warrant the development of a program of research that does not duplicate the work already done with other caregiver populations? As described in previous chapters, improving long-term survival of patients has corresponded with an increased incidence of brain metastases. This sequence of events in the trajectory of patients with cancer has extended the length of the caregiving experience. In addition, the universal concerns about disease recurrence or progression that are unique to cancer predisposes the patient and the caregiver to uncertainty and stress. Likewise, the diagnosis of cancer takes the patient and their caregiver through a journey that winds through unique mileposts (i.e., initial diagnosis, treatment, survivorship, recurrence, progression, and end of life). The route that the patient with cancer and the caregiver take can be a direct path to remission or end-of-life, but can also maneuver them in a path that circles through these mileposts. Lastly, developments in cancer research has increased the complexity of cancer treatment as new therapies, devices, and clinical trials are now available to patients when only a years ago, options for further treatment

would not have existed. All these contribute to the demands placed upon the patient and their caregivers.

The first paper presented in this dissertation, *The hidden morbidity of cancer-Burden in caregivers of patients with brain metastases*, is a literature review that describes the challenges of caregiving in brain metastases and highlight the implications for healthcare professionals. In this paper, we have described the critical attributes of caregiver burden: subjective perception, multidimensional phenomena, dynamic change, and overload. These attributes have been examined in many caregiver studies within a variety of diagnoses and health conditions. The paper also described the demands of caregiving, classifying them into primary and secondary demands, where primary demands are dictated by direct health-related needs of the care receiver and secondary demands are determined by factors outside the environment of the caregiver-patient dyad, i.e., family, work and society. Lastly, the paper presented the consequences and outcomes of caregiver burden. While the paper mostly describes the negative consequences of caregiving, it acknowledges the growing body of work highlighting positive outcomes and more general well-being considerations for the individual in the caregiving role.

The second paper, *Anxiety and Depression Associated with Caregiver Burden in Caregivers of Patients with Brain Metastasis*, presents the analysis of the relationships between caregiver burden and the affective disorders anxiety and depression. In this paper, we looked at how the dimensions of caregiver burden (i.e., disrupted schedule, financial problems, lack of family support, health problem, and caregiver esteem) can be used as a predictor of anxiety and/or depression in caregivers of patients with brain

metastases. In our sample, we found that caregivers who reported increased schedule burden were at an increased risk of screening positive for anxiety and depression. Healthcare providers need not only identify the caregivers at risk but proactively address the risk for schedule burden through effective interdisciplinary collaboration, improved communication, and commitment to patient and family-centered care. Findings from our study will be useful in developing a comprehensive caregiver assessment that must be incorporated as a formal program in institutions providing cancer care.

The third paper, *Cognitive dysfunction in patients with brain metastases: Influences on caregiver resilience and coping*, examined the impact of the patient's cognitive impairment on caregiver resilience and caregiver coping strategies. The patient's cognitive impairment can increase the demands placed on caregivers and this paper explored the relationship between the increased demand and the caregiver's response. With our small sample, we found a significant correlation between the coping strategy *acceptance* with two dimensions of the patient's cognitive and behavioral status. Findings from this study are valuable for identifying coping strategies and individualizing interventions to enhance the coping skills of individual caregivers. One of the personal research interests of the primary investigator is to determine congruence in cognitive assessment among a professional neuropsychological evaluation, cognitive assessment using a battery of validated tests, and caregiver's proxy rating as demonstrated in this study. Determining the reliability of a caregiver proxy rating has implications for instrumentation in caregiving research and in the screening or clinical assessment of patients in need of a cognitive evaluation.

Implications for Research

The findings on the impact of burden on caregiver health presented in the literature are equivocal. While there are numerous studies on caregiver burden in a variety of populations, it remains difficult to generalize findings across studies, in part because of the wide variety of instruments used to measure constructs related to caregiver burden and the conceptualization of caregiver burden in empirical research as either a predictor or an outcome. One such study that contradicts many published papers on caregiver burden reports that family caregiving in the context of chronic illness or disability is not associated with increased caregiver mortality but instead has been associated with modest survival benefits for caregivers (Roth et al., 2013). We need further research on the measurable impact of caregiver burden on caregiver physical health and immune functioning. Second, we need to build the evidence on patient and caregiver dyadic outcomes. A significant area of research need highlighted at a recent meeting on cancer caregiving convened by the National Institutes of Health and National Institute of Nursing Research is the need to identify the relationship between the physical and mental health outcomes of patients and caregivers (Kent et al., 2016). We need to answer the question of whether caregiver distress contributes to patient distress. One approach recommended by Kent et al. (2016) is to stratify caregivers by risk to identify highly stressed caregivers and determine impact of high burden on patient outcomes. Another area that require further exploration is the appraisal of the positive experiences of caregiving.

