Document related to the research project:

Long-term Survivors of High-grade glioma

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Background

High-grade glioma (HGG) occurs most frequently in patients 45-70 years of age (1, 2), with a male-to-female ratio of 1.5:1(3). Treated with optimal therapy the median survival rate for GBM (WHO grade IV) is approximately 15 months (4) with a two-year median survival rate of 30% and a five-year survival of 10% (5, 6). Standard initial treatment for HGG involves surgery either as diagnostic biopsy or maximal surgical resection (7). HGGs are infiltrating rapidly growing tumors(8), making total resection impossible and the majority recur within two cm of their original location(9, 10). HGGs are highly vascular and rich in a protein, which promotes angiogenesis(11). The Stupp regimen; i.e. concomitant chemoradiotherapy followed by adjuvant maintenance chemotherapy with temozolomide (TMZ) is currently the standard post-operative treatment for patients with newly diagnosed GBM(6, 12). TMZ is administrated during radiotherapy and for six maintenance cycles on five out of 28 days. The treatment response is evaluated by brain imaging and typically carried out prior to the third and sixth cycles. This regime has shown a statistically significant and clinically meaningful survival benefit from 12.1 to 14.6 months(13) with minimal additional toxicity(12). Even though multimodality treatments with neurosurgical resection or biopsy, radiotherapy and chemotherapy(14) have improved HGG prognosis(1), long-term survival is rare(15-17), however long-term survivorship (LTS) studies (> 5 years) have been published(17, 18). As there is currently no cure, progression-free survival is the primary outcome of the multimodal treatment. No standard treatment exists in the event of tumour progression (13) however; reoperation or treatment with an angiogenesis inhibitor (bevacizumab) in combination with chemotherapy (irinotecan) can be an option. The antiangiogenic therapy for HGG works by inhibiting new blood vessel formation and promotes regression of existing vessels(4). Future treatment options include vaccination and treating the tumour with electric fields(19-22). Recent discussions regarding treatment strategies and outcomes consider the consequences of survival time versus quality of life (QOL), the HRQOL being suggested to influence the treatment decision(23). The purpose of antineoplastic treatment is to achieve progression-free survival with delayed neurological and cognitive deterioration, and to maintain or increase HRQOL(11). HRQOL has become increasingly important next to more traditional outcome measures such as progression-free survival (24) and can guide a specific treatment strategy(23). The complexity of how a health-related issue interferes with QOL is not fully understood, mainly because HRQOL differs according to individual perspectives and preferences. Hence, the clinical outcome of long-term HGG survivorship and their caregivers´ QoL poorly understood.

Long-term survivors of HGG

HGG has a significant impact on the daily life of patients and their caregivers (25-27). Although research is emerging on patient-centered care and the psycho-social needs of patients with HGG and their caregivers, there is still lack of knowledge regarding long-term survivorship in experiences, needs and preferences for supportive care and palliation three years after the HGG diagnosis. LTS may face challenges as their survival permits them to be (re)-integrated into their previous life with deficits that make living troubling (18, 28) and at the same time realize that they are functioning relatively well after standard oncological treatment resulting in a survivorship feeling (29). Lovely et al. made one of the few existing studies that have included the caregivers' perspective, and found significant changes in the relationships among the HGG survivors and their caregivers, a high frequency of depression and worsened symptoms (17).

Caregivers of persons with HGG

An increasing number of relatives provide care at home as hospitalization is only offered to those in need of treatment or specialized care. In order to support best practice based on evidence, there is a need for an understanding of daily live experiences and how they can be met. A research group from Pittsburgh, USA studied the predictors of distress in caregivers of persons with primary malignant brain tumor (30, 31), lost working hours (32), perceptions of economic hardship (33) and sleep characteristics (34). Most of these studies recruit caregivers in the early stage of the HGG trajectory. Caregivers of patients with HGG are known to experience a caregiver burden resulting in negative health status as hypertension, altered immune function and overall poor physical health. Yet, research has also found that being a caregiver can add value as they experience satisfaction from completing tasks and assisting their love ones (the patient)(35). Limited research describes the emotional and physical stress response of caregivers of LTS of a HGG(17).

