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Title: Distress and psychological morbidity does not reduce over time in carers of patients with high grade glioma

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Running title: Carers' levels of distress over time

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Abstract

Purpose: This study aimed to determine how carer distress and psychological morbidity change over time following a patient's diagnosis of high grade glioma (HGG) and identify factors associated with changes in carers' psychological status.

Methods: Carers of patients with HGG planned for chemoradiotherapy were recruited to this longitudinal cohort study. Carers completed questionnaires during patients' chemoradiotherapy, three months, and six months later including: the Distress Thermometer (DT); General Health Questionnaire-12 (GHQ-12); and three single-item questions about understanding of information presented by health professionals, confidence to care and preparedness to care for their relative/friend. Linear latent growth models were applied.

Results: The Time 1 questionnaire was completed by 118 carers, of these 70 carers provided responses to the third time point. Carer distress and psychological morbidity were most prominent proximal to diagnosis, but remained high over time. 62% of participants had moderate or high distress on the DT at Time 1, 61% at Time 2 and 58% at Time 3. Scores on the DT and the GHQ-12 correlated significantly at all time points, as did changes in scores over time ($p < .001$). However, for individual carers, the DT or GHQ-12 scores at one time point did not strongly predict scores at subsequent time points.

Conclusion: In carers of patients with HGG distress levels are consistently high and cannot be predicted at any time point. Carers should be monitored over time to identify evolving psychological morbidity. The single-item DT correlates highly with GHQ-12 scores and is a suitable tool for rapid repeated screening.

Key messages:

This study demonstrates that in carers of patients with High Grade Glioma distress, anxiety and depression are consistently high and scores cannot be predicted at any time point based on that individual's previous scores. Carers need to be monitored over time to identify evolving psychological morbidity. The Distress Thermometer is a suitable tool for monitoring changes in carer distress.

Introduction

Patients with high grade glioma (HGG) experience progressive functional and neurological deficits, cognitive decline, and behavioural and personality changes, over a rapid terminal illness[9]. Their carers actively assist in treatment decision-making and activities of daily living, learn to manage patients' symptoms, and support oral chemotherapy administration[13]. Consequently, carers experience increased distress and burden[2, 14, 20, 21, 23], reduced quality of life[8], and high rates of anxiety[15]. Several studies have explored distress experienced by patients with HGG[10, 18]; however, carer distress may be higher still, and may increase at disease recurrence[24]. Our own data demonstrated that mean carer distress during chemoradiotherapy was significantly higher than patients' mean distress[5, 12]. Carers of patients with primary brain tumors experience health problems and are at increased risk of psychosomatic disorders relating to distress and exhaustion[25]. They also experience poorer social functioning, more mental health concerns and higher carer burden than carers of patients with other cancers[1, 7, 17]. However, most screening and support programs are directed at patients, and do not specifically address carer needs.

Studies with other cancer and palliative care patients have explored carers levels of confidence in caring[6, 16, 26]; however, research has not been conducted to determine whether there is a link between psychological distress and levels of confidence and preparedness in carers of patients with HGG.

We recently reported patients' and carers levels of distress during chemoradiotherapy[5, 12]. However, it is unclear whether carers distress changes over time and whether distress screening predicts psychological morbidity. This study aimed to determine how carer distress and psychological morbidity (anxiety and depression) changes over time and identify factors associated with changes, in order to inform screening, service delivery and carer support.

Methods

Human Research Ethics Committee approval was gained from Curtin University and participating sites. A longitudinal study design collected survey data at three time points: during chemoradiotherapy (T1), and three (T2) and six (T3) months later.

Carers of patients diagnosed with HGG were identified by physicians and recruited through neuro-oncology outpatient teams at four national sites. Patients, and their carer, were eligible if aged 18 years or older and the patient was diagnosed with Grade III-IV HGG, and commencing chemoradiotherapy. Exclusion criteria included inability to complete questionnaires. Data collection methods were described previously[5, 12].

Measures

Participants completed demographics questions, the Distress Thermometer (DT), The General Health Questionnaire (GHQ-12), and three single-item measures on information presented by health professionals; confidence to care for their relative/friend and preparedness to care for their relative/friend. In this manuscript we report on baseline, three and six month data.

Measures of psychological impact

The DT and GHQ-12 were used so it was possible to capture carer distress, as well as anxiety and depression. The DT is a validated visual analogue scale (0-no distress, to 10-extreme distress) used by participants to self-report how distressed they have felt over the past week[27]. Scores were categorised to: low distress=0-4; moderate distress=5-6; and high distress=7-10[3].