Implications for Health Policy

Currently, there is no international classification of diseases, ninth revision (ICD-9) or ICD-10 code for caregiver burden (Adelman, Tmanova, Delgado, Dion, & Lachs, 2014). Z68.3, a specific ICD-10-CM code that can be used to specify a diagnosis (ICD10Data.com, 2016), is applicable to the following diagnoses:

- Family discord, not otherwise specified (NOS)
- Family estrangement, NOS
- High expressed emotional level within family
- Inadequate family support, NOS
- Inadequate or distorted communication within family

and may be used for the following synonymous diagnoses:

- Caregiver role strain
- Caregiver stress
- Family conflict
- Family disruption
- Family disruption issues in remission
- Family maladjustment
- Family stress
- Family tension, and
- Stress due to family tension.

With an ICD-10 code specific to caregiver burden, healthcare professionals would be more likely to acknowledge the needs of the forgotten patient, the caregivers. This also has implications for scope of practice and practice authority and reimbursement for advanced practice nurses. In addition, in Congress, the American Association of Retired Persons (AARP) sponsored a legislation called the Caregiver Advise, Record and Enable Act- requires hospitals to record caregiver's name upon patient admission, notification prior to discharge, and provide instructions to transition care from the institution to home (Kent et al., 2016).

On the federal level, funding for programs that address caregiver needs through discretionary programs that include the National Family Caregiver Support Program, the Lifespan Respite Care Program, Medicaid, Medicare, VA Caregiver Support and Family Support must be preserved. Locally, health providers need to advocate for their patients and their Caregivers by reminding them of their rights under the Family and Medical Leave Act. We are hopeful that our study will help build the evidence to bring the needs of caregivers out of the shadows and into the forefront of routine adult care

Implications for Practice

It is worth noting that caregivers have regular interactions with the healthcare system and yet do not receive the attention they need (Adelman et al., 2014). Caregivers may continue to suffer in silence as they juggle the tasks and prioritize the needs of the patients. Some caregivers may knowingly suppress their needs so as not to contribute to the cancer patient's guilt or remorse over being the cause of burden. Findings from our study will help with the integration of caregivers into formal healthcare systems in cancer care. With robust data (forthcoming with future studies), we can assist with the creation of an infrastructure for a more comprehensive caregiver surveillance at national and/or state levels.

While routine interactions between patients and providers that are focused on an integrated care is the cornerstone of a quality comprehensive care, the well-being assessment of family caregivers is currently not considered standard of care. In the age of precision medicine, the care of the caregiver is several years behind the powerful advances in the diagnosis and treatment of cancer. We need to identify the factors that cause burden, relationship conflicts in the patient-caregiver dyad and among other

members of the household, and financial toxicity, in caregivers of patients with cancer. More importantly, we need to provide an individualized plan of care for caregivers, including respite for caregivers, supplemental services, interventions to reduce burden and improve health (Adelman et al., 2014).

Summary

Caregivers of patients with brain metastases are the hidden morbidity of cancer. While the healthcare industry has consistently recognized the contributions of caregivers, we have fallen behind in identifying and managing their needs. We need to continue to be perceptive of caregiver burden and be ready to administer the appropriate interventions that must be as unique and individualized as their experiences.

UCLA Jonsson Comprehensive Cancer Center

JCCC Internal Scientific Peer Review Committee
John Glaspy, MD & Albert Lai, MD, PhD, Co-Chairmen

01/31/2014

Marlon Garzo Saria, M.D.
Principal Investigator
c/o Sally Maliski, PhD, RN
Factor 2-948
MC: 691821

Re: **IRB Number:** 13-001619 Study Type: Institutional
Submission Type: New Protocol
Title: An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis

Dear Dr. Saria,

The ISPRC has received your protocol and the committee agrees that this study is exempt from the mandate of the ISPRC for scientific peer review based on the reason indicated below:

Exemption Reason:
☒ Observational research, descriptive research, questionnaires and focus groups
☐ Ancillary trials (i.e., pharmacokinetic research, pharmacogenetic research, and long-term follow up protocols)
☐ Use of Tissues (i.e., from an existing tissue bank, creating a tissue bank, genetic epidemiology, and collection of tissues for lab based trials (such as biomarker research) that pose no more than minimal risk to subjects)
☐ Single-case, compassionate-use protocols
☐ Treatment/management guidelines not asking a research question
☐ Retrospective chart reviews and review of databanks
☐ Not cancer
☐ Other:_____

Hence, we have not reviewed this study and will notify the IRB to process this protocol without ISPRC approval.

We wish you success with this protocol and with your research in general.

Sincerely,

John A. Glaspy, M.D.
ISPRC Co-Chair

Sincerely,

Albert Lai, M.D. Ph.D.
ISPRC Co-Chair

cc: MIRB #2
ISPRC file

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Los Angeles, CA 90095-1694

http://ohrpp.research.ucla.edu
GC-IRB: (310) 825-7122
M-IRB: (310) 825-5344

APPROVAL NOTICE
New Study

DATE:	2/6/2014
TO:	MARLON SARIA SCHOOL OF NURSING
FROM:	ALISON MOORE, MPH, MD Chair, SGIRB
RE:	IRB#13-001619 An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis

The UCLA Institutional Review Board (UCLA IRB) has approved the above-referenced study. The UCLA IRB's Federalwide Assurance (FWA) with Department of Health and Human Services is FWA00004642 (IRB00004474).

