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The added value of family caregivers' level of mastery in predicting survival of glioblastoma patients: A validation study

Florien W. Boele, PhD; Jason Weimer, MA; Amir H. Zamanipoor Najafabadi, BSc; Louise Murray, MD PhD; Charles W. Given, PhD; Barbara A. Given, PhD RN FAAN; Heidi S. Donovan, RN PhD; Jan Drappatz, MD; Frank S. Lieberman, MD; Paula R. Sherwood, RN PhD CNRN FAAN.

Author Affiliations: Leeds Institute of Medical Research at St James's, University of Leeds, Beckett Street, Leeds LS9 7TF, United Kingdom (Drs Boele and Murray); Leeds Institute of Health Sciences, University of Leeds, Leeds LS2 9NL, United Kingdom (Dr Boele); University of Pittsburgh, School of Nursing, 336 Victoria Bldg, Pittsburgh, PA 15261 (Mr Weimer, Drs Donovan and Sherwood); University Neurosurgical Center Holland, Leiden University Medical Center, Haaglanden Medical Center and Haga Teaching Hospital, Leiden and The Hague, the Netherlands (Mr Zamanipoor Najafabadi); Michigan State University, College of Nursing C346 Life Sciences Bldg. 1355 Bogue St East Lansing, MI, 48824 (Dr C Given); Michigan State University, College of Nursing, C383 Life Sciences Bldg, 1355 Bogue St., East Lansing, MI 48824 (Dr B Given); Division of Hematology/Oncology, Hillman Cancer Center, University of Pittsburgh Medical Center, 5115 Centre Avenue, Pittsburgh, PA 15232 (Drs Drappatz and Lieberman).

Running Title: Caregiver mastery and GBM patient survival

Correspondence: Florien W. Boele, BSc MSc PhD, Patient-Centred Outcomes Research Group, Level 6, Bexley Wing, St James's Institute of Oncology, Beckett Street, LEEDS LS9 7TF, United Kingdom (f.boele@leeds.ac.uk).

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Dr Boele: conceptualization, methodology, data curation, formal analysis, funding acquisition, investigation, methodology, validation, writing (original draft)

Dr Sherwood: conceptualization, investigation, methodology, data curation, supervision, funding acquisition, writing (review & editing)

Dr Donovan: conceptualization, investigation, supervision, funding acquisition, writing (review & editing)

Mr Zamanipoor Najafabadi: methodology, formal analysis, writing (review & editing)

Mr Weimer: investigation, data curation, project administration, writing (review & editing)

Drs Murray, C Given, and B Given: methodology, writing (review & editing)

Drs Drappatz and Lieberman: resources, writing (review & editing)

Introduction

Glioblastoma (GBM, World Health Organization (WHO) grade IV) is the most common primary malignant brain tumor in adults and is followed by an extremely poor prognosis; with standard treatment, median survival is less than 15 months.[1] Standard treatment, i.e. surgery followed by radiotherapy with concomitant and adjuvant temozolomide, is aimed at stabilizing disease and extending survival, while maintaining quality of life (QOL). In addition to treatment, longer survival following diagnosis is associated with younger age at diagnosis, better performance status, unifocal tumor location, O6-methylguanine-DNA-methyltransferase (MGMT) promotor methylation and IDH1 status.[2-4]

In addition to high mortality rates, morbidity following diagnosis often includes debilitating physical and neurological sequelae[5] creating a high demand for assistance from family caregivers (typically spouses).[5,6] While providing care can be rewarding, neuro-oncology family caregivers report considerable burden and distress[7] as well as effects on physical health.[8,9] Caregiver mastery (the feeling of being in control of the care situation) has been shown to be a strong predictor of positive caregiver outcomes across multiple patient populations.[10-12]

Caregivers' emotional health is often assumed to influence the quality of care delivered in the home thus affecting patient outcomes, yet little evidence exists to support this hypothesis. In certain populations (e.g., dementia, end-of-life care), some evidence exists for an association between lower levels of caregiver wellbeing and worse patient outcomes (e.g., time to institutionalization, survival).[13-17] However, these populations differ greatly from cancer, and brain cancer in particular as a brain tumor has both oncological and neurological sequelae. Like many cancers, GBM typically has a rapid onset and complex treatment regimen with often severe side effects, but also presents with dementia-like sequelae including neuropsychological

dysfunction.[18] This presents unique challenges for neuro-oncology caregivers, with different disease-specific issues impacting on their emotional health and potentially, affecting patient outcomes differently.

