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Title

Investigating the impact of headaches upon the quality of life of glioblastoma multiforme patients: a qualitative study

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Keywords

Glioblastoma multiforme, headache, quality of life, qualitative, neuro-oncology

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Abstract

Objectives

Headaches and facial pain have been identified as the most prevalent form of pain amongst patients with glioblastoma multiforme, the most common malignant primary brain tumour. Despite this, minimal research has been undertaken investigating the direct and indirect impact these headaches have upon their quality of life. Therefore, in this study we aimed at gaining a personal insight into the importance and impact that these headaches have upon the quality of life of glioblastoma multiforme patients.

Design

Exploratory study utilising face-to-face semi-structured interviews. Interviews were audio-recorded, transcribed verbatim and then qualitatively analysed using thematic analysis.

Setting

Participants recruited from a tertiary referral hospital in Birmingham, UK.

Participants

Purposive sampling of 14 registered outpatients recently diagnosed with glioblastoma multiforme.

Results

Three themes were identified: 1) An underlying attitude of determination and positivity. 2) Impact of headache unpredictability upon social interaction. 3) Headaches found to act as a springboard onto thoughts regarding their disease and future.

Conclusion

Whilst the quality of life of patients with glioblastoma multiforme is clearly multifactorial, headaches do indeed play a part for some. However, it is not the direct pain of the headache as one might expect that impacts upon the quality of life of these patients, but the indirect effect of headaches through limiting patients' social lives and

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3 by serving as a painful psychological reminder of having a life threatening illness. In clinical practice, utilising
4
5 headache diaries for these patients may help provide a more comprehensive assessment and further aid
6
7 management plans. Alongside acting as an important reminder of the potential secondary implications of this
8
9 disease, suggestions for future research include quantitatively investigating whether headaches can act as a
10
11 prognostic indicator for quality of life within this patient demographic and determining whether these
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13 conclusions also hold true for a wider spectrum of brain tumour patients.
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Strengths of this study

- As far as the authors know this is the first descriptive exploratory study that has investigated the impact that headaches have upon patients with terminal brain tumours and the subsequent coping mechanisms that patients develop in response to this.
- The nature of the semi-structured interviews and iterative process of analysis allowed emerging themes to be built upon as the research progressed and hence develop a deeper understanding of the issues discussed.

Limitations of this study

- Family members present during the interviews may have had the potential to affect the way in which participants answered questions, especially when discussing such a personal and emotive subject as quality of life. However overall it was seen as a benefit having them present as in most cases they aided in participant memory recall.
- Participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their quality of life - potentially missing patients who were eligible as far as the inclusion and exclusion criteria were concerned, but unwilling to discuss their quality of life and symptoms.
- All participants were newly diagnosed with a glioblastoma multiforme tumour and therefore the results may not be directly transferable to patients with recurrent glioblastoma multiforme who have had more time to process and live with their condition.
- Due to resource and time limitations, participant feedback and checking was not possible.

Background

Glioblastoma Multiforme (GBM) tumours are histologically the second most frequently reported primary brain and central nervous system tumour (accounting for 16%) and the most common form of malignancy within this subset of neoplasms,[1] with an annual incidence in the US and Europe of 3 per 100,000 people.[2] The median age of diagnosis of this 2:1 male predominant disease is 64 years and it is the most aggressive form of the group of brain tumours known as astrocytomas (themselves a form of glioma).[3] GBM tumours are categorised as a grade IV astrocytoma, stipulated by the 2000 World Health Organisation system, which grades astrocytomas from I-IV.[4] Despite advances in treatment technology over the last few years, in particularly with regards to chemotherapy,[5] due to the widely infiltrative nature and rapid growth of this tumour, associated life expectancy is still low,[3] with a median survival of 15 months from diagnosis and a 2 year life expectancy ranging from 8-26%.[6] To improve patient survival, standard treatment usually involves surgical debulking and biopsy of the tumour, followed by radiotherapy and chemotherapy.[5] As a result of this poor prognosis in GBM, matters of quality of life (QoL) become of utmost importance to patients and those around them.[7]

The term QoL encompasses multiple aspects of a patient's overall well-being, including physical, material, social and emotional wellbeing.[8] Over the last 2 decades, as survivorship of GBM has gradually increased and patients have survived longer to experience the co-morbidities of associated treatments,[6, 9, 10] QoL has become an ever more important factor in the management of such patients. Recommendations have been made for randomised trials to include QoL and palliative care outcomes as endpoints,[11] although reliably measuring QoL in high grade glioma patients has proven difficult due to high rates of drop out bias and loss of participants' ability to complete complex forms.[12]

A significantly reduced overall QoL is seen in the majority of newly diagnosed high grade glioma patients, when compared with healthy controls.[13, 14] Descriptive research into the specific symptoms that affect QoL in glioma patients has primarily focused on 6 manifestations: fatigue, sleep, pain, seizures, mood disturbance and cognitive function.[15] However, despite headaches having been reported as the most prevalent form of glioma associated pain, experienced by up to 52% of GBM patients,[16] no widely available or published

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3 research has investigated the impact that these headaches have upon the QoL of GBM patients. This may partly
4
5 be due to the multi-faceted complexity of investigating QoL and gaining patients' perspectives within this
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7 population.
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11 Hence, with up to half of patients with GBM being affected by headaches,[16] if an association between
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13 headaches and QoL is identified, a deeper understanding of this could lead to the implementation of appropriate
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15 precautions or interventions, with the aim of improving the management of headaches in GBM patients and
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17 subsequent QoL.
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Aims

1. To establish an insight into the importance of headaches to glioblastoma multiforme patients.
2. To investigate the impact of headaches upon the mindset of patients being treated for a terminal brain cancer.

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Methods

Design

This exploratory qualitative study employed face-to-face semi-structured interviews with patients being treated for GBM at the Queen Elizabeth Hospital Birmingham (QEHB) – all of which were interviewed between 5-21 weeks post-radiotherapy. Each participant was only interviewed once. The purpose of selecting this time period was to interview participants in a position where they felt they had enough experience to talk and reflect about their condition, symptoms and associated QoL, whilst not being in an intensive part of their treatment pathway. Additionally, all participants were required to be over the age of 18 at the time of being informed of the study. Potential participants with a WHO Performance Status >2 (not capable of self-care) were excluded from the study.

Sample size

Of the 21 eligible participants identified and informed of the study using purposive sampling, 14 were subsequently interviewed, within the Cancer Centre Department of the QEHB. Of the 8 who were not interviewed, 5 were because of late hospital appointment changes, with only 3 actively declining to take part.

Data collection

Over a 5 month period (February-April, July and September 2015) potential participants were identified and informed of the study by a MacMillan Clinical Nurse Specialist in their existing care team. This was carried out either face-to-face or by telephone, using a participant information sheet to explain the purpose of the research, with interviews scheduled to coincide with their next outpatient appointment at the QEHB. The interviews, each lasting 15-40 minutes, were undertaken by a senior medical student (SB), as part of a qualitative focused intercalated research degree, following a pre-written interview topic guide (Supplementary File 1). This topic guide was designed by the research team (SB and AL) to explore both headache and non-headache participants' views regarding the changes in their life and symptoms experienced in the build up to and since their diagnosis of GBM. This specifically focused upon QoL and the impact that headaches or the potential for headaches and what they had now come to represent had upon this. The reasoning for asking additional questions, not just

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2
3 related to headaches, was so that the interviewer could immerse themselves and grasp as much as possible
4 regarding the personal challenges that these patients now face - in turn allowing for a more comprehensive
5 understanding and analysis of the impact and role that headaches play within this. Due to the small scale nature
6 of the study and time restrictions, the topic guide was not pilot tested with participants; however, the semi-
7 structured nature of these interviews and iterative process of analysis allowed a continuous adaption of the
8 interview guide throughout the study, so as to build upon emerging themes. As the study progressed, no
9 questions were added or removed from the interview guide, but a greater emphasis was placed upon the
10 thoughts and feelings that participants associated with headaches. No field notes were made during the
11 interviews, however each interview was transcribed as soon as possible so as to retain non-verbal information
12 that the interviewer identified during the interview.
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25 **Data analysis**

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27 Data was analysed following Braun and Clarke's 6 Step Thematic Analysis, allowing identification and analysis
28 of patterns and themes.[17] The interviews, audio recorded digitally, were transcribed verbatim (including notes
29 on participant body language), with transcripts read and re-read to ensure familiarity, before deriving codes.
30
31 Once interviews were coded, they were then collated to generate themes and extract important issues,
32 viewpoints and dynamics, which led to a subsequent active data search for disconfirming evidence.[18]
33
34 Analysis of derived codes and theme recognition was carried out independently by the interviewer, a lecturer in
35 qualitative methods (AL) and an additional senior medical student (SM), to identify and understand potential
36 multiple interpretations of the data and reduce the likelihood of producing results which were partial or
37 biased.[19] This theme identification began before data collection was complete in order to explore initial
38 findings in greater depth. All research activities were recorded in detail to allow methodological critical
39 appraisal and increase trustworthiness, a concept used to describe reliability in qualitative research.[20]
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41 However, due to the limited time frame, further validity checking utilising participant verification was not
42 feasible.
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56 Interviews were selected over focus groups due to the highly sensitive nature of discussing QoL within this
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3 population, where participants may have felt reluctant to divulge such personal information in front of strangers.