Rationale for the study protocol

This study builds on the limited body of existing literature combined with the results from our previous research conducted with 30 *newly diagnosed* patients with HGG and 33 of their caregivers. We established an overview of the daily life experiences when diagnosed with a HGG or being a caregiver. Descriptions of needs and preferences from time of diagnosis to one year exist (36, 37). However, such data are still lacking the representation from LTS and their caregivers. We identified that *newly diagnosed* patients and their caregivers used an *individual strategy for acquiring prognostic information* (PI) and this revealed two different strategies for obtaining additional PI that involved either seeking or limiting the amount and content of PI. How and whether these or other strategies are applied as long-term survivors of HGG is unknown. Patients and caregivers *shared hope,* and it concerns a strong sense of solidarity between the patient and their caregiver. However, at the same time our findings also revealed that the caregivers experienced a burden due to the changed role from relative to becoming a caregiver. Hence, the relationship between the patients and their caregiver was often challenged by lack of energy and difficulties in managing the patients' limitations, e.g. the cognitive changes. How this might be expressed for caregivers to LTS has not been described before. Finally, the newly diagnosed patients were found to be *engaged in health promotion activities,* involved the joining forces of patients and caregivers towards a healthier lifestyle, facilitated by shared hope reflecting that being involved and taking responsibility were highly valued. For the 12-month survivors who participated in our former study we identified a decrease in this engagement. Therefore it is of great interest to explore the level of such engagement among the 3 years survivors and their caregivers. Moreover, it is of great interest to explore their preferences for involvement in treatment decisions and thereby be able to discuss its implication for clinical practice.

Aim

This mixed methods study aims to address perspectives on daily life experiences of long-term survivors with HGG and their caregivers as well as the needs and preferences for support, rehabilitation and palliation.

Methods

This mixed-method study applies separate telephone interviews with patients and their caregivers and self-reported questionnaires for patients. The mixed methods design is a convergent sequential design using an identical sampling.

Study participants and sampling

The inclusion criteria are participants ≥18 years of age, diagnosed with HGG for a minimum of 3 years with the ability to speak and understand Danish. Caregivers are eligible if they are named by the patient as being one of the closest relative(s) providing care at home on a regular basis.

Recruitment

Patients were identified via a database at the Department of Oncology, Rigshospitalet, University of Copenhagen. A nurse coordinator contacted the patients diagnosed with GBM for more than 3 years. The identification of patients was given to the principal investigator (KP) in case they accepted to be contacted for further information. Patients were also asked to name their closest caregivers, and these were contacted regardless the patients´ acceptability. The participant flow is scheduled at Figure 1.

Design

The dominant status relies on the qualitative data as the interviews are emphasized as the best suited method to address the primary aim of this study(38). The interviews follow a semi-structured interview guide for patients and for caregivers (Tables 1 and 1).