We previously investigated whether key indicators of caregiver distress (i.e., anxiety, depressive symptoms, caregiver burden and mastery) were predictive of glioblastoma patient survival.[19] In a sample of 88 dyads of patients newly diagnosed with GBM and their caregivers, higher levels of caregiver mastery were associated with a significant reduction in the probability of the patient dying sooner (Hazard Ratio (HR)=0.839 (95% confidence interval (CI)=0.771-0.913)), after correcting for other known predictors. This was the first study to investigate these associations, yet important molecular markers such as MGMT promotor methylation status were not routinely collected at the time, which could have biased results. Moreover, replicability of findings is a known difficulty in psychosocial and medical sciences.[20] Therefore, we now aimed to verify the predictive value of caregiver mastery independent of other known predictors, and the added value of caregiver mastery over other predictors to predict 15-month survival within a new sample of GBM patients and caregivers. Further knowledge on links between caregivers' emotional wellbeing and patient outcomes are key to intervention design aimed at improving both patient and caregiver wellbeing.

Materials and methods

Participants

Caregiver/patient dyads were recruited from a randomized controlled trial aimed at evaluating the effects of a computer mediated, nurse-facilitated representational (problem solving) intervention (SmartCare©)[21] on family caregivers' wellbeing (NCI R01-NR013170). Dyads were

recruited within 3-6 months of the patient's initial diagnosis from NCI designated cancer centers. Caregiver eligibility criteria were: 1) presence of depressive symptoms as measured with the shortened Center for Epidemiological Studies-Depression Scale; 2) ≥ 21 years of age; 3) able to read and speak English; 4) identified by patients as the primary non-professional person who provided the majority of emotional, financial and/or physical support; and 5) not currently a primary caregiver for anyone else other than children under age 21. Patient eligibility criteria were: 1) ≥21 years old, 2) diagnosed (verified via pathology) with a primary malignant brain tumor, and 3) able to read and speak English.

For the current analysis, only patients newly diagnosed with glioblastoma (≤4 months) and their caregivers were included. Only baseline data were used because: a) it eliminated bias from the intervention tested, and; b) we were able to test caregivers' baseline level of mastery irrespective of the patient's place in the disease trajectory.

Procedure and outcome measures

Sociodemographic and clinical data, patient functional status, and other covariates described in subsequent sections were obtained via interviews and medical record review. Caregiver survey data were obtained via online questionnaires completed by caregivers. We used only data collected at baseline (if done within 4 months of diagnosis) as potential predictors of patients' time to death. The institutional review board approved the study protocol and all participants provided informed consent. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

Caregiver outcomes

Caregivers' sociodemographic information (age, sex, education, relationship with patient) were self-report. Caregivers' feelings of mastery (perception of control over the care situation) were

assessed with the Caregiver Mastery Scale based on Pearlin & Schooler's structure of coping.[22] The 7-item Likert-type instrument was administered (α=0.65). Scales range from strongly disagree to strongly agree, with a neutral 'no opinion' answer. A total score is calculated with higher scores indicating a higher level of perceived control.

Patient outcomes

Patients' date of diagnosis was defined as date of the surgery. Date of death was collected by medical record review and/or by checking obituaries and the Social Security Death Index through May 2019. Patients were classified as alive, deceased, or lost to follow up. Performance status was measured with the Karnofsky Performance Status (KPS) scale. Data on other factors known to influence survival e.g. extent of resection, postsurgical treatment, and molecular markers (MGMT; IDH) were obtained through medical record review.