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5 However, a family member was allowed to contribute to the interview, if requested so by the participant.
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8 9 **Research ethics**

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11 All patients who took part in this study participated voluntarily. Written informed consent was taken from all
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13 participants prior to starting each scheduled interview, which were all undertaken within a quiet confidential
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15 setting in the Cancer Centre, QEHB. Participants were also informed that they could stop the interview at any
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17 point for any reason. All confidential participant information was stored on encrypted memory sticks, accessible
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19 only to the researchers. This research was approved by the 'West Midlands – Solihull' National Research Ethics
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21 Committee (15/WM/0012) with subsequent site-specific approval from the QEHB Research and Development
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23 Department.
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Results

Of the 14 participants (median age = 47.5 (IQR 38 - 63) years; 8 male) interviewed, 6 reported as experiencing headaches within the last month, 1 reported a unilateral facial pain and 1 other with light-headedness, but no headaches (Table 1). The remaining 6 patients reported as having neither headaches nor facial pain nor lightheadedness. All participants reported varying levels of tiredness and fatigue. Additionally, all participants requested to have a family member or carer present during the interviews.

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Table 1

Participant No.	Gender	No. of weeks interviewed post-radiotherapy	Headaches experienced within the last month
1	Male	12	Yes
2	Female	8	Yes
3	Male	8	Yes
4	Female	5	Yes
5	Female	13	No
6	Female	13	Yes
7	Female	12	No
8	Male	5	No (but facial sensitivity/pain)
9	Male	5	Yes
10	Male	20	No
11	Male	15	No (but light-headedness)
12	Male	8	No
13	Male	18	No
14	Female	17	No

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3 Grouping and interlinking of codes, derived from all of the transcribed interviews, yielded three themes,
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5 however only the first two of these, 'Underlying determination and positivity' and 'Headache of social
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7 situations', were initially apparent. These themes primarily describe the thoughts, feelings and emotions
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9 conveyed by the participants, regarding their approach to the challenges that day-to-day life now presents and
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11 the role of headaches within this. Only after full data immersion and code collaboration was the third theme,
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13 'Psychological springboard of headaches', developed. This final theme aims to provide an insight into the
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15 potential implications that headaches, and what they have now come to represent, may have upon self-
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17 contemplation in this population regarding their condition and future. Of these themes, 'Underlying
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19 determination and positivity' was developed from all participants (both headache and non-headache), with the
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21 remaining two themes developed only from the 6 participants who developed headaches and the 2 participants
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23 who reported a reported facial pain and lightheadedness.
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26 27 **Underlying determination and positivity**

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29 A consistent theme amongst almost all participants was a resounding determination to 'get on with life' and not
30
31 to be bound by the symptomatic implications of their condition, referred to by several as 'the nature of the
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33 beast':
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36 'I try not to think about it, which may not be the healthiest psychological way to go about it. However, it just
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38 means I can get on throughout the day, getting on with things that I like to do and want to do.' (P2)
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41 Acceptance of the situation, alongside the want and almost need to block it out in order to carry on with as
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43 normal a life as possible, was a commonly reported trait. Potential reasoning to partially explain this behaviour
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45 can be drawn from the frequently reported frustration that came with participant's self-recognition of dwelling
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47 on their illness:
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50 'obviously I think about the future, because I know it's not curable, it's a controllable cancer. I think if,
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52 it's a bit frustrating if you think about it too much, but then you've got to be thankful for what you've still got
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54 don't you' (P5)

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56 Whilst this theme is not directly related to headaches, the principle of leading as normal life as possible was the
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3 fundamental aspect of most of the participants' approach to their brain tumour, expressed by 12 of the 14
4 interviewed. With this in mind, this then helps contextualise the next 2 themes, discussing ways in which
5 headaches were found to disrupt normality.
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10 11 **Headache of social situations**

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13 Whilst not all participants reported as having headaches, 3 of the 6 who did noted the subsequent impact upon
14 their social lives:
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18 'I do kind of think if I'm on good form I'll be alright and it'll be fun, but if I don't feel good it won't
19 be fun because I'll just be a bit like, I don't really know what to say or how to join in' (P4)
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25 For this participant the key issue with group interaction was that her symptoms of headaches and
26 fatigue were experienced unpredictably and when they were experienced 'you kind of feel like you're
27 a bit disconnected, like you can't think properly and it's hurting'. Whilst admitting that the headaches
28 she experienced were not 'debilitating', they or the concern of them had prevented her from so far
29 socialising with groups of friends. Similar reservations regarding socialising in a group were also
30 reported by other participants:
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39 'I'm very happy to see my friends one-to-one, but the thought of seeing people in a group, I don't
40 know if I feel that's a bit more intimidating than I would have done beforehand, but I don't know if
41 that's because I haven't, or because I'm a bit worried about how it might be' (P2)
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48 Whilst feeling comfortable socialising one-to-one with people, this participant expressed worry about
49 interacting in a group in case they started having headaches – their concern stemming from the fact that
50 they would not then want the rest of the group to start worrying about them.
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Psychological springboard of headaches

The final theme that emerged was an awareness, and in some cases fear, of the negative connotations that headaches had now become associated with. When feeling 'tired and headachey', several participants reported it made them think 'oh, what is going on in my head' and acted as a springboard onto subsequent negative thoughts regarding their condition and future:

'You start to think "oh is there something else going on upstairs", you know, so it does make you aware' (P11)

Here this participant talked about the consequent effect on thought process and rationale that their lightheadedness and frequent twinges in their forehead now held for them. Whilst they expressed their determination to maintain a positive outlook, these symptoms were often an untimely and certainly unwanted reminder of their cancer.

As identified in the first theme, a positive mentality was the overwhelming attitude conveyed by the participants. To maximise this positive outlook and avoid these psychological reminders of their condition, participants voiced that they had adapted their lives to minimise the chance of headaches:

'The only thing that I don't do is drink alcohol anymore, and that's not because I'm not allowed to, it's just something I don't fancy. It's probably the fact that I don't want to have a glass of wine if that's going to give me a headache or make me feel more tired' (P6)

With this participant, if headaches were to become more regular, she admitted she would irrationally conclude the worst and think 'oh, it's growing and growing and growing and taking over my head', even if the headache etiology could clearly be associated with some far more benign behavioural activity (such as caffeine or alcohol). Similar participant reflection revealed an insight into how headaches may not only act as a psychological springboard but also as a further symptomatic springboard:

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5 'They may possibly have been part of the reason that I wasn't sleeping properly, because, they were
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7 part of the reason I wasn't feeling great' (P3)
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11 Whilst this participant was confident that the sporadic headaches he had been experiencing were not
12
13 the cause of his waking at night, they may have contributed to him struggling to fall back asleep,
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15 leading to not only contemplation of his condition and future at night, but also to day time tiredness,
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17 subsequently limiting activities of daily living. This is a crucial point, as the double-edge of cancer is
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19 that it not only limits life expectancy, but also limits the amount that patients are capable of doing in
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21 this remaining time. In terminal cancer this is even more so relevant, where treatment often shifts
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23 towards prioritising QoL.
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Discussion

During analysis three themes emerged: 'Underlying determination and positivity', 'Headache of social situations' and 'Psychological springboard of headaches'. Whilst most participants agreed that headaches themselves did not cause great direct physical pain, and would only start to worry about headache pain more if they were 'more prolonged' or 'severe', this may have been affected by pre-diagnostic symptoms, of which several had severe headaches. If these participants had experienced mild headaches prior to their disease, they may have worried more about the physical implications, where as now, due to experience of severe headaches, diagnosis of GBM and adequate time to reflect upon their situation, the emotional and psychological impact of headaches and coming to terms with their condition was more often (n=5 of 6 headache participants) found to be greater than their physical sequela.

Furthermore, a seemingly key aspect within this population, to maintaining QoL and partaking in normal activities of daily living, was to focus upon the positive and not the negative aspects of their lives – with participants reporting both actively trying not to think negatively, and passively by immersing themselves in hobbies, socialising, travelling or even returning to work. This participant behaviour of seeking normality and attempts to distance themselves from the taboo of cancer has been previously identified in similar qualitative interviews focusing upon the QoL of patients with anal cancer.[21] However, when symptoms were experienced and impacted upon day-to-day life, it became harder for participants to forget about their condition. Within this, some symptoms were seen to be associated with fewer negative connotations, for example tiredness and fatigue, to which participants reported incorporating increased rest and daytime sleep into their daily routine, but did not tend to think too much into them. However, headaches, had more scope to play on the mind (reported by 4 of the 6 participants with headaches). This may be due to the more direct and potentially easier link to psychologically make between headaches and the knowledge of having a brain tumour, than fatigue and a brain tumour. Hence, the presence of headaches may make the ability to forget about the situation that these patients are facing harder, subsequently indirectly impacting upon QoL. Additionally, of the 8 participants who reported as not having headaches, 5 voiced that if they did start experiencing headaches, they would likely jump to conclusions and panic about the etiology.