Submission and Review Information

Type of Review	Full Board Review
Approval Date	2/6/2014
Expiration Date of the Study	1/13/2015

Specific Conditions for Approval

– **UCLA Serving as Reviewing IRB** - The UCLA IRB has agreed to serve as the reviewing IRB for UC San Diego's involvement in this research according to the provisions of the UC MOU.

Regulatory Determinations

– **Waiver of Informed Consent** - The UCLA IRB waived the requirement for informed consent from secondary subjects (patients) under 45 CFR 46.116(d)(1-3).

– **Waiver of Signed Informed Consent** - The UCLA IRB waived the

requirement for signed informed consent for screening under 45 CFR 46.117(c)(2).

Documents Reviewed included, but were not limited to:

Document Name	Document Version #
13-001619_Screening_Contact_Information.pdf.pdf	0.01
13-001619_Flyer.pdf.pdf	0.01
13-001619_Informed_consent.pdf.pdf	0.01
13-001619_Cover_Letter.pdf.pdf	0.01
13-001619_Recruitment_and_Screening_Script.pdf.pdf	0.01

Important Note: Approval by the Institutional Review Board does not, in and of itself, constitute approval for the implementation of this research. Other UCLA clearances and approvals or other external agency or collaborating institutional approvals may be required before study activities are initiated. Research undertaken in conjunction with outside entities, such as drug or device companies, are typically contractual in nature and require an agreement between the University and the entity.

General Conditions of Approval
As indicated in the PI Assurances as part of the IRB requirements for approval, the PI has ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human subjects, and strict adherence to any stipulations imposed by the IRB.

The PI and study team will comply with all UCLA policies and procedures, as well as with all applicable Federal, State, and local laws regarding the protection of human subjects in research, including, but not limited to, the following:

- Ensuring that the personnel performing the project are qualified, appropriately trained, and will adhere to the provisions of the approved protocol,
- Implementing no changes in the approved protocol or consent process or documents without prior IRB approval (except in an emergency, if necessary to safeguard the well-being of human subjects and then notifying the IRB as soon as possible afterwards),
- Obtaining the legally effective informed consent from human subjects of their legally responsible representative, and using only the currently approved consent process and stamped consent documents, as appropriate, with human subjects,
- Reporting serious or unexpected adverse events as well as protocol violations or other incidents related to the protocol to the IRB according to the OHRPP reporting requirements.
- Assuring that adequate resources to protect research participants (i.e., personnel, funding, time, equipment and space) are in place before implementing the research project, and that the research will stop if adequate resources become unavailable.
- Arranging for a co-investigator to assume direct responsibility of the study if the PI will be unavailable to direct this research personally, for example, when on sabbatical leave or vacation or other absences. Either this person is named as co-investigator in this application, or advising IRB via webIRB in advance of such arrangements.

UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

Date: February 18, 2014

To: Santosh Kesari, MD, PhD (UCSD)
Marlon Saria (UCLA)

Re: Notice of Intent to Rely (NOITR)

Title of Study: *An Exploratory Study of Caregiver Burden Among Caregivers of Cancer Patients with Brain Metastasis*
Reviewing Campus: *University of California, Los Angeles*
Reviewing Campus Tracking Number: *13-001619*
Reviewing Campus Approval Date: *2/6/2014*
Reviewing Campus Expiration Date: 1/13/2015
Level of Review: *Full*

Dear Mr. Saria & Dr. Kesari,

This letter is to acknowledge that the University of California, San Diego (UCSD), operating under Federalwide Assurance number, FWA00004495, has received the NOITR documentation from the PI at University of California Los Angeles. The PI, Santosh Kesari, MD, PhD, at University of California San Diego, intends to rely upon the determination made by the University of California, Los Angeles. The research, as described in the approved UC Los Angeles research protocol, is now authorized to begin on the UCSD campus.

Any amendments to the protocol, annual renewals, and other required notifications should be submitted to the UC Los Angeles IRB for approval, with copies of all submission to the UCSD IRB, if appropriate. The authorization to conduct research on the UCSD campus will expire on the date noted above.

The research must be conducted in accordance with all applicable Federal and State Laws, University of California and UCSD policies, and with the terms of the UC MOU for IRB Review of Multi-Campus Research.

If additional assistance and/or clarification are needed, please feel free to contact me at (858) 657-5100.

On behalf of the Institutional Review Board,

Lorena A. Smith, MBA, MS
Associate Director of Committees, Human Research Protections Program
(858) 657-5100

SCREENING CONSENT SCRIPT

An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis

Thank you for agreeing to speak with me about the possibility of participating in an exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis. My name is (name). I am a (role) at (UC Irvine, UCLA, or UC San Diego). I would like to ask you a few questions in order to determine whether you may be eligible for the research. Before I begin the screening I would like to tell you a little bit about the research. The purpose of this study is to look at caregiver burden and the coping behavior of caregivers of patients with brain metastasis. Should you decide to participate, you will be asked to complete and pen and paper survey at your convenience. Findings of this study may direct future intervention studies to reduce caregiver burden and improve outcomes for the many individuals caring for family members with brain metastases.