Figure 1 Study Flow

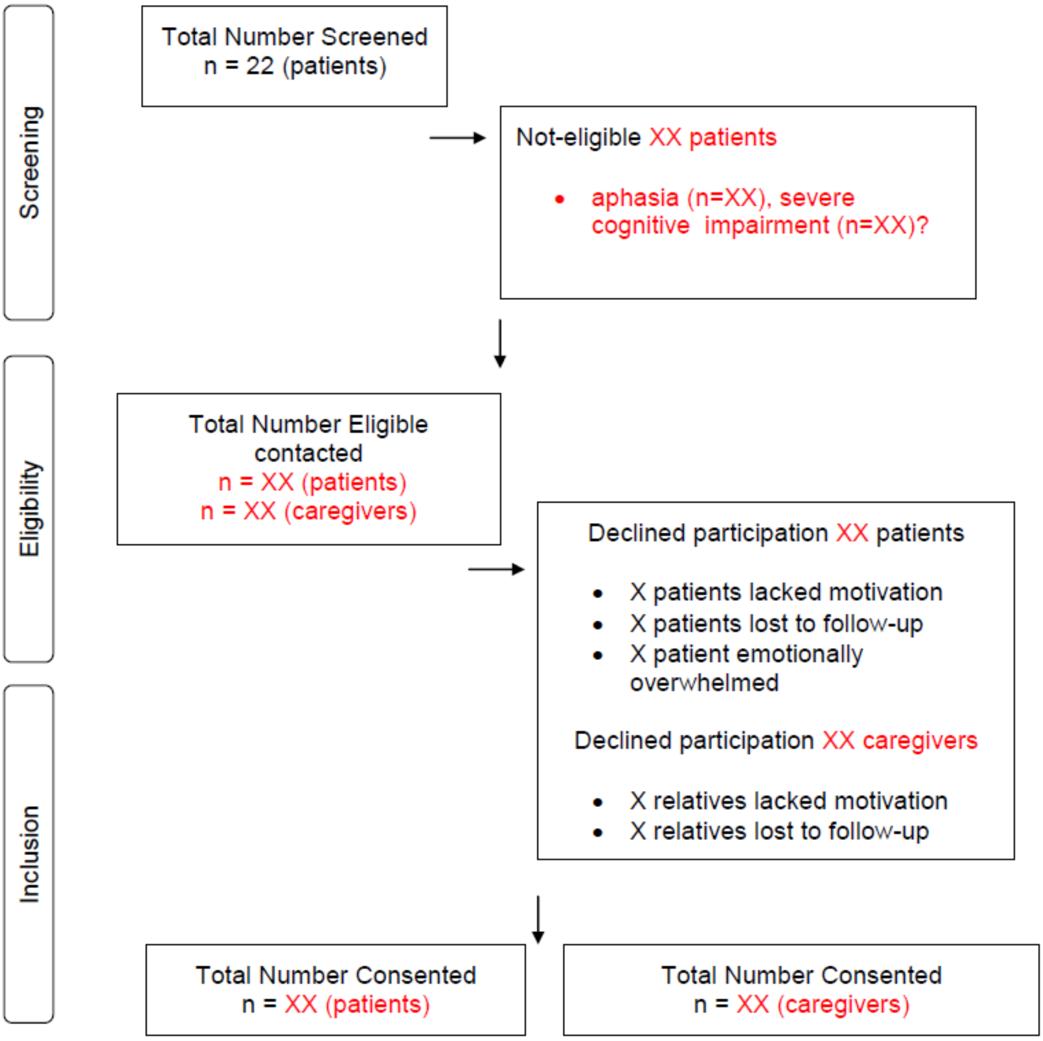

Table 1: Interview topics for patients

Research questions	Examples of interview questions
What happened and how did the patient experience the time between the first symptoms and the operation?	Please describe your overall disease- and treatment trajectory - what happened and how did you experienced the episodes?
Does the patient experience any symptoms/side effects, and what are the consequences and how are they managed?	Do you have any complaints/symptoms/side effects? Does it have any effect on the way that you manage your life? Is there anything that has helped you to overcome symptoms / side effects? Have you noticed difficulties in remembering, reading, or in attention? Have you noticed whether you have changed your way of behaving? How do you cope/manage with this? How is your mood? Do you receive medical treatment for depression? Do you feel depressed?
How are everyday life, work, network and support experienced? Are there any changes in lifestyle?	Can you describe a typical day? Has it changed from earlier? What do you usually do in your spare time? Do you/can you enjoy yourself now? How would you describe your network? Do you have children? How are they affected? What attitudes / reactions have you experienced to your disease? How is your working situation? Have you changed anything in the way you live your life (e.g. diet, sleep quality, exercise, everyday activities, social contacts)
How does the patient experience the communication and information with the health professionals?	What have the health professionals told you about your disease? What do you think about that information? Do you lack any information? Have you looked for information - of what kind and where? How do you think about the way the health professionals address you?
Does the patient experience challenges during everyday activities? What are the needs for rehabilitation?	Is there anything you find difficult to do? What is your need for rehabilitation? Do you have any experience with rehabilitation services, at hospitals or within the municipality?
Is the patient motivated to meet her/his needs? Any preferences?	What would be the best thing that anyone could do for you these days? Do you need any advice on how to handle your situation/condition/symptoms or everyday activities? Are you getting the support you need from the family / hospital / general practitioner?
What are the preferences of the patient in relation to support and rehabilitation & palliation?	Can you imagine being physically active now, and how do you prefer to be active? How many hours a week are you physically active now? Can you imagine accepting psychological support to handle your situation? Can you imagine getting help to exercise your memory and attention? What do you do to help yourself? Would you like to participate in physical exercise, cognitive training and/or psychosocial support? (think about preferences, type, location, frequency, duration, supervised or not supervised). What you are hoping for? Have you ever discussed the notion of hope with anyone? Have you been introduced for palliative care?
Does the patient seek help from alternative therapy as a supplement to standard treatment?	Have you considered any alternative treatment to relieve your situation/condition? Please tell me about your considerations. Have you discussed this with someone?
Are there financial worries and how important are they?	Are you worried about your financial situation?