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5 Due to this study being the first of its kind in this specific area of research, use of questionnaires and a
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7 quantitative approach was dismissed as it was felt this may miss out on in-depth specific details regarding
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9 QoL. When investigating the complexity of human behaviour, a qualitative approach may more likely highlight
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11 these due to the themes that emerge when participants are allowed to discuss what is important to them.[20]
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13 Such an approach has been successful in similar research in patients with other cancers and congenital heart
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15 disease.[21, 22] Additionally, due to the limited time frame and resources, the feasibility of recruiting a sample
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17 size capable of statistical significance from questionnaire data would have been low.
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20 21 **Recommendations**

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23 Potential interventions could include transferring lifestyle management strategies from the standard treatment of
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25 tension-type headaches, such as keeping a headache diary to identify triggers or exacerbating factors as well as
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27 aiming to relieve GBM patients of the worry surrounding the etiology of their headaches;[23] however, a
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29 downside of this could be even further contemplation of their condition. Whilst it was felt that saturation was
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31 reached in this study (with themes becoming repetitive by the latter stages and no new themes emerging), if
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33 similar qualitative research was to be conducted, assessing whether the results of this study also holds true for a
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35 range of other malignant or even benign brain tumours, a larger sample size would be recommended if multiple
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37 disease pathologies were to be allowed within the inclusion criteria. It could also be investigated whether
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39 headaches can be used to predict QoL within this population, by undertaking a prospective longitudinal study
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41 aiming to identify whether the presence of headaches immediately post-radiotherapy (when QoL is considered
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43 to be at its worst) can act as a prognostic indicator for QoL during the adjuvant phase of treatment. Validated
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45 questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of Life
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47 Questionnaire C30 and BN20, could be provided to patients post-radiotherapy and then again several months
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49 later. Here an upward trend of QoL would be expected, with this proposed study aiming to identify whether the
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51 presence of headaches affects the trajectory of this upward curve.
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Limitations

Limitations include: a small sample size (however this is normal for qualitative research) and family present during the interview having the potential to affect participants' answers. In addition, participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their QoL (potentially missing patients who were eligible as far as the inclusion and exclusion criteria were concerned, but unwilling to discuss their QoL and symptoms). Additionally, the participants interviewed within this study were all undergoing treatment for a newly diagnosed GBM tumour and hence the results may not be transferable to patients with recurrent GBM. A further difficulty encountered was classifying exactly who had headaches, with one participant reporting a unilateral facial pain and another with pronounced light-headedness, however both were quite adamant they were not experiencing headaches and as such were recorded that way. Memory recall of headaches experienced was not seen as a limitation, as when a participant was unsure of the timings of their headaches, they were offered help by their family member in attendance.

Despite these limitations, generalisability in qualitative research is rarely an all or nothing phenomenon, with the principles raised in this study possibly applicable, at least to varying extents, to a larger population of not just GBM patients, but potentially also other high grade malignant and terminal brain cancer patients or even patients with benign brain tumours experiencing headaches.

Conclusion

The aim of this qualitative study was to investigate and address the impact, importance and interaction of headaches experienced by GBM patients, upon their QoL. Whilst not all participants reported as experiencing headaches, those that did considered the physical pain of their headaches not to be severe or prolonged enough to directly impact upon QoL. However, during interview analysis, three participant themes emerged regarding the strive to not be bound by the symptomatic implications of their condition, the indirect impact of headaches upon socialisation and headaches acting as a painful psychological reminder in certain participants of the significance of the threat to their autonomy and survival. These emergent themes should act as important reminders to clinicians of the secondary impacts and underlying mindset of patients having been diagnosed or undergoing treatment for GBM, in particularly if they have been experiencing headaches. Implications for clinical practice include the potential for providing patients with headache diaries to allow a more comprehensive holistic assessment of GBM patients experiencing headaches. Directions for further research include investigating whether headaches can be of clinical value by being utilised as a prognostic indicator for QoL and exploring if the themes raised in this study also bear relevance to subsets of patients with a wider spectrum of brain tumours.

Contributors

This study was devised by SRB and subsequently designed together with GC and AL. SRB interviewed, transcribed and provided subsequent coding. Thematic development of these codes was performed independently by SRB, AL and SRM, to which SRB then collaborated with both, agreeing upon the final 3 key themes. SRM wrote the first drafts of the paper, which were then critiqued and edited by GC, AL and SRM – with the final version approved by all.

Competing Interests

None declared.

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None declared.

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3 Semi-structured Interview Topic Guide
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- 5 1. Yourself, your life and living with cancer.
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7 2. What has changed the most since your diagnosis?
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9 3. Have you experienced any headaches since your diagnosis of glioblastoma multiforme?
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11 4. Do you think about the cause of these headaches?
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13 5. Impact of headaches upon sleep?
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15 6. Enquire into coping mechanisms. Do headaches affect ability to cope?
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17 7. If you were to experience more severe headaches what would go through your mind?
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A qualitative study investigating the impact of headaches on the quality of life of glioblastoma multiforme patients. Version 1 – 12/12/2014.

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Table 1

Participant No.	Gender	No. of weeks interviewed post-radiotherapy	Headaches experienced within the last month
1	Male	12	Yes
2	Female	8	Yes
3	Male	8	Yes
4	Female	5	Yes
5	Female	13	No
6	Female	13	Yes
7	Female	12	No
8	Male	5	No (but facial sensitivity/pain)
9	Male	5	Yes
10	Male	20	No
11	Male	15	No (but light-headedness)
12	Male	8	No
13	Male	18	No
14	Female	17	No

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Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:

Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

YOU MUST PROVIDE A RESPONSE FOR ALL ITEMS. ENTER N/A IF NOT APPLICABLE

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Methods (p.10) and Contributors (p.23)
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Title Page (p.1, 2)
3. Occupation	What was their occupation at the time of the study?	Title Page (p.1, 2)
4. Gender	Was the researcher male or female?	Title Page (p.1, 2) and Methods (p.10)
5. Experience and training	What experience or training did the researcher have?	Title Page (p.1, 2) and Methods (p.10)
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	N/A
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Methods (p.10)
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Competing Interests (p. 23)
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Methods (p.10, 11)
<i>Participant selection</i>		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive,	Methods (p.10)

	snowball	
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Methods (p.10)
12. Sample size	How many participants were in the study?	Methods (p.10) and Results (p.13)
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Methods (p.10)
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Methods (p.10)
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Methods (p.11) and Results (p.13)
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Results (p.13, 14)
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Methods (p.10, 11)
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	Methods (p.10)
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Methods (p.11)
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Methods (p.11)
21. Duration	What was the duration of the inter views or focus group?	Methods (p.10)
22. Data saturation	Was data saturation discussed?	Discussion (p.20)
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Methods (p.11)
Domain 3: analysis and findings		
<i>Data analysis</i>		
24. Number of data coders	How many data coders coded the data?	Methods (p.10) and Contributors (p.23)
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	Results (p.15-18)
27. Software	What software, if applicable, was used to manage the data?	NA
28. Participant checking	Did participants provide feedback on the findings?	Strengths and Limitations (p.6) and Methods (p.11)
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results (p.15-18)
30. Data and findings	Was there consistency between the data	Results (p.15-18)

consistent	presented and the findings?	and Discussion (p.19, 20)
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results (p.15-18), Discussion (p.19, 20) and Conclusion (p.22)
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results (p.15-18), Discussion (p.19, 20)

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has been uploaded. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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Investigating the impact of headaches upon the quality of life of glioblastoma multiforme patients: a qualitative study

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Keywords:	Neurological oncology < NEUROLOGY, QUALITATIVE RESEARCH, glioblastoma, quality of life

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Investigating the impact of headaches upon the quality of life of glioblastoma multiforme patients: a qualitative study

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Keywords

Glioblastoma multiforme, headache, quality of life, qualitative, neuro-oncology

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Abstract

Objectives

Headaches and facial pain have been identified as the most prevalent form of pain amongst patients with glioblastoma multiforme, the most common malignant primary brain tumour. Despite this, minimal research has been undertaken investigating the direct and indirect impact these headaches have upon their quality of life. Therefore, in this study we aimed at gaining a personal insight into the importance and impact that these headaches have upon the quality of life of glioblastoma multiforme patients.

Design

Exploratory study utilising face-to-face semi-structured interviews. Interviews were audio-recorded, transcribed verbatim and then qualitatively analysed using thematic analysis.

Setting

Participants recruited from a tertiary referral hospital in Birmingham, UK.

Participants

Purposive sampling of 14 registered outpatients recently diagnosed with glioblastoma multiforme.

Results

Three themes were identified: 1) An underlying attitude of determination and positivity. 2) Impact of headache unpredictability upon social interaction. 3) Headaches found to act as a springboard onto thoughts regarding their disease and future.

Conclusion

Whilst the quality of life of patients with glioblastoma multiforme is clearly multifactorial, headaches do indeed play a part for some. However, it is not the direct pain of the headache as one might expect that impacts upon the quality of life of these patients, but the indirect effect of headaches through limiting patients' social lives and

1
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3 by serving as a painful psychological reminder of having a life threatening illness. In clinical practice, utilising
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5 headache diaries for these patients may help provide a more comprehensive assessment and further aid
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7 management plans. Alongside acting as an important reminder of the potential secondary implications of this
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9 disease, suggestions for future research include quantitatively investigating whether headaches can act as a
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11 prognostic indicator for quality of life within this patient demographic and determining whether these
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13 conclusions also hold true for a wider spectrum of brain tumour patients.
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Strengths of this study

- As far as the authors know this is the first descriptive exploratory study that has investigated the impact that headaches have upon patients with aggressive brain tumours and the subsequent coping mechanisms that patients develop in response to this.
- The nature of the semi-structured interviews and iterative process of analysis allowed emerging themes to be built upon as the research progressed and hence develop a deeper understanding of the issues discussed.

Limitations of this study

- Family members present during the interviews may have had the potential to affect the way in which participants answered questions, especially when discussing such a personal and emotive subject as quality of life. However overall it was seen as a benefit having them present as in most cases they aided in participant memory recall.
- Participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their quality of life - potentially missing patients who were eligible as far as the inclusion and exclusion criteria were concerned, but unwilling to discuss their quality of life and symptoms.
- All participants were newly diagnosed with a glioblastoma multiforme tumour and therefore the results may not be directly transferable to patients with recurrent glioblastoma multiforme who have had more time to process and live with their condition.
- Due to resource and time limitations, participant feedback and checking was not possible.