Would you like to continue with the screening? The screening will take about *2 to 5 minutes*. I will ask you about your age, role as caregiver, and availability. You do not have to answer any questions you do not wish to answer or are uncomfortable answering, and you may stop at any time. Your participation in the screening is voluntary.

Your answers will be confidential. No one will know your answers except for the research team. After this encounter, the screening form will be kept in a locked file cabinet in a locked room for the duration of study. Note that there are no identifying information on this form. If you qualify, I will give you more detailed information about the study that will help you decide if you want to continue to participate.

Would you like to continue with the screening? [*If no, thank the person and end the encounter.*]

If yes, continue with the screening - please include all screening questions in this script

Are you over 18 years of age?	( ) Y ( ) N
Do you consider yourself to be the primary caregiver?	( ) Y ( ) N
Would you be able to read and complete survey forms in English?	( ) Y ( ) N
Would you be willing to participate in completion of surveys that may take 1-2 hours?	( ) Y ( ) N
Do you live with the patient in the same residence?	( ) Y ( ) N
Do you providing a minimum of 4 hours of direct care for at least 3 days per week?	( ) Y ( ) N

Thank you for answering the screening questions. *[Indicate whether the person is eligible, requires additional screening, or is not eligible and explain why.]*

Do you have any questions about the screening or the research? I am going to give you a list of telephone numbers to call if you have any questions later.

If you have questions about your rights as a research subject or if you wish to voice any problems or concerns you may have about the study to someone other than the researchers, please call [UCLA Office of the Human Research Protection Program at (310) 825-7122; e-mail UC Irvine Human Research Program at IRB@research.uci.edu; or UC San Diego Human Research Protections Program at (858) 657-5100].

Thank you again for your willingness to answer our questions.

Protocol ID:IRB#13-001619 UCLA IRB Approved Approval Date: 1/18/2015 Through: 12/8/2015 Committee: South General IRB

If you are the primary caregiver for a patient who was diagnosed with brain metastasis, we would like to talk to you about your own health and well-being.

Caregiver Research

A UCLA-UCSD Research Study

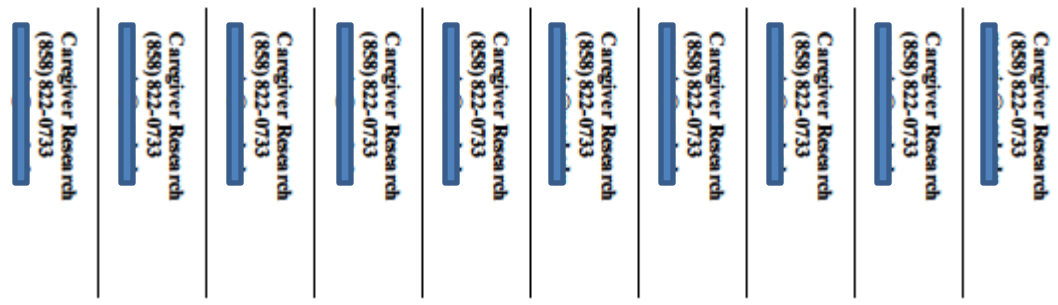
Purpose: This proposed study will look at caregiver burden and the coping behavior of caregivers of patients with brain metastasis. Findings of this study may direct future intervention studies to reduce caregiver burden and improve outcomes for the many individuals caring for family members with brain metastases.

Benefits: You will not directly benefit from your participation in the research.

Time Commitment: Participation will take a total of about 1 to 2 or more hours, depending on how much time you will need to complete the questionnaires.

This research study is completely voluntary and is not part of the patient's treatment. Your decision to participate will not impact the care provided by the healthcare team here at the Moores Cancer Center.

Moores Cancer Center, UC San Diego
3855 Health Sciences Drive, La Jolla, CA 92093



Protocol ID:IRB#13-001619 UCLA IRB Approved Approval Date: 3/10/2014 Through: 1/13/2015 Committee: South General IRB

The Caregiver Study

UCLA School of Nursing
UC Irvine, Chao Family Comprehensive Cancer Center
UC San Diego, Moores Cancer Center

Marlon Garzo Saria, MSN, RN, FAAN
Principal Investigator
(858) 822-0733

Sally Maliski, PhD, RN, FAAN
Faculty Sponsor, UCLA
310-206-3782

Dan Beverly Fu, MBA, MSN, PHN, NP-C
Neuro-Oncology Program, UC Irvine
714-456-7097

Santosh Kesari, MD, PhD
Director of Neuro-Oncology, UCSD
858-822-7524

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UCLA School of Nursing | Chao Family Comprehensive Cancer Center, University of California - Irvine | University of California San Diego Medical Center, Moores Cancer Center

An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis

Dear Caregiver:

You are invited to participate in a research study titled "An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis". This study is being conducted by Marlon Garzo Saria with the approval of his dissertation committee from the School of Nursing at the University of California Los Angeles in collaboration with the Neuro-Oncology Programs at UC Irvine and UC San Diego. The purpose of this study is to look at caregiver burden and the coping behavior of caregivers of patients with brain metastasis. Findings of this study may direct future intervention studies to reduce caregiver burden and improve outcomes for the many individuals caring for family members with brain metastases.