How does the patient prioritize her/his needs? Is the patient offered help and by whom?	What needs are the most important for you to be met? Have you done anything to solve an unmet need? Do you have suggestions to how we could improve the situation/condition for future patients? Is there any advice you would give other patients being diagnosed with this type of brain tumor? Is there anything else you would like to tell me/or ask me about?

Table 2 Interview topics for caregivers

Research questions	**Examples of interview questions**
How did you experience the period between the first symptoms and the operation?	How did you find out that X was sick? Describe what you observed, what happened and how you did experience that period? How was it to be a caregiver while X was admitted to hospital? What has happened since the last interview?
Does the caregiver experience the patient has any symptoms/side effects, what are the consequences and how are they managed?	How would you describe what X experiences these days? Do you observe any symptoms/side effects? Does it have any effect on the way you live your life? Is there anything that has helped you to manage X´s symptoms / side effects? Have you observed any difficulties in remembering, reading or attending for X? Has he/she changed personality/ way of behaving? How does that affect you? Have you ever thought that brain cancer differs from other types of cancer? Please tell me about this.
How is everyday life, network and support? What norms and attitudes do the caregivers experience? Are there any changes in behaviour?	Can you describe a typical day? Has that changed from earlier? What do you usually do during your spare time? Do you enjoy yourself now? Are there family / friends that have special meaning to you after X got sick? How? Do you have children? How are they affected? How would you describe your network? What attitudes / reactions to the disease, do you meet? How is your working situation right now? Have you changed anything in the way you live your life (e.g. diet, every day activities)?
How does the caregiver experience the communication and information with the health professionals?	What have the health professionals told you about X´s disease? Did you receive the right amount of information? How did you find the written information? Do you lack any information? Have you looked for information, of what kind and where? How do you find the way the health professionals address you?
Does the caregiver experience any challenges in the physical environment? What are the needs of rehabilitation?	Do you experience practical problems in your life after X became diseased? Have you taken on another role since X became sick? How does it affect you?
Is the caregiver motivated to meet her/his own needs? Any preferences?	What would be the best thing someone can do for you right now? Do you need any advice on how to handle your situation? Are you getting the support you need from family / hospital / general practitioner? What does hop mean to you? Have you discussed this with anyone? Is this a stressful period for you? Do you experience any symptoms, physical problems? Have you received help to manage your changed responsibilities? Have you been involved in decisions regarding X´s treatment plan?
What are the preferences of the caregivers in relation to support and rehabilitation & palliation?	What do you do to help yourself (physical, social and psychological activities)? Would you like to participate in a support group/information group? Think about preferences, type, location, frequency, duration, supervised or not supervised support. Have you been introduced to palliative care?
Does the caregiver seek help from alternative methods as a supplement to standard treatment?	Have you considered any alternative treatment to relieve your or X´s situation/condition?

Are there financial worries and how important are they?	Are you worried about your financial situation now that X is sick?
How does the caregiver prioritize her/his own needs?	What needs are most important for you to be meet? Have you done anything to solve an unmet need? Do you have suggestions on how we could improve the situation/condition in the future for caregivers and for patients with a brain tumor? Is there any advice you would give to other caregivers? Is there anything else you would like to tell me/or ask me about?