Background

Glioblastoma Multiforme (GBM) tumours are histologically the second most frequently reported primary brain and central nervous system tumour (accounting for 16%) and the most common form of malignancy within this subset of neoplasms,[1] with an annual incidence in the US and Europe of 3 per 100,000 people.[2] The median age of diagnosis of this 2:1 male predominant disease is 64 years and it is the most aggressive form of the group of brain tumours known as astrocytomas (themselves a form of glioma).[3] GBM tumours are categorised as a grade IV astrocytoma, stipulated by the World Health Organisation system, which grades astrocytomas from I-IV.[4] Despite advances in treatment technology over the last few years, in particularly with regards to chemotherapy,[5] due to the widely infiltrative nature and rapid growth of this tumour, associated life expectancy is still low,[3] with a median survival of 15 months from diagnosis and a 2 year life expectancy ranging from 8-26%.[6] To improve patient survival, standard treatment usually involves surgical debulking and biopsy of the tumour, followed by radiotherapy and chemotherapy.[5] As a result of this poor prognosis in GBM, matters of quality of life (QoL) become of utmost importance to patients and those around them.[7]

The term QoL encompasses multiple aspects of a patient's overall well-being, including physical, material, social and emotional wellbeing.[8] Over the last 2 decades, as survivorship of GBM has gradually increased and patients have survived longer to experience the co-morbidities of associated treatments,[6, 9, 10] QoL has become an ever more important factor in the management of such patients. Recommendations have been made for randomised trials to include QoL and palliative care outcomes as endpoints,[11] although reliably measuring QoL in high grade glioma patients has proven difficult due to high rates of drop out bias and loss of participants' ability to complete complex forms.[12]

A significantly reduced overall QoL is seen in the majority of newly diagnosed high grade glioma patients, when compared with healthy controls.[13, 14] Descriptive research into the specific symptoms that affect QoL in glioma patients has primarily focused on 6 manifestations: fatigue, sleep, pain, seizures, mood disturbance and cognitive function.[15] However, despite headaches having been reported as the most prevalent form of glioma associated pain, experienced by up to 52% of GBM patients,[16] most commonly as dull tension-type

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3 headaches,[17, 18] and control of primary central nervous system tumour headaches being noted as
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5 crucial,[19] no widely available or published research has investigated the impact that these headaches have
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7 upon the QoL of GBM patients. This may partly be due to the multi-faceted complexity of investigating QoL
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9 and gaining patients' perspectives within this population.
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12 Hence, with up to half of patients with GBM being affected by headaches,[16] if an association between
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14 headaches and QoL is identified, a deeper understanding of this could lead to the implementation of appropriate
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16 precautions or interventions, with the aim of improving the management of headaches in GBM patients and
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18 subsequent QoL.
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Aims

1. To establish an insight into the importance of headaches to glioblastoma multiforme patients.
2. To investigate the impact of headaches upon the mindset of patients being treated for an aggressive brain cancer.

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Methods

Design

This exploratory qualitative study employed face-to-face semi-structured interviews with patients being treated for GBM at the Queen Elizabeth Hospital Birmingham (QEHB) – all of which were interviewed between 5-21 weeks post-radiotherapy. At the time of the interview, participants were at various stages of their adjuvant temozolomide chemotherapy cycle, with each participant only interviewed once. The purpose of selecting this time period was to interview participants in a position where they felt they had enough experience to talk and reflect about their condition, symptoms and associated QoL. Additionally, all participants were required to be over the age of 18 at the time of being informed of the study. Potential participants with a WHO Performance Status >2 (not capable of self-care) were excluded from the study due to the severity of their illness. Due to this study being the first of its kind in this specific area of research, use of questionnaires and a quantitative approach was dismissed as it was felt this may miss out on in-depth specific details regarding QoL. When investigating the complexity of human behaviour, a qualitative approach may more likely highlight these due to the themes that emerge when participants are allowed to discuss what is important to them.[20] Such an approach has been successful in similar research in patients with other cancers and congenital heart disease.[21, 22] Additionally, due to the limited time frame and resources, the feasibility of recruiting a sample size capable of statistical significance from questionnaire data would have been low.

Sample size

Of the 21 eligible participants, identified from neuro-oncology clinic lists and informed of the study using purposive sampling, 14 were subsequently interviewed within the Cancer Centre Department of the QEHB. Of the 7 who were not interviewed, 4 were because of late hospital appointment changes, with only 3 actively declining to take part.

Data collection

Over a 5 month period (February-April, July and September 2015) potential participants were identified and

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3 informed of the study by a MacMillan Clinical Nurse Specialist in their existing care team. This was carried out
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5 either face-to-face or by telephone, using a participant information sheet to explain the purpose of the research,
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7 with interviews scheduled to coincide with their next outpatient appointment at the QEHB. The interviews, each
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9 lasting 15-40 minutes, were undertaken by a senior medical student (SB), as part of a qualitative focused
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11 intercalated research degree, following a pre-written interview topic guide (Supplementary File 1). This topic
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13 guide was designed by the research team (SB and AL) to explore both headache and non-headache participants'
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15 views regarding the changes in their life and symptoms experienced in the build up to and since their diagnosis
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17 of GBM. This specifically focused upon QoL and the impact that headaches or the potential for headaches and
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19 what they had now come to represent had upon this. The reasoning for asking additional questions, not just
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21 related to headaches, was so that the interviewer could immerse themselves and grasp as much as possible
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23 regarding the personal challenges that these patients now face - in turn allowing for a more comprehensive
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25 understanding and analysis of the impact and role that headaches play within this. Due to the small scale nature
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27 of the study and time restrictions, the topic guide was not pilot tested with participants; however, the semi-
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29 structured nature of these interviews and iterative process of analysis allowed a continuous adaptation of the
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31 interview guide throughout the study, so as to build upon emerging themes. As the study progressed, no
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33 questions were added or removed from the interview guide, but greater emphasis was placed upon the
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35 thoughts and feelings that participants associated with headaches. No field notes were made during the
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37 interviews, however each interview was transcribed as soon as possible so as to retain non-verbal information
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39 that the interviewer identified during the interview.
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44 **Data analysis**

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46 Data was analysed following Braun and Clarke's 6 Step Thematic Analysis, allowing identification and analysis
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48 of patterns and themes.[23] The interviews, audio recorded digitally, were transcribed verbatim (including notes
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50 on participant body language), with transcripts read and re-read to ensure familiarity, before deriving codes.

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52 Once interviews were coded, they were then collated to generate themes and extract important issues,

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54 viewpoints and dynamics, which led to a subsequent active data search for disconfirming evidence.[21]

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56 Analysis of derived codes and theme recognition was carried out independently by the interviewer (SB), a
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3 lecturer in qualitative methods (AL) and an additional senior medical student (SM), to identify and understand
4 potential multiple interpretations of the data and reduce the likelihood of producing results which were partial or
5 biased.[24] This theme identification began before data collection was complete in order to explore initial
6 findings in greater depth. All research activities were recorded in detail to allow methodological critical
7 appraisal and increase trustworthiness, a concept used to describe reliability in qualitative research.[25]
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9 However, due to the limited time frame, further validity checking utilising participant verification was not
10 feasible.
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20 Interviews were selected over focus groups due to the highly sensitive nature of discussing QoL within this
21 population, where participants may have felt reluctant to divulge such personal information in front of strangers.
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23 However, a family member was allowed to contribute to the interview, if requested so by the participant.
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28 **Research ethics**

29 All patients who took part in this study participated voluntarily. Written informed consent was taken from all
30 participants prior to starting each scheduled interview, which were all undertaken within a quiet confidential
31 setting in the Cancer Centre, QEHB. Participants were also informed that they could stop the interview at any
32 point for any reason. All confidential participant information was stored on encrypted memory sticks, accessible
33 only to the researchers. This research was approved by the 'West Midlands – Solihull' National Research Ethics
34 Committee (15/WM/0012) with subsequent site-specific approval from the QEHB Research and Development
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Results

Of the 14 participants (median age = 47.5 (IQR 38 - 63) years; 8 male) interviewed, 6 reported as experiencing headaches within the last month, 1 reported a unilateral facial pain and 1 other with light-headedness, but no headaches (Table 1). The remaining 6 patients reported as having neither headaches nor facial pain nor lightheadedness. All participants reported varying levels of tiredness and fatigue. Additionally, all participants requested to have a family member or carer present during the interviews.

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Table 1

Participant No.	Gender	No. of weeks interviewed post-radiotherapy	Headaches experienced within the last month
1	Male	12	Yes
2	Female	8	Yes
3	Male	8	Yes
4	Female	5	Yes
5	Female	13	No
6	Female	13	Yes
7	Female	12	No
8	Male	5	No (but facial sensitivity/pain)
9	Male	5	Yes
10	Male	20	No
11	Male	15	No (but light-headedness)
12	Male	8	No
13	Male	18	No
14	Female	17	No

1
2
3 Grouping and interlinking of codes, derived from all of the transcribed interviews, yielded three themes,
4
5 however only the first two of these, 'Underlying determination and positivity' and 'Headache of social
6
7 situations', were initially apparent. These themes primarily describe the thoughts, feelings and emotions
8
9 conveyed by the participants, regarding their approach to the challenges that day-to-day life now presents and
10
11 the role of headaches within this. Only after full data immersion and code collaboration was the third theme,
12
13 'Psychological springboard of headaches', developed. This final theme aims to provide an insight into the
14
15 potential implications that headaches, and what they have now come to represent, may have upon self-
16
17 contemplation in this population regarding their condition and future. Of these themes, 'Underlying
18
19 determination and positivity' was developed from all participants (both headache and non-headache), with the
20
21 remaining two themes developed only from the 6 participants who developed headaches and the 2 participants
22
23 who reported facial pain and lightheadedness.
24