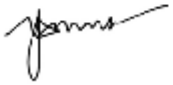
In this study, you will be asked to complete and pen and paper survey at your convenience. Your participation is voluntary and you are free to withdraw your participation from this study at any time. The survey should take anywhere from 60-120 or more minutes to complete. Upon completion, please put all survey materials in the self-addressed, stamped envelope provided in the package. Please do not put any personally identifiable information anywhere on the packet.

This survey has been approved by the Institutional Review Board of UCLA with UC San Diego and UC Irvine intending to rely upon the determination made by UCLA. There are minimal risks associated with participating in this study and you should have already been informed of your rights as a participant prior to receiving this package. In addition, you should have already signed a document that confirms that you agree to participant in this study.

If you have any questions regarding the survey or this research project in general, please contact Marlon Garzo Saria at 858-822-0733 or email at [redacted] or his advisor at UCLA, Dr. Sally Maliski at 310-206-3782 or email at [redacted] If you have any questions concerning your rights as a research participant, please contact UCLA OHRPP at (310) 825-7122. At UC Irvine, you can contact Dan Beverly Fu at (714) 456-7097 or UC Irvine HRP by email at IRB@research.uci.edu. At UC San Diego, you can also contact Dr. Santosh Kesari at (858) 822-07524 or UC San Diego HRPP at (858) 657-5100.

Thank you for participating in this research study. Please accept the $5.00 starbucks gift card as a small token of our appreciation for completing this study.

Sincerely,



Marlon Garzo Saria
PhD candidate, UCLA School of Nursing

Protocol ID:IRB#13-001619 UCLA IRB Approved Approval Date: 1/18/2015 Through: 12/8/2015 Committee: South General IRB

University of California, Los Angeles; UC Irvine, and UC San Diego

CONSENT TO PARTICIPATE IN RESEARCH

An exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis.

Marlon Garzo Saria, RN, doctoral student,Sally Maliski, PhD, RN, FAAN, faculty sponsor from University of California, Los Angeles (UCLA), Dan Beverly Fu, MBA, MSN, Nurse Practitioner at UC Irvine; Daniela Bota, MD, PhD, Associate Professor and Director of Neuro-Oncology at UC Irvine; and Santosh Kesari, MD, PhD, Professor and Director of Neuro-Oncology at UC San Diego are conducting a research study.

You were chosen as a possible subject in this study because *you are a primary caregiver for a cancer patient with brain metastasis (hereafter referred to as brain mets).* Your participation in this research study is voluntary.

Why is this study being done?

This proposed study will look at caregiver burden and the coping behavior of caregivers of patients with brain mets. Through this study, the research team will look at the link between patient and caregiver attributes, and caregiver burden. The findings of this study may direct future studies to reduce caregiver burden and improve outcomes for persons caring for family members with brain mets.

This study is not part of the patient's treatment. Your decision about joining will not impact the care provided by the healthcare team.

What will happen if I take part in this research study?

If you volunteer to join this study, the researcher will ask you to do the following:

- *Complete survey forms that will ask information on your physical and mental health, and your view of the patient's mental health. The survey will also ask for personal data (age, gender, income, education, race/ethnicity, et al.), personality, social support, and coping behaviors.*
- *The survey will include items that you will rate based on certain criteria. This includes frequency and the degree to which you agree or disagree with the statement.*
- *You have the option of completing the survey at the study site or taking the survey home with you. You can complete the survey at your own convenience.*
- *You may refuse to answer any questions that you do not want to answer and still remain in the study.*

How long will I be in the research study?

The study may take a total of about *1 to 2 or more hours. It will depend on how much time you will need to complete the survey.*

Are there any potential risks or discomforts that I can expect from this study?

- *Physical. None. Caregivers will not be asked to perform any physical tasks as a part of the study.*

- *Psychological. Caregivers will be asked to provide info about their self-reported physical and mental health, view of the patient's mental health, and personal info. Personal info includes age, gender, income, education, race/ethnicity etc. These questions have a small chance of low risk if participants are upset by certain questions. Some questions may ask them to think about their own poor health or problems that are disturbing for them. In addition, recalling traumatic or distressing events is normally a distressing activity. This may cause some level of suffering for the caregivers. Should any of these happen, you have access to services provided by Family Support and Hospital at UCLA, the Brain Tumor Education and Support Group at UC Irvine, and the Patient & Family Support Service at UC San Diego.*

Are there any potential benefits if I participate?

Study subjects will not directly benefit from joining the research.

The results of the research may direct future studies to reduce caregiver burden and improve outcomes for persons caring for family members with brain mets.

Will I be paid for participating?

A $5.00 gift card will be provided as a small token of appreciation for joining the study.

Will information about me and my participation be kept confidential?

Any data obtained in this study and that can identify subjects will remain confidential. It will be disclosed only if you allow us to or as required by law. Confidentiality will be maintained by means of de-identifying all responses received. Records will be linked to persons only through a unique identifier. The information used to link records with identifying information will be kept in a securely locked file drawer. Only the research team will have access. Names and any other identifying information collected from the subjects of the self-survey will be kept in a locked file drawer. Also, only the research team will have access.