Quantitative Data

Information about socio-economic conditions, disease and treatment variables will be obtained by the investigator at baseline. Disease, treatment and clinical variables will be collected including the WHO performance scale (PS) which will be obtained by medical chart review. The self-reported questionnaires (quantitative data) are viewed as a useful supplemental data source, and embrace the topics as distress, anxiety and depressive symptoms:

- Anxiety/depression – The Hospital Anxiety and Depression Scale (HADS)
- HRQOL - The Functional Assessment of Cancer Therapy, General and Brain (FACT-G and FACT-Br)
- Physical Activity - Questionnaire on leisure time physical activity level

The qualitative and quantitative data will be integrated during the interpretation and findings will draw inferences using both approaches.

Theoretical Framework

The qualitative and quantitative research components represent different paradigmatic traditions including diverse ontological, epistemological and methodological assumptions. However, these paradigms are not necessarily incompatible (39). This study applied a pragmatic paradigm, reflecting a pluralistic view using both inductive and deductive reasoning. Applying a qualitative perspective, the present interviews seek to capture the subjective experiences of the study participants related to their life situation.

Ethical issues

This study poses no serious ethical problems. The study is registered at The Research Ethics Committees at the Regional capital (file No. xxx) and the Danish Data Protection Agency (file No. xxx) and carried out in accordance with the Declaration of Helsinki (40). Written consent will be obtained from each participant, including permission to record the interviews and to use anonymized quotes in future presentations. Participants will not be identifiable and the authors will disseminate the findings in peer reviewed publications and at relevant conferences.

Data collection

This study involves individual semi-structured telephone interviews with LTS of HGG and their caregivers. Socio-economic conditions, PS, disease and treatment variables are obtained from the medical records. Participants receive a questionnaire by mail with written instructions on how to complete and return their responses in an enclosed, addressed envelope.

Analysis

The semi-structured interviews will be recorded and transcribed in full length by either the interviewer or a research assistant. Interview data will be transferred to NVivo 10 software program(41). A thematic analysis will be conducted for the analysis of the semi-structured interviews. Thematic analysis is a basic method for qualitative analysis as it identifies, analyzes and reports themes and patterns within data(42). The findings will be presented in themes and subthemes. A theme is an expression or context being defined as important by the researchers. In this study a theme is not necessarily dependent on quantifiable measures, but rather captures an important meaning in relation to the research questions and aims(42). Data from the interviews are descriptive in nature and reflect the subjective experience of the life situation of patients with HGG and their caregivers. The steps for thematic analysis are inspired by Braun and Clarke and as follows(42); Step 1) Data are transcribed immediately after an interview by the investigator or a research assistant. Transcriptions are read several times until the investigators are familiar with the depth and extent of the content. This process guides the investigators to the next level of analysis. Step 2) The text is read and divided into units of meanings, which are identified by the investigators. Some meaning units are sentences, others a whole paragraph. In this process data are coded in order to organize them into meaningful groups. This process assures that the whole dataset is systematically worked through by the investigators. Step 3) Then, the codes are analyzed in order to consider if different codes can be combined into mutual themes. This three step process will result in a collection of themes and sub-themes.

Statistical analysis

The KPS, the HADS sub-scales, the FACT-Br sub-scales and the responses to the ordinal items of the leisure time physical activity scale were analysed separately. Socio-economic information and data from questionnaires will be entered into a database. The questionnaires will be analyzed according to their manuals. Categorical variables are reported as frequencies and percentages, while continuous variables are reported as mean and standard deviations (s.d.) using a significance level of p\0.05. HADS and FACT-Br data refer to the normative values. The statistical analysis was performed with SAS statistical software, version 9.3.

Perspectives

This study will add new evidence to the existing knowledge in regard to the needs and preferences of the LTS and their caregivers and could be incorporated into future clinical guidelines for rehabilitation and supportive care. Discussion of implication for clinical practice will be included in future publications.

Publication plan

Patient and caregiver perspective on long-term survivorship of HGG – a mixed methods study

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