25 26 27 **Underlying determination and positivity**

28
29 A consistent theme amongst almost all participants was a resounding determination to 'get on with life' and not
30
31 to be bound by the symptomatic implications of their condition, referred to by several as 'the nature of the
32
33 beast':
34

35
36 'I try not to think about it, which may not be the healthiest psychological way to go about it. However, it just
37
38 means I can get on throughout the day, getting on with things that I like to do and want to do.' (P2)
39

40
41 Acceptance of the situation, alongside the want and almost need to block it out in order to carry on with as
42
43 normal a life as possible, was a commonly reported trait. Potential reasoning to partially explain this behaviour
44
45 can be drawn from the frequently reported frustration that came with participant's self-recognition of dwelling
46
47 on their illness:
48

49
50 'obviously I think about the future, because I know it's not curable, it's a controllable cancer... it's a bit
51
52 frustrating if you think about it too much, but then you've got to be thankful for what you've still got' (P5)
53

54
55 Whilst this theme is not directly related to headaches, the principle of leading as normal life as possible was the
56
57 fundamental aspect of most of the participants' approach to their brain tumour, expressed by 12 of the 14
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2
3 interviewed. With this in mind, this then helps contextualise the next 2 themes, discussing ways in which
4
5 headaches were found to disrupt normality.
6
7

8 9 **Headache of social situations**

10
11 Whilst not all participants reported as having headaches, 3 of the 6 who did noted the subsequent impact upon
12
13 their social lives:

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15
16
17 ‘I do kind of think if I’m on good form I’ll be alright and it’ll be fun, but if I don’t feel good it won’t
18
19 be fun... I don’t really know what to say or how to join in’ (P4)
20
21

22
23 For this participant the key issue with group interaction was that her symptoms of headaches and
24
25 fatigue were experienced unpredictably and when they were experienced ‘you kind of feel like you’re
26
27 a bit disconnected, like you can’t think properly and it’s hurting’. Whilst admitting that the headaches
28
29 she experienced were not ‘debilitating’, they or the concern of them had prevented her from so far
30
31 socialising with groups of friends. Similar reservations regarding socialising in a group were also
32
33 reported by other participants:
34
35

36
37
38 ‘I’m very happy to see my friends one-to-one, but the thought of seeing people in a group, I don’t
39
40 know if I feel that’s a bit more intimidating than I would have done beforehand’ (P2)
41
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43
44 Whilst feeling comfortable socialising one-to-one with people, this participant expressed worry about
45
46 interacting in a group in case they started having headaches – their concern stemming from the fact that
47
48 they would not then want the rest of the group to start worrying about them.
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51 52 53 54 **Psychological springboard of headaches**

55
56 The final theme that emerged was an awareness, and in some cases fear, of the negative connotations that
57
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1
2
3 headaches had now become associated with. When feeling ‘tired and headachey’, several participants
4
5 reported it made them think ‘oh, what is going on in my head’ and acted as a springboard onto subsequent
6
7 negative thoughts regarding their condition and future:
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9

10
11 ‘You start to think “oh is there something else going on upstairs”’ (P11)
12
13

14
15 Here this participant talked about the consequent effect on thought process and rationale that their
16
17 lightheadedness and frequent twinges in their forehead now held for them. Whilst they expressed their
18
19 determination to maintain a positive outlook, these symptoms were often an untimely and certainly
20
21 unwanted reminder of their cancer.
22
23

24
25 As identified in the first theme, a positive mentality was the overwhelming attitude conveyed by the
26
27 participants. To maximise this positive outlook and avoid these psychological reminders of their condition,
28
29 participants voiced that they had adapted their lives to minimise the chance of headaches:
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31

32
33 ‘The only thing that I don’t do is drink alcohol anymore, and that’s not because I’m not allowed to... It’s
34
35 probably the fact that I don’t want to have a glass of wine if that’s going to give me a headache’ (P6)
36
37

38
39 With this participant, if headaches were to become more regular, she admitted she would assume the worst and
40
41 think ‘oh, it’s growing and growing and growing and taking over my head’, even if the headache etiology could
42
43 clearly be associated with some far more benign behavioural activity (such as caffeine or alcohol). Similar
44
45 participant reflection revealed an insight into how headaches may not only act as a psychological springboard
46
47 but also as a further symptomatic springboard:
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49

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51 ‘They may possibly have been part of the reason that I wasn’t sleeping properly, because, they were
52
53 part of the reason I wasn’t feeling great’ (P3)
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3 Whilst this participant was confident that the sporadic headaches he had been experiencing were not
4 the cause of his waking at night, they may have contributed to him struggling to fall back asleep,
5 leading to not only contemplation of his condition and future at night, but also to day time tiredness,
6 subsequently limiting activities of daily living. This is a crucial point, as the double-edge of cancer is
7 that it not only limits life expectancy, but also limits the amount that patients are capable of doing in
8 this remaining time. In terminal cancer this is even more so relevant, where treatment often shifts
9 towards prioritising QoL.
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Discussion

During analysis three themes emerged: 'Underlying determination and positivity', 'Headache of social situations' and 'Psychological springboard of headaches'. Whilst most participants agreed that headaches themselves did not cause great direct physical pain, and would only start to worry about headache pain more if they were 'more prolonged' or 'severe', this may have been affected by the symptoms experienced in the run up to diagnosis, of which several had severe headaches. Due to previous experience of severe headaches, diagnosis of GBM and adequate time to reflect upon their situation, the emotional and psychological impact of headaches and coming to terms with their condition was more often (n=5 of 6 headache participants) found to be greater than their physical sequela.

Furthermore, a seemingly key aspect within this population, to maintaining QoL and partaking in normal activities of daily living, was to focus upon the positive and not the negative aspects of their lives – with participants reporting both actively trying not to think negatively, and passively by immersing themselves in hobbies, socialising, travelling or even returning to work. This participant behaviour of seeking normality and attempts to distance themselves from the taboo of cancer has been previously identified in similar qualitative interviews focusing upon the QoL of patients with anal cancer.[21] However, when symptoms were experienced and impacted upon day-to-day life, it became harder for participants to forget about their condition. Within this, some symptoms were seen to be associated with fewer negative connotations, for example tiredness and fatigue, to which participants reported incorporating increased rest and daytime sleep into their daily routine, but did not tend to think too much into them. However, headaches, had more scope to play on the mind (reported by 4 of the 6 participants with headaches). This may be due to the more direct and potentially easier link to psychologically make between headaches and the knowledge of having a brain tumour, than fatigue and a brain tumour. Hence, the presence of headaches may make the ability to forget about the situation that these patients are facing harder, subsequently indirectly impacting upon QoL. Additionally, of the 8 participants who reported not having headaches, 5 voiced that if they did start experiencing headaches, they would likely jump to conclusions and panic about the etiology.

Recommendations

Potential interventions could include transferring lifestyle management strategies from the standard treatment of tension-type headaches, such as keeping a headache diary to identify triggers or exacerbating factors as well as aiming to relieve GBM patients of the worry surrounding the etiology of their headaches;[26] however, a downside of this could be even further contemplation of their condition. Whilst it was felt that saturation was reached in this study (with themes becoming repetitive by the latter stages and no new themes emerging), if similar qualitative research was to be conducted, assessing whether the results of this study also holds true for a range of other malignant or even benign brain tumours, a larger sample size would be recommended if multiple disease pathologies were to be allowed within the inclusion criteria. It could also be investigated whether headaches can be used to predict QoL within this population, by undertaking a prospective longitudinal study aiming to identify whether the presence of headaches immediately post-radiotherapy (when QoL is considered to be at its worst) can act as a prognostic indicator for QoL during the adjuvant phase of treatment. Validated questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BN20, could be provided to patients post-radiotherapy and then again several months later. Here an upward trend of QoL would be expected, with this proposed study aiming to identify whether the presence of headaches affects the trajectory of this upward curve.

Limitations

Limitations include: a small sample size (however this is normal for qualitative research) and family present during the interview having the potential to affect participants' answers. In addition, participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their QoL (potentially missing patients who were eligible as far as the inclusion criteria, but unwilling to discuss their QoL and symptoms). Additionally, participants interviewed within this study were all undergoing treatment for a newly diagnosed GBM tumour and hence the results may not be transferable to patients with recurrent GBM. Participants were either undergoing or had recently undertaken adjuvant temozolomide in the chemotherapy phase of their treatment, however the exact phase of the chemotherapeutic cycle that they were in at the time of the interview was not recorded and neither was their current medication regime. Initially inclusion criteria stipulated that patients be 5-9 weeks post-radiotherapy at the time of interview, however due to the limited time period of the study, it was realised this would not be feasible to recruit enough participants and hence was expanded to 5-21 weeks. A further difficulty encountered was classifying exactly who had headaches, with one participant reporting a unilateral facial pain and another with pronounced light-headedness, however both were quite adamant they were not experiencing headaches and as such were recorded that way. Memory recall of headaches experienced was not seen as a limitation, as when a participant was unsure of the timings of their headaches, they were offered help by their family member in attendance.

Despite these limitations, the principles raised in this study may possibly be applicable, at least to varying extents, to a larger population of not just GBM patients, but potentially also other high grade malignant and terminal brain cancer patients or even patients with benign brain tumours experiencing headaches.

Conclusion

The aim of this qualitative study was to investigate and address the impact, importance and interaction of headaches experienced by GBM patients, upon their QoL. Whilst not all participants reported as experiencing headaches, those that did considered the physical pain of their headaches not to be severe or prolonged enough to directly impact upon QoL. However, during interview analysis, three participant themes emerged regarding the strive to not be bound by the symptomatic implications of their condition, the indirect impact of headaches upon socialisation and headaches acting as a painful psychological reminder in certain participants of the significance of the threat to their autonomy and survival. These emergent themes should act as important reminders to clinicians of the secondary impacts and underlying mindset of patients having been diagnosed or undergoing treatment for GBM, in particularly if they have been experiencing headaches. Implications for clinical practice include the potential for providing patients with headache diaries to allow a more comprehensive holistic assessment of GBM patients experiencing headaches. Directions for further research include investigating whether headaches can be of clinical value by being utilised as a prognostic indicator for QoL and exploring if the themes raised in this study also bear relevance to subsets of patients with a wider spectrum of brain tumours.