The research team may not be able to keep confidential any disclosure or endorsement of thoughts to harm yourself or others. In the event that you provide information that you are thinking about harming yourself or others, the research team will ask you more

questions about the thoughts. Depending on how intense your thoughts are or how much you feel like hurting yourself or others, the research team may provide you with referrals for treatment. The research team may also work with you to contact your personal physician, trusted family member, or therapist to discuss your thoughts of harming yourself or others. They may also work with you on a plan that may include getting you to a hospital for safety.
Under California law, we will not maintain as confidential, information about known or reasonably suspected incidents of abuse or neglect of a child, dependent adult or elder. These includes, but are not limited to, physical, sexual, emotional, and financial abuse or neglect. If any member of the study personnel has or is given such information, he or she is required to report it to the authorities.

What are my rights if I take part in this study?

- You can choose whether or not you want to be in this study. You may withdraw your consent and stop participation at any time.
- Whatever decision you make, there will be no penalty to you. There will be no loss of benefits to which you were otherwise entitled.
- You may refuse to answer any questions that you do not want to answer and still remain in the study.

Who can I contact if I have questions about this study?

- **The research team:**
  If you have any questions, comments or concerns about the research, you can talk to the research team. Please contact:

  Marlon Garzo Saria, Doctoral student
  [redacted] *or call 858-822-0733*

  Sally Maliski, RN, PhD, FAAN, Faculty sponsor, UCLA
  [redacted] *or call 310-206-3782*

  Dan Beverly Fu, MBA, MSN, BSN, PHN, NP-C, Nurse Practitioner, UC Irvine
  [redacted] *call 714-456-7097*

  Daniela Bota, MD, PhD, Associate Professor and Medical Director, UC Irvine
  [redacted] *or call 877-824-9111*

  Santosh Kesari, MD, PhD, Professor and Director of Neuro-Oncology, UCSD
  [redacted] *or call 858-822-7524*

- **UCLA Office of the Human Research Protection Program (OHRPP):**

Please call the UCLA OHRPP at (310) 825-7122 if:

- You have questions about your rights while taking part in this study
- You have concerns or suggestions and you want to talk to someone other than the research team about the study

You can also write to:
UCLA Office of the Human Research Protection Program
11000 Kinross Avenue, Suite 211, Box 951694
Los Angeles, CA 90095-1694

- **UC San Diego Human Research Protections Program (HRPP):**

  At UCSD, you can call the UCSD HRPP at (858) 657-5100 or write to:
  University of California, San Diego
  Human Research Protections Program
  9500 Gilman Drive, Mail Code 0052
  La Jolla, California, 92093-0052

- **UC Irvine Human Research Protections (HRP)**

  At UC Irvine, you can e-mail the UC Irvine HRP at IRB@research.uci.edu or write to:
  University of California, Irvine
  Office of Research
  5171 California, Suite 150
  Irvine, CA 92697

You will be given a copy of this information to keep for your records.

SIGNATURE OF STUDY PARTICIPANT

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____ _____
Name of Person Obtaining Consent Contact Number

_____ _____
Signature of Person Obtaining Consent Date

Saria, Marlon

From: [redacted]
Sent: Wednesday, November 06, 2013 2:14 PM
To: Saria, Marlon
Cc: Linda Teri
Subject: Re: Permission Request to Use RMBC for Dissertation Research

You have my permission,
Best if luck!

On Nov 6, 2013, at 9:11 AM, "Saria, Marlon" <[redacted]> wrote:

> Dr. Linda Teri:
>
> I am a PhD student at the UCLA School of Nursing. My dissertation will be an exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis. One of the relationships I am looking at is the effect of the patient's cognitive dysfunction (as perceived by the caregiver) on caregiver burden. Your instrument, the Revised Memory and Behavioral Problems Checklist was very highly recommended by Dr. George Niederehe. I am therefore writing to seek permission to use this instrument in my dissertation.
>
> Please let me know if there are any other information that you will need from me.
>
> Thank you.
>
> Kind Regards,
> *Marlon*
>
> Marlon Garzo Saria, PhD(c), RN, AOCNS
> Clinical Nurse Researcher
> Center for Translational Neuro-Oncology
> Translational Neuro-Oncology Laboratories
> Moores Cancer Center, UC San Diego
> 3855 Health Sciences Drive, Suite 3304
> La Jolla, California 92093-0819
> Office: (858)822-0733
> Fax: (858)822-3033
> Website: kesarilab.ucsd.edu
>
> Click here to learn more about brain tumor research in San Diego

INTELLECTUAL PROPERTY LICENSE AGREEMENT
Students & Residents of Developing Countries

This Intellectual Property License Agreement ("Agreement") is made and effective this 10 January 2014 ("Effective Date") by and between The Resilience Center, PLLP ("Licensor") and Marlon Saria ("Licensee").

Licensor has developed and licenses to users its Intellectual Property, marketed under the names "the Resilience Scale", "RS", "the 14-Item Resilience Scale", and "the RS-14" (the "Intellectual Property").

Licensee desires to use the Intellectual Property.