The GHQ-12 is a validated 12-item psychometric scale which measures self-reported anxiety and depression[4]. A 0-3 Likert score was employed for each item and a total calculated (range 0-36), with higher scores indicating higher levels of anxiety and depression. Total scores were

categorised to: low distress=1-15; psychological distress=16-20; and severe psychological distress=21-36[4].

Potential correlates of change

Based on a priori hypotheses, the following variables (T1 values) were assessed as potential predictors of changes in distress levels: carer age, carer gender, relationship to patient (spouse/partner vs other), education level (≤ 12 vs > 12 years), significant financial impact of diagnosis (yes vs no), time from diagnosis to T1 (<1 month; 1-2 months; >2 months), patient age and patient ECOG score (0-4).

Also assessed as potential correlates were whether the carer found information presented by health professionals difficult to understand, and their confidence and preparedness to care at each time point. The decision to use single-item questions was made rather than including an additional questionnaire because we did not wish to overburden participants with additional questionnaires yet wished to understand whether these single-items could be introduced into clinical practice. Participants were asked: “How difficult was it to understand the information provided by health professionals?” with a Likert Scale response ranging from 1=not difficult; 3=moderately difficult and 5=very difficult. Participants’ level of confidence was assessed using this question: “How confident do you feel about caring for your friend/relative?” with a Likert scale response ranging from 1=not confident, 3=moderately confident and 5=highly confident. Participants were also asked: “How prepared do you feel about caring for your relative/friend in the future?” with a Likert scale ranging from 1=not prepared at all, 3=moderately prepared and 5=highly prepared. Responses were dichotomised to very difficult (scores 4-5) vs less difficult (scores 1-3); highly confident (scores 4-5) vs less than highly confident (scores 1-3) and highly prepared (scores 4-5) versus less than highly prepared (scores 1-3).

Data analysis

Descriptive statistics, correlation coefficients, t-tests and linear regression were performed using SPSS v21. Linear latent growth models were fitted in Mplus7 to model the change in DT levels and GHQ-12 over time and variables associated with that change. Full information maximum likelihood (FIML) methods were applied to account for missing values due to carer withdrawal. FIML has been shown to give similar results to multiple imputation methods for continuous outcomes[19]. Initially, the trend over time in levels of the dependent variable was estimated before subsequently including explanatory variables in the model. Variables significantly correlated with the dependent variable were identified in univariable analyses ($p < .10$). These were then included in the model and backward elimination applied to identify the most parsimonious multivariable model. Sensitivity analyses revealed the final models were robust to the order in which variables were excluded.

Growth or change over time in a dependent variable is represented in latent growth models by means of an intercept and a slope term. In our models the intercept represents the mean score at T1 (during chemoradiotherapy), and the linear slope the mean change in the dependent variable scores from T1 to T3. Associations are estimated between explanatory variables and the intercept and the slope respectively, allowing for variables to be associated with initial levels of the dependent variable as well as associated with the rate of change in that variable over time. Findings are reported as significant with a $p < 0.05$.

Results

Patient and carer dyads (165) were screened and consented from July 2008 to June 2012. Baseline patient and carer data is reported separately[5, 12]. The T1 questionnaire was completed by 118 carers (71.5% response rate), of these 70 carers provided data up to T3 (59.3%). Ten did not provide data because the patient died before the next data collection point

(2 died before T2 and 8 before T3), and 38 withdrew. For seven of this latter group, the patient died within 2 months of the time at which the missing data would have been collected. To ascertain whether withdrawal was a potential source of bias i.e. whether participant loss was related to patient disease status and hence whether the results may be biased toward carers of patients with less rapidly progressive disease the remaining 31 carers who withdrew were compared with the 70 carers who did not. There was no significant difference in patient survival or ECOG performance between the two groups (Table 1), nor were there any significant differences at T1 in demographic variables, baseline DT and GHQ-12 scores.

Change in distress over time

Table 2 summarises carers' distress scores over time and the prevalence of distress. Sixty-two percent of participants had moderate or high distress on the DT at T1, 61% at T2 and 58% at T3.

Using a linear latent growth model with FIML methods to account for missing values, we examined the change in distress over time and variables associated with that change. DT scores remained relatively stable over time (slope coefficient = -0.133, s.e. = 0.163, $z = -0.814$, $p = 0.415$). A non-significant decrease in DT score of approximately 0.1 (on a scale of 0 to 10) was estimated per three month period. Thus, on average, carers' distress levels declined slightly, but not significantly, from chemoradiotherapy treatment to 6 months after treatment. In multivariable analyses, baseline variables independently associated with change over time in DT scores were time from diagnosis to T1, financial impact of diagnosis, and the carer's expressed level of confidence to care for the patient. Whether the carer found information presented by health professionals difficult to understand and their preparedness to care were not significantly associated with change over time.