Contributors

This study was devised by SRB and subsequently designed together with GC and AL. SRB interviewed, transcribed and provided subsequent coding. Thematic development of these codes was performed independently by SRB, AL and SRM, to which SRB then collaborated with both, agreeing upon the final 3 key themes. SRM wrote the first drafts of the paper, which were then critiqued and edited by GC, AL and SRM – with the final version approved by all.

Competing Interests

None declared.

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None declared.

Data Sharing Statement

No additional data available.

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3 Semi-structured Interview Topic Guide
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- 5 1. Yourself, your life and living with cancer.
6
7 2. What has changed the most since your diagnosis?
8
9 3. Have you experienced any headaches since your diagnosis of glioblastoma multiforme?
10
11 4. Do you think about the cause of these headaches?
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13 5. Impact of headaches upon sleep?
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15 6. Enquire into coping mechanisms. Do headaches affect ability to cope?
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17 7. If you were to experience more severe headaches what would go through your mind?
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A qualitative study investigating the impact of headaches on the quality of life of glioblastoma multiforme patients. Version 1 – 12/12/2014.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:

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YOU MUST PROVIDE A RESPONSE FOR ALL ITEMS. ENTER N/A IF NOT APPLICABLE

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Methods (p.10) and Contributors (p.23)
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Title Page (p.1, 2)
3. Occupation	What was their occupation at the time of the study?	Title Page (p.1, 2)
4. Gender	Was the researcher male or female?	Title Page (p.1, 2) and Methods (p.10)
5. Experience and training	What experience or training did the researcher have?	Title Page (p.1, 2) and Methods (p.10)
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	N/A
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Methods (p.10)
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Competing Interests (p. 23)
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Methods (p.10, 11)
<i>Participant selection</i>		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive,	Methods (p.10)

	snowball	
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Methods (p.10)
12. Sample size	How many participants were in the study?	Methods (p.10) and Results (p.13)
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Methods (p.10)
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Methods (p.10)
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Methods (p.11) and Results (p.13)
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Results (p.13, 14)
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Methods (p.10, 11)
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	Methods (p.10)
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Methods (p.11)
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Methods (p.11)
21. Duration	What was the duration of the inter views or focus group?	Methods (p.10)
22. Data saturation	Was data saturation discussed?	Discussion (p.20)
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Methods (p.11)
Domain 3: analysis and findings		
<i>Data analysis</i>		
24. Number of data coders	How many data coders coded the data?	Methods (p.10) and Contributors (p.23)
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	Results (p.15-18)
27. Software	What software, if applicable, was used to manage the data?	NA
28. Participant checking	Did participants provide feedback on the findings?	Strengths and Limitations (p.6) and Methods (p.11)
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results (p.15-18)
30. Data and findings	Was there consistency between the data	Results (p.15-18)

consistent	presented and the findings?	and Discussion (p.19, 20)
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results (p.15-18), Discussion (p.19, 20) and Conclusion (p.22)
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results (p.15-18), Discussion (p.19, 20)

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has been uploaded. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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BMJ Open

Investigating the impact of headaches upon the quality of life of glioblastoma multiforme patients: a qualitative study

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Keywords:	Neurological oncology < NEUROLOGY, QUALITATIVE RESEARCH, glioblastoma, quality of life

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Investigating the impact of headaches upon the quality of life of glioblastoma multiforme patients: a qualitative study

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Keywords

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Abstract

Objectives

Headaches and facial pain have been identified as the most prevalent form of pain amongst patients with glioblastoma multiforme, the most common malignant primary brain tumour. Despite this, minimal research has been undertaken investigating the direct and indirect impact these headaches have upon their quality of life. Therefore, in this study we aimed at gaining a personal insight into the importance and impact that these headaches have upon the quality of life of glioblastoma multiforme patients.

Design

Exploratory study utilising face-to-face semi-structured interviews. Interviews were audio-recorded, transcribed verbatim and then qualitatively analysed using thematic analysis.

Setting

Participants recruited from a tertiary referral hospital in Birmingham, UK.

Participants

Purposive sampling of 14 registered outpatients recently diagnosed with glioblastoma multiforme.

Results

Three themes were identified: 1) An underlying attitude of determination and positivity. 2) Impact of headache unpredictability upon social interaction. 3) Headaches found to act as a springboard onto thoughts regarding their disease and future.

Conclusion

Whilst the quality of life of patients with glioblastoma multiforme is clearly multifactorial, headaches do indeed play a part for some. However, it is not the direct pain of the headache as one might expect that impacts upon the quality of life of these patients, but the indirect effect of headaches through limiting patients' social lives and

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3 by serving as a painful psychological reminder of having a life threatening illness. In clinical practice, utilising
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5 headache diaries for these patients may help provide a more comprehensive assessment and further aid
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7 management plans. Alongside acting as an important reminder of the potential secondary implications of this
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9 disease, suggestions for future research include quantitatively investigating whether headaches can act as a
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11 prognostic indicator for quality of life within this patient demographic and determining whether these
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13 conclusions also hold true for a wider spectrum of brain tumour patients.
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Strengths of this study

- As far as the authors know this is the first descriptive exploratory study that has investigated the impact that headaches have upon patients with aggressive brain tumours and the subsequent coping mechanisms that patients develop in response to this.
- The nature of the semi-structured interviews and iterative process of analysis allowed emerging themes to be built upon as the research progressed and hence develop a deeper understanding of the issues discussed.

Limitations of this study

- Family members present during the interviews may have had the potential to affect the way in which participants answered questions, especially when discussing such a personal and emotive subject as quality of life. However overall it was seen as a benefit having them present as in most cases they aided in participant memory recall.
- Participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their quality of life - potentially missing patients who were eligible as far as the inclusion and exclusion criteria were concerned, but unwilling to discuss their quality of life and symptoms.
- All participants were newly diagnosed with a glioblastoma multiforme tumour and therefore the results may not be directly transferable to patients with recurrent glioblastoma multiforme who have had more time to process and live with their condition.
- Due to resource and time limitations, participant feedback and checking was not possible.

Background

Glioblastoma Multiforme (GBM) tumours are histologically the second most frequently reported primary brain and central nervous system tumour (accounting for 16%) and the most common form of malignancy within this subset of neoplasms,[1] with an annual incidence in the US and Europe of 3 per 100,000 people.[2] The median age of diagnosis of this 2:1 male predominant disease is 64 years and it is the most aggressive form of the group of brain tumours known as astrocytomas (themselves a form of glioma).[3] GBM tumours are categorised as a grade IV astrocytoma, stipulated by the World Health Organisation system, which grades astrocytomas from I-IV.[4] Despite advances in treatment technology over the last few years, in particularly with regards to chemotherapy,[5] due to the widely infiltrative nature and rapid growth of this tumour, associated life expectancy is still low,[3] with a median survival of 15 months from diagnosis and a 2 year life expectancy ranging from 8-26%.[6] To improve patient survival, standard treatment usually involves surgical debulking and biopsy of the tumour, followed by radiotherapy and chemotherapy.[5] As a result of this poor prognosis in GBM, matters of quality of life (QoL) become of utmost importance to patients and those around them.[7]

The term QoL encompasses multiple aspects of a patient's overall well-being, including physical, material, social and emotional wellbeing.[8] Over the last 2 decades, as survivorship of GBM has gradually increased and patients have survived longer to experience the co-morbidities of associated treatments,[6, 9, 10] QoL has become an ever more important factor in the management of such patients. Recommendations have been made for randomised trials to include QoL and palliative care outcomes as endpoints,[11] although reliably measuring QoL in high grade glioma patients has proven difficult due to high rates of drop out bias and loss of participants' ability to complete complex forms.[12]

A significantly reduced overall QoL is seen in the majority of newly diagnosed high grade glioma patients, when compared with healthy controls.[13, 14] Descriptive research into the specific symptoms that affect QoL in glioma patients has primarily focused on 6 manifestations: fatigue, sleep, pain, seizures, mood disturbance and cognitive function.[15] However, despite headaches having been reported as the most prevalent form of glioma associated pain, experienced by up to 52% of GBM patients,[16] most commonly as dull tension-type

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3 headaches,[17, 18] and control of primary central nervous system tumour headaches being noted as
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5 crucial,[19] no widely available or published research has investigated the impact that these headaches have
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7 upon the QoL of GBM patients. This may partly be due to the multi-faceted complexity of investigating QoL
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9 and gaining patients' perspectives within this population.
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12 Hence, with up to half of patients with GBM being affected by headaches,[16] if an association between
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14 headaches and QoL is identified, a deeper understanding of this could lead to the implementation of appropriate
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16 precautions or interventions, with the aim of improving the management of headaches in GBM patients and
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18 subsequent QoL.
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Aims

1. To establish an insight into the importance of headaches to glioblastoma multiforme patients.
2. To investigate the impact of headaches upon the mindset of patients being treated for an aggressive brain cancer.