Statistical analyses

All statistical analyses were performed with SPSS version 26.0. Descriptive statistics were performed to explore sociodemographic (age, sex, educational level, relationship), clinical variables (extent of resection, postsurgical treatment, tumor location, IDH mutation status, MGMT methylation status, KPS, symptom burden, survival at 15 months), and caregiver mastery. Multiple imputation techniques using fully conditional specification with five iterations[23,24] were used if less than 10% of data for a given predictor were missing and missingness was determined to be at random through pattern analysis (caregiver mastery (2.4% missing); KPS (9.7% missing); MGMT methylation status (7.3% missing)). Multivariable Cox regression analyses were run for different models to predict GBM patient survival. First, model 1 was run to confirm the associations between known clinical predictors and patient survival:

patients' age, KPS, extent of resection, plus MGMT methylation status. Then, model 2 was run to investigate the added value of caregiver mastery: patients' age, KPS, extent of resection, MGMT methylation status, plus caregiver mastery. For IDH mutation, data was too incomplete for imputation (14.6% missing), with only 2 cases of mutation recorded, so this could not be included in the models. Postsurgical treatment was removed as a predictor variable as all participants received postsurgical chemo- and radiotherapy, and due to multicollinearity concerns with KPS. All Cox regression models presented include the pooled estimate from five multiple imputation rounds, and P-values $\leq .05$ were considered statistically significant. Performance of the two multivariable models (original, non-imputed data only) was assessed with Harrell's concordance-index (C-index),[25] which estimates the probability of concordance between predicted and observed responses. For both models (original, non-imputed data only) Kaplan-Meier curves were generated for which the patient group was split into two groups based on the model-specific median prognostic index, representing patients with the lowest and highest chance of survival at 15 months.[26] The further the survival curves lie from each other, the better the discrimination. These curves also give insight on how the discrimination capacity changes over time.

Results

Participant characteristics

In the main trial (recruitment period 2015-2017), 120 patient-caregiver dyads participated. Based on in- and exclusion criteria used for the present analyses, 34.2% of the study sample (N=41) could be included. Most caregivers were women (68.3%) and patients' spouses (78%). The majority of patients were men (58.5%), and most received a surgical resection of the tumor

(70.7%) as well as postoperative chemotherapy and radiotherapy (97.6%, data from 1 participant missing), see Table 1. Median overall survival was 15 months (range 2-61 months; 4 cases censored).

Known clinical predictors and patient survival

A multivariable Cox regression model including patient age, KPS, extent of resection and MGMT methylation status (model 1, table 2), showed significant associations between patient survival and KPS (HR=0.974, 95%CI=0.949-1.000), and patient age (HR=1.045, 95%CI=1.002-1.091), based on 41 cases (C=0.659). Figure 1a shows Kaplan-Meier curves for patients with the lowest and highest chance of survival at 15 months.

Caregiver mastery, known clinical predictors and patient survival

A multivariable Cox regression model (model 2, table 2) where caregiver mastery was added to the known clinical predictors (patient age, KPS, extent of resection, MGMT status), showed significant associations between patient survival and patient age (HR=1.056, 95%CI=1.004-1.111), KPS (HR=0.973, 95%CI=0.947-1.000), and caregiver mastery (HR=0.843, 95%CI=0.755-0.940), based on 41 cases (C=0.737). Figure 1b shows Kaplan-Meier curves for patients with the lowest and highest chance of survival at 15 months.

Discussion

This is our second study examining relationships between caregiver mastery and GBM patient survival. In both reports, we focused only on GBM patients as these are the most common primary malignant brain tumors in adults and form a relatively homogenous group in terms of treatment and survival time. Data from the current study confirms previous findings.[19] Corrected for other factors known to influence GBM patient survival, caregiver mastery measured shortly

after diagnosis is associated with time to patient death. Indeed, a strong association (HR between 0.839 and 0.843) was consistently found and remained strong in models that included known predictors such as patient functional status (KPS), age, extent of resection, and MGMT methylation status. Adding caregiver mastery resulted in a higher C-statistic (0.737, compared to 0.659 without mastery) indicating the added value of caregiver mastery over known predictors at discriminating between patients who survive to 15 months and those who do not – which is also reflected in Kaplan-Meier curves (Figure1a&b).