NOW, THEREFORE, in consideration of the mutual promises set forth herein, Licensor and Licensee agree as follows:

1. License.
   Licensor hereby grants to Licensee a 1-year, non-exclusive, limited license to use the Intellectual Property as set forth in this Agreement.
2. Restrictions.
   Licensee shall not modify, license or sublicense the Intellectual Property, or transfer or convey the Intellectual Property or any right in the Intellectual Property to anyone else without the prior written consent of Licensor. Licensee may make sufficient copies of the Intellectual Property and the related Scoring Sheets to measure the individual resilience of an unlimited number of subjects, for non-commercial purposes only.
3. Fee.
   In consideration for the grant of the license and the use of the Intellectual Property, subject to the Restrictions above, Licensee agrees to pay Licensor the sum of US$50.
4. Term.
   This license is valid for twelve months, starting at midnight on the Effective Date.
5. Termination.
   This license will terminate at midnight on the date twelve months after the Effective Date.
6. Warranty of Title.
   Licensor hereby represents and warrants to Licensee that Licensor is the owner of the Intellectual Property or otherwise has the right to grant to Licensee the rights set forth in this Agreement. In the event any breach or threatened breach of the foregoing representation and warranty, Licensee's sole remedy shall be to require Licensor to do one of the following: i) procure, at Licensor's expense, the right to use the Intellectual Property, ii) replace the Intellectual Property or any part thereof that is in breach and replace it with Intellectual Property of comparable functionality that does not cause any breach, or iii) refund to Licensee the full amount of the license fee upon the return of the Intellectual Property and all copies thereof to Licensor.
7. Warranty of Functionality.
   Licensor provides to Licensee the Intellectual Property "as is" with no direct or implied warranty.
8. Payment.
   Any payment shall be made in full prior to shipment. Any other amount owed by Licensee to Licensor pursuant to this Agreement shall be paid within thirty (30) days following invoice from Licensor. In the event any overdue amount owed by Licensee is not paid following ten (10) days written notice from Licensor, then in addition to any other amount due, Licensor may impose and Licensee shall pay a late payment charge at the rate of one percent (1%) per month on any overdue amount.
9. Taxes.
   In addition to all other amounts due hereunder, Licensee shall also pay to Licensor, or reimburse Licensor as appropriate, all amounts due for tax on the Intellectual Property that are measured directly by payments made by Licensee to Licensor. In no event shall Licensee be obligated to pay any tax paid on the income of Licensor or paid for Licensor's privilege of doing business.
10. Warranty Disclaimer.
    LICENSOR'S WARRANTIES SET FORTH IN THIS AGREEMENT ARE EXCLUSIVE AND ARE IN LIEU OF ALL OTHER WARRANTIES, EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE.

11. Limitation of Liability.
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    Licensor agrees to provide limited, e-mail-only support for issues and questions raised by the Licensee that are not answered in the current version of the *Resilience Scale User's Guide*, available on www.resiliencescale.com, limited to the Term of this Agreement. Licensor will determine which issues and questions are or are not answered in the current *User's Guide*.
13. Notice.
    Any notice required by this Agreement or given in connection with it, shall be in writing and shall be given to the appropriate party by personal delivery or by certified mail, postage prepaid, or recognized overnight delivery services.
    If to Licensor:
    The Resilience Center, PLLC
    PO Box 313
    Worden, MT 59088-0313
    If to Licensee:
    Name: Marlon Saria
    Address: [redacted]
    UNITED STATES

14. Governing Law.
    This Agreement shall be construed and enforced in accordance with the laws of the United States and the state of Montana. Licensee expressly consents to the exclusive forum, jurisdiction, and venue of the Courts of the State of Montana and the United States District Court for the District of Montana in any and all actions, disputes, or controversies relating to this Agreement.
15. No Assignment.
    Neither this Agreement nor any interest in this Agreement may be assigned by Licensee without the prior express written approval of Licensor.
16. Final Agreement.
    This Agreement terminates and supersedes all prior understandings or agreements on the subject matter hereof. This Agreement may be modified only by a further writing that is duly executed by both Parties.
17. Severability.
    If any term of this Agreement is held by a court of competent jurisdiction to be invalid or unenforceable, then this Agreement, including all of the remaining terms, will remain in full force and effect as if such invalid or unenforceable term had never been included.
18. Headings.
    Headings used in this Agreement are provided for convenience only and shall not be used to construe meaning or intent.

IN WITNESS WHEREOF, the Parties hereto have duly caused this Agreement to be executed in its name on its behalf, all as of the day and year first above written.

Licensee	**The Resilience Center, PLLP**
Signature:	
Printed Name: Marlon Saria	Gail M. Wagnild, PhD
Title: Student	Owner and CEO
Date: 8 January 2014	8 January 2014

Saria, Marlon

From: Neal Krause [redacted]
Sent: Tuesday, October 08, 2013 2:20 AM
To: Saria, Marlon
Subject: Re: Perceived Support Scale
Attachments: stressw6.doc

Marlon:

I have attached a copy of the questionnaire that was used in one of the waves of the study you cite. You will find the negative interaction questions on page 28.