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Methods

Design

This exploratory qualitative study employed face-to-face semi-structured interviews with patients being treated for GBM at the Queen Elizabeth Hospital Birmingham (QEHB) – all of which were interviewed between 5-21 weeks post-radiotherapy. At the time of the interview, participants were at various stages of their adjuvant temozolomide chemotherapy cycle, with each participant only interviewed once. The purpose of selecting this time period was to interview participants in a position where they felt they had enough experience to talk and reflect about their condition, symptoms and associated QoL. Additionally, all participants were required to be over the age of 18 at the time of being informed of the study. Potential participants with a WHO Performance Status >2 (not capable of self-care) were excluded from the study due to the severity of their illness. Due to this study being the first of its kind in this specific area of research, use of questionnaires and a quantitative approach was dismissed as it was felt this may miss out on in-depth specific details regarding QoL. When investigating the complexity of human behaviour, a qualitative approach may more likely highlight these due to the themes that emerge when participants are allowed to discuss what is important to them.[20] Such an approach has been successful in similar research in patients with other cancers and congenital heart disease.[21, 22] Additionally, due to the limited time frame and resources, the feasibility of recruiting a sample size capable of statistical significance from questionnaire data would have been low.

Sample size

Of the 21 eligible participants, identified from neuro-oncology clinic lists and informed of the study using purposive sampling, 14 were subsequently interviewed within the Cancer Centre Department of the QEHB. Of the 7 who were not interviewed, 4 were because of late hospital appointment changes, with only 3 actively declining to take part.

Data collection

Over a 5 month period (February-April, July and September 2015) potential participants were identified and informed of the study by a MacMillan Clinical Nurse Specialist in their existing care team. This was carried out

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3 either face-to-face or by telephone, using a participant information sheet to explain the purpose of the research,
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5 with interviews scheduled to coincide with their next outpatient appointment at the QEHB. The interviews, each
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7 lasting 15-40 minutes, were undertaken by a senior medical student (SB), as part of a qualitative focused
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9 intercalated research degree, following a pre-written interview topic guide (Supplementary File 1). This topic
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11 guide was designed by the research team (SB and AL) to explore both headache and non-headache participants'
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13 views regarding the changes in their life and symptoms experienced in the build up to and since their diagnosis
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15 of GBM. This specifically focused upon QoL and the impact that headaches or the potential for headaches and
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17 what they had now come to represent had upon this. The reasoning for asking additional questions, not just
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19 related to headaches, was so that the interviewer could immerse themselves and grasp as much as possible
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21 regarding the personal challenges that these patients now face - in turn allowing for a more comprehensive
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23 understanding and analysis of the impact and role that headaches play within this. Due to the small scale nature
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25 of the study and time restrictions, the topic guide was not pilot tested with participants; however, the semi-
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27 structured nature of these interviews and iterative process of analysis allowed a continuous adaptation of the
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29 interview guide throughout the study, so as to build upon emerging themes. As the study progressed, no
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31 questions were added or removed from the interview guide, but greater emphasis was placed upon the
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33 thoughts and feelings that participants associated with headaches. No field notes were made during the
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35 interviews, however each interview was transcribed as soon as possible so as to retain non-verbal information
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37 that the interviewer identified during the interview.
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42 **Data analysis**

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44 Data was analysed following Braun and Clarke's 6 Step Thematic Analysis, allowing identification and analysis
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46 of patterns and themes.[23] The interviews, audio recorded digitally, were transcribed verbatim (including notes
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48 on participant body language), with transcripts read and re-read to ensure familiarity, before deriving codes.

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50 Once interviews were coded, they were then collated to generate themes and extract important issues,
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52 viewpoints and dynamics, which led to a subsequent active data search for disconfirming evidence.[21]

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54 Analysis of derived codes and theme recognition was carried out independently by the interviewer (SB), a
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56 lecturer in qualitative methods (AL) and an additional senior medical student (SM), to identify and understand
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3 potential multiple interpretations of the data and reduce the likelihood of producing results which were partial or
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5 biased.[24] This theme identification began before data collection was complete in order to explore initial
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7 findings in greater depth. All research activities were recorded in detail to allow methodological critical
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9 appraisal and increase trustworthiness, a concept used to describe reliability in qualitative research.[25]
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11 However, due to the limited time frame, further validity checking utilising participant verification was not
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13 feasible.

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17 Interviews were selected over focus groups due to the highly sensitive nature of discussing QoL within this
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19 population, where participants may have felt reluctant to divulge such personal information in front of strangers.
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21 However, a family member was allowed to contribute to the interview, if requested so by the participant.
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24 25 **Research ethics**

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27 All patients who took part in this study participated voluntarily. Written informed consent was taken from all
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29 participants prior to starting each scheduled interview, which were all undertaken within a quiet confidential
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31 setting in the Cancer Centre, QEHB. Participants were also informed that they could stop the interview at any
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33 point for any reason. All confidential participant information was stored on encrypted memory sticks, accessible
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35 only to the researchers. This research was approved by the 'West Midlands – Solihull' National Research Ethics
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37 Committee (15/WM/0012) with subsequent site-specific approval from the QEHB Research and Development
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39 Department.
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Results

Of the 14 participants (median age = 47.5 (IQR 38 - 63) years; 8 male) interviewed, 6 reported as experiencing headaches within the last month, 1 reported a unilateral facial pain and 1 other with light-headedness, but no headaches (Table 1). The remaining 6 patients reported as having neither headaches nor facial pain nor lightheadedness. All participants reported varying levels of tiredness and fatigue. Additionally, all participants requested to have a family member or carer present during the interviews.

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Table 1

Participant No.	Gender	No. of weeks interviewed post-radiotherapy	Headaches experienced within the last month
1	Male	12	Yes
2	Female	8	Yes
3	Male	8	Yes
4	Female	5	Yes
5	Female	13	No
6	Female	13	Yes
7	Female	12	No
8	Male	5	No (but facial sensitivity/pain)
9	Male	5	Yes
10	Male	20	No
11	Male	15	No (but light-headedness)
12	Male	8	No
13	Male	18	No
14	Female	17	No

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3 Grouping and interlinking of codes, derived from all of the transcribed interviews, yielded three themes,
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5 however only the first two of these, 'Underlying determination and positivity' and 'Headache of social
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7 situations', were initially apparent. These themes primarily describe the thoughts, feelings and emotions
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9 conveyed by the participants, regarding their approach to the challenges that day-to-day life now presents and
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11 the role of headaches within this. Only after full data immersion and code collaboration was the third theme,
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13 'Psychological springboard of headaches', developed. This final theme aims to provide an insight into the
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15 potential implications that headaches, and what they have now come to represent, may have upon self-
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17 contemplation in this population regarding their condition and future. Of these themes, 'Underlying
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19 determination and positivity' was developed from all participants (both headache and non-headache), with the
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21 remaining two themes developed only from the 6 participants who developed headaches and the 2 participants
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23 who reported facial pain and lightheadedness.
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25 26 27 **Underlying determination and positivity**

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29 A consistent theme amongst almost all participants was a resounding determination to 'get on with life' and not
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31 to be bound by the symptomatic implications of their condition, referred to by several as 'the nature of the
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33 beast':
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36 'I try not to think about it, which may not be the healthiest psychological way to go about it. However, it just
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38 means I can get on throughout the day, getting on with things that I like to do and want to do.' (P2)
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41 Acceptance of the situation, alongside the want and almost need to block it out in order to carry on with as
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43 normal a life as possible, was a commonly reported trait. Potential reasoning to partially explain this behaviour
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45 can be drawn from the frequently reported frustration that came with participant's self-recognition of dwelling
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47 on their illness:
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50 'obviously I think about the future, because I know it's not curable, it's a controllable cancer... it's a bit
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52 frustrating if you think about it too much, but then you've got to be thankful for what you've still got' (P5)
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55 Whilst this theme is not directly related to headaches, the principle of leading as normal life as possible was the
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57 fundamental aspect of most of the participants' approach to their brain tumour, expressed by 12 of the 14
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3 interviewed. With this in mind, this then helps contextualise the next 2 themes, discussing ways in which
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5 headaches were found to disrupt normality.
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8 9 **Headache of social situations**

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11 Whilst not all participants reported as having headaches, 3 of the 6 who did noted the subsequent impact upon
12
13 their social lives:

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17 ‘I do kind of think if I’m on good form I’ll be alright and it’ll be fun, but if I don’t feel good it won’t
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19 be fun... I don’t really know what to say or how to join in’ (P4)
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23 For this participant the key issue with group interaction was that her symptoms of headaches and
24
25 fatigue were experienced unpredictably and when they were experienced ‘you kind of feel like you’re
26
27 a bit disconnected, like you can’t think properly and it’s hurting’. Whilst admitting that the headaches
28
29 she experienced were not ‘debilitating’, they or the concern of them had prevented her from so far
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31 socialising with groups of friends. Similar reservations regarding socialising in a group were also
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33 reported by other participants:
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38 ‘I’m very happy to see my friends one-to-one, but the thought of seeing people in a group, I don’t
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40 know if I feel that’s a bit more intimidating than I would have done beforehand’ (P2)
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44 Whilst feeling comfortable socialising one-to-one with people, this participant expressed worry about
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46 interacting in a group in case they started having headaches – their concern stemming from the fact that
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48 they would not then want the rest of the group to start worrying about them.
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51 52 **Psychological springboard of headaches**