At T1 carers who completed their baseline assessment within 1 month of diagnosis were significantly more distressed than either carers with a 1-2 month ($z = 3.080, p = .002$) or greater than 2 month ($z = 2.988, p = .003$) gap between diagnosis and baseline assessment. The estimated slopes or changes over time in distress also differed between the most recently diagnosed group and the 1-2 month ($z = -3.234, p = .001$) and greater than 2 month ($z = -2.891, p = .004$) groups. These differences in trends are evident in Figure 1A – distress levels in the first group declined over time from their higher initial value, whilst those for other carer groups remained stable (Fig 1A).

Carers for whom the patients' diagnosis had a significant financial impact were also significantly more distressed at T1 ($z = 4.177, p < .001$); however, their distress levels declined over time more than was the case for carers for whom the financial impact was not significant at T1 ($z = -2.809, p = .005$). By T3, both groups had similar distress levels (Fig1B).

Whilst carers who were highly confident and less than highly confident in caring for the patient were similarly distressed at T1 ($z = 0.310, p = .757$), changes over time in their distress levels differed significantly ($z = -2.500, p = .012$). The mean distress levels of carers who lacked confidence increased over time from a mean of 5.1 (SD=1.84) to 5.9 (SD=1.26) at T3, whilst the levels decreased for the highly confident carers from the same mean of 5.1 (SD=1.61) to 4.4 (SD=1.55) at T3 (Figure 1C).

Change in psychological morbidity over time

Forty-one percent of participants had signs of psychological stress or severe psychological distress at T1; 48% at T2; and 37% at T3 (Table 2).

Using the same methods as described above, we assessed changes in GHQ-12 scores, and examined factors associated with trends over time. Similar to findings on the DT, GHQ-12 scores remained relatively stable over time on average, with a non-significant trend to a slight

decrease which equates to around 0.5 points per three month time period on a scale of 0 to 36 (slope coefficient = -0.54, s.e.= 0.32, $z = -1.7$, $p = 0.09$). The only significant predictor of change was time from diagnosis to T1. Carers of patients diagnosed less than a month prior reported significantly higher GHQ-12 scores at baseline than carers for whom this period was 1-2 months ($z = -3.946$, $p < .001$) or longer than 2 months ($z = -2.873$, $p = .008$). However, mean GHQ-12 scores declined in carers of the more recently diagnosed patients at T2 and T3, but remained relatively stable in those caring for patients who had received a diagnosis more than a month before the baseline assessment. The decreasing trend in the group with the most recent diagnosis differed significantly from the stable trends in the “1-2 month group” ($z = 2.806$, $p = .005$) and the “longer than 2 month group” ($z = 2.172$, $p = .030$). By T3 all three groups had similar GHQ-12 scores (Fig 2).

Scores on the DT and the GHQ-12 correlated significantly at T1 ($r = .602$, $p < .001$), T2 ($r = .694$, $p < .001$) and T3 ($r = .569$, $p < .001$). Correlation between changes in DT and GHQ-12 scores were also evident from T1 to T2: $r = .498$ ($p < .001$), from T1 to T3: $r = .517$ ($p < .001$) and from T2 to T3: $r = .546$ ($p < .001$).

Stability in distress over time

Linear regression analyses were conducted to ascertain whether later distress scores could reliably be predicted based on prior scores. In the regression of the DT score measured at T2 regressed on the T1 score, the R-squared value was 0.194 ($r = .441$). Hence, only 19% of the variability in the T2 score was explained by the T1 score. Similarly, the R-squared for predicting T3 from T1 was 0.143 ($r = .378$), for predicting T3 from T2 was 0.264 ($r = .514$). Hence, a carer's distress levels at one time point were not predicted strongly based on levels at a previous time point.

The R-squared values in regressions of later GHQ-12 scores regressed on earlier scores, were: T2 from T1: R-squared = 0.369 ($r = .607$), T3 from T1: R-squared = 0.216 ($r = .465$), T3 from T2: R-squared = 0.372 ($r = .610$). Although a higher percentage of the variability in the later scores were explained by earlier GHQ-12 levels than was the case for the DT data, substantial variation was left unexplained. Hence, individual carers' DT and GHQ-12 scores were highly changeable from one time point to the next.

Discussion

This study aimed to determine how carer distress and psychological morbidity changes over time and identify factors associated with changes in these states, in order to inform screening, service delivery and carer support. The experience of caring for someone with HGG is not static over time. While some patients diagnosed with glioblastoma remain clinically stable over six months, only 50% of patients who receive chemoradiotherapy have not progressed by six months from starting treatment[22].