Previous studies in other populations (e.g., elderly, dementia, non-central nervous system cancer), also show associations between aspects of caregiver wellbeing and patient outcomes. Most of these show a link between caregiver distress and patients' physical functioning,[27-30] although findings are not entirely consistent – one study found a relationship between patient self-efficacy and caregiver physical health instead.[31] This does highlight the interdependence of caregiver and patient outcomes. Furthermore, unmet caregiver needs have been associated with poorer quality of care delivered,[13] and higher burden as well as poorer caregiver training have been linked to time to patient institutionalization and/or death.[15-17] The GBM patient-caregiver population is different from those investigated before, with its unique neurological and cognitive symptom pattern, rapid onset and decline in patient health. We have now confirmed our initial findings, highlighting that in this population, caregiver mastery is consistently linked to patient survival.

The next logical step in this research trajectory is to determine what constitutes mastery, and through which mechanisms mastery might influence patients' physical health. In our previous report, mastery was not related to sociodemographic variables (age, sex, educational level, relationship with patient).[19] Other studies link caregiver mastery to caregivers' physical

functioning[32] and depressive symptoms, as well as patients' problem behaviors.[10] As mastery is conceptually closely related to resilience and coping, it is likely influenced by social (e.g., social support), biological (e.g., gene-environment), and personal factors (e.g., optimism, hope).[33] While the precise contribution of these factors warrants further research, we have previously demonstrated that it is possible to improve mastery through psychosocial intervention during the disease trajectory.[34] This underscores that caregiver mastery is a flexible state, rather than a fixed trait. Of note, our trial was the only out of eight randomized controlled trials aimed to improve neuro-oncology caregiver wellbeing in our recent Cochrane systematic review, that included a mastery outcome measure.[35] Further work in this area is clearly warranted.

Study limitations included the following. First, the study sample from the intervention study was smaller than anticipated (N=41, as 34.2% of the sample met our criteria). This is reflected in larger confidence intervals than found in our first report. However, this investigation did not aim to build a new predictive model, but rather, aimed to verify a predictive model previously investigated within a larger sample. Second, there was too little variation in IDH status and postsurgical treatment for us to include these variables into the predictive models. Further validation studies of the association between caregiver mastery and GBM patient survival should aim for larger sample sizes so that all known clinical predictors can be incorporated. However, the added value of mastery to other known clinical predictors could still be demonstrated. Third, the Cox regression models performed are tests of association rather than causality. While we made efforts to focus on newly diagnosed patients, used baseline assessments of caregiver mastery to ensure minimal influence of each individual patient's disease trajectory, and corrected for patient variables known to influence survival, causality cannot be ascertained until tested in a randomized, controlled setting. While investigating this as

a primary aim may be unethical, further secondary analysis of caregiver intervention study data could help shed light on this.

This report confirms that in neuro-oncology, caregiver mastery is associated with GBM patient survival. This is vital as replicability of findings is a known difficulty in psychosocial and medical sciences. The need for support among neuro-oncology caregivers is well-defined and systematically high,[5] and yet, caregiver support is often not part of standard care. Our work strengthens the argument that supporting family caregivers will not only improve their own wellbeing, but also has great potential to affect patient outcomes. Within the GBM population which is affected by high symptom burden, dismal prognosis, and limited treatment options, these data propose a new avenue through which both caregiver and patient outcomes may be improved.

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Figures Legends

Figure 1a. Kaplan-Meier curves for the group surviving longer than 15 months, and the group that does not (model 1: patient age, KPS, extent of resection, MGMT status; *N*=35).

Figure 1b. Kaplan-Meier curves for the group surviving longer than 15 months, and the group that does not (model 2: patient age, KPS, extent of resection, MGMT status, caregiver mastery; *N*=34).