Neal

Neal Krause, Ph.D.
Marshall H. Becker Collegiate Professor
Department of Health Behavior and Health Education
School of Public Health
The University of Michigan
1415 Washington Heights
Ann Arbor, MI 48109-2029
Telephone: (734) 763-5583; Fax (734) 763-7379

On Mon, Oct 7, 2013 at 4:30 PM, Saria, Marlon <[redacted]> wrote:

Hi Dr. Krause,

I am a PhD student at UCLA and I am looking at social support as one of my variables. My committee wanted me to find a tool that can measure negative social interaction. Would you be able to share your perceived support scale [Krause, N. (1995). Negative interaction and satisfaction with social support among older adults. Journal of Gerontology: Psychological Sciences, 50B, 59-73; Krause, N., & Borawski-Clark, E. (1995). Social class differences in social support among older adults. The Gerontologist, 35, 498-508.] so I can review and present to my committee?

Thank you.

Kind Regards,

Saria, Marlon

From: Terry Kessler [redacted]
Sent: Thursday, April 18, 2013 3:24 PM
To: Saria, Marlon
Subject: Re: Permission to Use Cognitive Appraisal of Health Scale (Kessler, 1998)
Attachments: CAHSwithScoring tak.doc

Marlon,

Yes, you have permission to use the instrument. I am attaching it for you along with the scoring. I developed the instrument to include both primary and secondary appraisals. I believe conceptually they are both important to the process of appraisal.

If you are asking caregivers to complete the instrument, you may need to specify clearly in the directions that the words "this health condition" refer to the caregiver situation.

I ask that you share the final psychometric outcomes from the use of the instrument so that I can continue to look at reliability and validity of the CAHS in different populations.

Good luck with your work, an exciting process.

Terry

On Thu, Apr 18, 2013 at 1:07 PM, Saria, Marlon <[redacted]> wrote:

Dr. Kessler:

I am a PhD student at the UCLA School of Nursing. My dissertation will be an exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis. One of the relationships I am looking at is the effect of cognitive appraisal on caregiver burden. I am writing to request permission to use the instrument for my dissertation research.

Please let me know if there is any other information that you will need from me. Thank you for your time.

Kind Regards,

Marlon

Saria, Marlon

From: Annette Stanton [redacted]
Sent: Tuesday, April 23, 2013 4:25 PM
To: Saria, Marlon
Subject: RE: Permission for COPE and EAC scales

Hi Marlon, The COPE does not require permission, and I'm happy for you to use the EAC scales. Annette

Annette L. Stanton, Ph.D.
Professor, Psychology & Psychiatry/Biobehavioral Sciences
Member, Jonsson Comprehensive Cancer Center
Senior Research Scientist, Cousins Center for Psychoneuroimmunology
Address:
Department of Psychology
1285 Franz Hall, Box 951563
405 Hilgard Avenue
UCLA
Los Angeles, CA 90095-1563
Phone: 310-825-3105; 310-267-2835
Fax: 310-206-3566
[redacted]

From: Saria, Marlon [redacted]
Sent: Thursday, April 18, 2013 10:43 AM
To: [redacted]
Subject: Permission for COPE and EAC scales

Dr. Stanton,

I am working on the permissions for the instruments for my dissertation. I may have prematurely assumed to already have your permission to use the EAC scales. I just want to make sure that I ask. Also, since the EAC will be "embedded" in the COPE questionnaire, would that mean that permission to use the COPE scale is implied? I will contact Dr. Carver if I need to ask permission for the COPE scale as well.

Thank you for your time.

Kind Regards,
Marlon

Saria, Marlon

From: fcs temp [redacted]
Sent: Friday, April 19, 2013 5:57 AM
To: Saria, Marlon
Subject: FW: Permission to use Caregiver
Attachments: Caregiver Reaction Assessment Given 1992.pdf; FCRP Caregiver Reaction Assessment Instrument.pdf

Marlon,

We are happy to provide you with the Caregiver Reaction Assessment (CRA) from the Family Care Research Program at Michigan State University.

I am attaching a pdf version of the tool, as well as an article that discusses it.

Should you have any questions or comments, please do not hesitate to contact us.

Dorothy Luckie
Michigan State University
College of Nursing
Bott Building
C360I 1355 Bogue St
East Lansing MI 48824
(517) 353-0306
[redacted]

From: Saria, Marlon [redacted]
Sent: Thursday, April 18, 2013 2:29 PM
To: Barb Given
Subject: Permission to use Caregiver

Dr. Given:

I am a PhD student at the UCLA School of Nursing. My dissertation will be an exploratory study of caregiver burden among caregivers of cancer patients with brain metastasis. I am writing to request permission to use the Caregiver Reaction Assessment (Given at al, 1992) for my dissertation research.

Please let me know if there is any other information that you will need from me for this request. Thank you for your time.

Kind Regards,
Marlon

Marlon Garzo Saria, MSN, RN, AOCNS
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Center for Translational Neuro-Oncology
Translational Neuro-Oncology Laboratories
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References

Adelman, R. D., Tmanova, L. L., Delgado, D., Dion, S., & Lachs, M. S. (2014). Caregiver burden: A clinical review. *JAMA, 311*(10), 1052-1060. doi: 10.1001/jama.2014.304

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