Carer distress and psychological morbidity are most prominent proximal to diagnosis, but remain high over time

The higher distress reported by carers who completed questionnaires more proximate to the diagnosis was notable, although distress improved over time more in this group than in carers completing questionnaires later. This likely reflects heightened distress immediately after diagnosis, which may have been experienced by all carers if surveyed within the first month of diagnosis. This finding suggests that carers may need enhanced psychological support early in the post-diagnostic period, which often corresponds to a period of uncertainty regarding final diagnosis, prognosis and treatment. Immediate distress was partially ameliorated after the first month from diagnosis; similar findings have been reported previously[24]. The finding of early distress highlights the need to ensure carers receive appropriate support services after hospital

discharge and during development of a treatment plan. We have shown in our previous work that poor communication about prognosis is particularly distressing for patients and carers[11].

From one month after diagnosis, distress levels remained high and did not attenuate over six months. Findings for the DT and the GHQ-12 were consistent. This may reflect the effect of some carers with progressing patients experiencing increased distress, and others with stable or improving patients experiencing reduced distress, or it may reflect continuing high distress levels in this group as a whole. Although others have reported increased carer distress at the point of recurrence[24], our study design did not allow us to test this.

As reported in our previous paper [12], consistency between the GHQ-12 and the one-item DT supports use of the DT for carer screening in routine clinical practice and suggests that a more detailed screening tool is unnecessary. As distress scores for individuals were not reliably predicted based on their prior scores, carer screening for distress at a single time point is likely to be inadequate; there is no point at which screening for carer distress is optimal, or can be foregone. Healthcare providers should remain vigilant in monitoring carer distress throughout the patient's illness.

Unconfident carers are more distressed

Distress levels of carers who were less than highly confident increased over time, while they decreased for highly confident carers. Our findings suggest that using a simple screening question such as "To date, how confident do you feel about caring for your friend/relative?" may be a useful tool to identify less confident carers. Nevertheless, confidence in caring is likely to be a multidimensional construct which may have different meaning for individual carers, and may variably incorporate the caregiver's perception of their competence with physical or intimate care, ability to perform unfamiliar household tasks, preparedness to provide emotional support, and confidence in providing medication or symptom care and

liaising with healthcare professionals, as well as their ability to care for the patient in the context of pre-existing work or parenting responsibilities. A previous study in carers of patients with cancers demonstrated an increase in carer confidence after attending a six hour group-based carer education program[16]. Carers of bone marrow transplant recipients also gained confidence following attendance at a series of education sessions[26]. Additional research has been conducted around carer confidence in palliative care [6]. In carers who screen as less than highly confident, healthcare providers should explore areas where they lack confidence, and open a dialogue about additional support strategies promoting carer enablement and autonomy. To our knowledge interventions to improve confidence for carers of people with brain cancer have not been tested.

Limitations

This study followed participants over a six month post-diagnostic period, but we acknowledge that it may have also been informative to target key clinical events, such as time of disease progression. Time points were selected to balance the information obtained with participant burden. Completion rates declined over time, as anticipated in a group who are juggling competing demands of caring with other duties. However, data analysis accounted for participant withdrawal and neither carer or patient characteristics, nor distress levels differed between those who continued and those who withdrew. Additional data collection after six months would have provided further insight into carers' distress; however, we were cognisant of the difficulties of maintaining compliance and chose to stop at 6 months because after this point the proportion of deceased patients would increase substantially, with a commensurate increase in missing data.

Conclusion

Our findings have implications for service delivery, some of which can be readily implemented. Carers of patients with HGG can be screened for distress with two simple tools: the Distress Thermometer, and a single-item question about confidence in caring. Distress is highest most proximal to diagnosis; it is unclear whether additional support, information, and certainty about management plans may be able to modify early distress. The construct of carer confidence needs to be better understood, and interventions to improve carer confidence developed and tested for their ability to reduce psychological morbidity. Distress screening must not be limited to the early post-diagnostic period; there is a requirement for ongoing evaluation of carer distress and vigilance for psychological morbidities. Resourcing for psychological and psychiatric assessment and management of carers must be an integral part of brain tumour services.

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Tables

Table 1: Patient Survival, time from diagnosis to T1, ECOG and distress scores at T1 by drop-out status

Table 2: Distress and GHQ-12 scores at each time point (for overall sample)

Figures

Fig 1A: Mean Distress Thermometer score by data collection time point and time from diagnosis to T1

Fig 1B: Mean Distress Thermometer score by time and baseline financial impact

Fig 1C: Mean Distress Thermometer score by time and baseline confidence to care

Figure 2. Mean GHQ-12 score by data collection time point and time from diagnosis to T1

Conflict of Interest Statement

The authors have no conflicts of interest to declare. We have full control of all primary data and agree to allow the journal to review the data if requested.

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