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54 The final theme that emerged was an awareness, and in some cases fear, of the negative connotations that
55
56 headaches had now become associated with. When feeling ‘tired and headachey’, several participants
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3 reported it made them think ‘oh, what is going on in my head’ and acted as a springboard onto subsequent
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5 negative thoughts regarding their condition and future:
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9 ‘You start to think “oh is there something else going on upstairs”’ (P11)
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12 Here this participant talked about the consequent effect on thought process and rationale that their
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14 lightheadedness and frequent twinges in their forehead now held for them. Whilst they expressed their
15
16 determination to maintain a positive outlook, these symptoms were often an untimely and certainly
17
18 unwanted reminder of their cancer.
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22 As identified in the first theme, a positive mentality was the overwhelming attitude conveyed by the
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24 participants. To maximise this positive outlook and avoid these psychological reminders of their condition,
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26 participants voiced that they had adapted their lives to minimise the chance of headaches:
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31 ‘The only thing that I don’t do is drink alcohol anymore, and that’s not because I’m not allowed to... It’s
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33 probably the fact that I don’t want to have a glass of wine if that’s going to give me a headache’ (P6)
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37 With this participant, if headaches were to become more regular, she admitted she would assume the worst and
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39 think ‘oh, it’s growing and growing and growing and taking over my head’, even if the headache etiology could
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41 clearly be associated with some far more benign behavioural activity (such as caffeine or alcohol). Similar
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43 participant reflection revealed an insight into how headaches may not only act as a psychological springboard
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45 but also as a further symptomatic springboard:
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50 ‘They may possibly have been part of the reason that I wasn’t sleeping properly, because, they were
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52 part of the reason I wasn’t feeling great’ (P3)
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56 Whilst this participant was confident that the sporadic headaches he had been experiencing were not
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3 the cause of his waking at night, they may have contributed to him struggling to fall back asleep,
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5 leading to not only contemplation of his condition and future at night, but also to day time tiredness,
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7 subsequently limiting activities of daily living. This is a crucial point, as the double-edge of cancer is
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9 that it not only limits life expectancy, but also limits the amount that patients are capable of doing in
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11 this remaining time. In terminal cancer this is even more so relevant, where treatment often shifts
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13 towards prioritising QoL.
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Discussion

During analysis three themes emerged: ‘Underlying determination and positivity’, ‘Headache of social situations’ and ‘Psychological springboard of headaches’. Whilst most participants agreed that headaches themselves did not cause great direct physical pain, and would only start to worry about headache pain more if they were ‘more prolonged’ or ‘severe’, this may have been affected by the symptoms experienced in the run up to diagnosis, of which several had severe headaches. Due to previous experience of severe headaches, diagnosis of GBM and adequate time to reflect upon their situation, the emotional and psychological impact of headaches and coming to terms with their condition was more often (n=5 of 6 headache participants) found to be greater than their physical sequela.

Furthermore, a seemingly key aspect within this population, to maintaining QoL and partaking in normal activities of daily living, was to focus upon the positive and not the negative aspects of their lives – with participants reporting both actively trying not to think negatively, and passively by immersing themselves in hobbies, socialising, travelling or even returning to work. This participant behaviour of seeking normality and attempts to distance themselves from the taboo of cancer has been previously identified in similar qualitative interviews focusing upon the QoL of patients with anal cancer.[21] However, when symptoms were experienced and impacted upon day-to-day life, it became harder for participants to forget about their condition. Within this, some symptoms were seen to be associated with fewer negative connotations, for example tiredness and fatigue, to which participants reported incorporating increased rest and daytime sleep into their daily routine, but did not tend to think too much into them. However, headaches, had more scope to play on the mind (reported by 4 of the 6 participants with headaches). This may be due to the more direct and potentially easier link to psychologically make between headaches and the knowledge of having a brain tumour, than fatigue and a brain tumour. Hence, the presence of headaches may make the ability to forget about the situation that these patients are facing harder, subsequently indirectly impacting upon QoL. Additionally, of the 8 participants who reported not having headaches, 5 voiced that if they did start experiencing headaches, they would likely jump to conclusions and panic about the etiology.

Recommendations

Potential interventions could include transferring lifestyle management strategies from the standard treatment of tension-type headaches, such as keeping a headache diary to identify triggers or exacerbating factors as well as aiming to relieve GBM patients of the worry surrounding the etiology of their headaches;[26] however, a downside of this could be even further contemplation of their condition. Whilst it was felt that saturation was reached in this study (with themes becoming repetitive by the latter stages and no new themes emerging), if similar qualitative research was to be conducted, assessing whether the results of this study also holds true for a range of other malignant or even benign brain tumours, a larger sample size would be recommended if multiple disease pathologies were to be allowed within the inclusion criteria. It could also be investigated whether headaches can be used to predict QoL within this population, by undertaking a prospective longitudinal study aiming to identify whether the presence of headaches immediately post-radiotherapy (when QoL is considered to be at its worst) can act as a prognostic indicator for QoL during the adjuvant phase of treatment. Validated questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BN20, could be provided to patients post-radiotherapy and then again several months later. Here an upward trend of QoL would be expected, with this proposed study aiming to identify whether the presence of headaches affects the trajectory of this upward curve.

Limitations

Limitations include: a small sample size (however this is normal for qualitative research) and family present during the interview having the potential to affect participants' answers. In addition, participation in the study was completely voluntary, hence all participants were willing to talk about the impact of their symptoms upon their QoL (potentially missing patients who were eligible as far as the inclusion criteria, but unwilling to discuss their QoL and symptoms). Additionally, participants interviewed within this study were all undergoing treatment for a newly diagnosed GBM tumour and hence the results may not be transferable to patients with recurrent GBM. Participants were either undergoing or had recently undertaken adjuvant temozolomide in the chemotherapy phase of their treatment, however the exact phase of the chemotherapeutic cycle that they were in at the time of the interview was not recorded and neither was their current medication regime. Initially inclusion criteria stipulated that patients be 5-9 weeks post-radiotherapy at the time of interview, however due to the limited time period of the study, it was realised this would not be feasible to recruit enough participants and hence was expanded to 5-21 weeks. A further difficulty encountered was classifying exactly who had headaches, with one participant reporting a unilateral facial pain and another with pronounced light-headedness, however both were quite adamant they were not experiencing headaches and as such were recorded that way. Memory recall of headaches experienced was not seen as a limitation, as when a participant was unsure of the timings of their headaches, they were offered help by their family member in attendance.

Due to the multi-faceted complexity that quality of life presents in brain tumour patients, research specifically focusing upon the burden of just one symptom that plays a role in this is challenging. Whilst headaches are not the most prevalent symptom experienced by this population, they are indeed experienced by a significant proportion. Through identifying themes consistent amongst GBM patients with headaches, we seek to gain a deeper understanding of the day to day challenges that this cohort faces, with the aim of further facilitating patient management.

Despite these limitations, the principles raised in this study may possibly be applicable, at least to varying extents, to a larger population of not just GBM patients, but potentially also other high grade malignant and

terminal brain cancer patients or even patients with benign brain tumours experiencing headaches.

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Conclusion

The aim of this qualitative study was to investigate and address the impact, importance and interaction of headaches experienced by GBM patients, upon their QoL. Whilst not all participants reported as experiencing headaches, those that did considered the physical pain of their headaches not to be severe or prolonged enough to directly impact upon QoL. However, during interview analysis, three participant themes emerged regarding the strive to not be bound by the symptomatic implications of their condition, the indirect impact of headaches upon socialisation and headaches acting as a painful psychological reminder in certain participants of the significance of the threat to their autonomy and survival. These emergent themes should act as important reminders to clinicians of the secondary impacts and underlying mindset of patients having been diagnosed or undergoing treatment for GBM, in particular if they have been experiencing headaches. Implications for clinical practice include the potential for providing patients with headache diaries to allow a more comprehensive holistic assessment of GBM patients experiencing headaches. Directions for further research include investigating whether headaches can be of clinical value by being utilised as a prognostic indicator for QoL and exploring if the themes raised in this study also bear relevance to subsets of patients with a wider spectrum of brain tumours.

Contributors

This study was devised by SRB and subsequently designed together with GC and AL. SRB interviewed, transcribed and provided subsequent coding. Thematic development of these codes was performed independently by SRB, AL and SRM, to which SRB then collaborated with both, agreeing upon the final 3 key themes. SRM wrote the first drafts of the paper, which were then critiqued and edited by GC, AL and SRM – with the final version approved by all.

Competing Interests

None declared.

Funding

None declared.

Data Sharing Statement

No additional data available.

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3 Semi-structured Interview Topic Guide
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- 5 1. Yourself, your life and living with cancer.
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7 2. What has changed the most since your diagnosis?
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9 3. Have you experienced any headaches since your diagnosis of glioblastoma multiforme?
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11 4. Do you think about the cause of these headaches?
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13 5. Impact of headaches upon sleep?
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15 6. Enquire into coping mechanisms. Do headaches affect ability to cope?
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17 7. If you were to experience more severe headaches what would go through your mind?
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A qualitative study investigating the impact of headaches on the quality of life of glioblastoma multiforme patients. Version 1 – 12/12/2014.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:

Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

YOU MUST PROVIDE A RESPONSE FOR ALL ITEMS. ENTER N/A IF NOT APPLICABLE

No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Interviewer/facilitator	Which author/s conducted the interview or focus group?	Methods (p.10) and Contributors (p.23)
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	Title Page (p.1, 2)
3. Occupation	What was their occupation at the time of the study?	Title Page (p.1, 2)
4. Gender	Was the researcher male or female?	Title Page (p.1, 2) and Methods (p.10)
5. Experience and training	What experience or training did the researcher have?	Title Page (p.1, 2) and Methods (p.10)
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	N/A
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Methods (p.10)
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Competing Interests (p. 23)
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Methods (p.10, 11)
<i>Participant selection</i>		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive,	Methods (p.10)

	snowball	
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Methods (p.10)
12. Sample size	How many participants were in the study?	Methods (p.10) and Results (p.13)
13. Non-participation	How many people refused to participate or dropped out? Reasons?	Methods (p.10)
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Methods (p.10)
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	Methods (p.11) and Results (p.13)
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Results (p.13, 14)
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Methods (p.10, 11)
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	Methods (p.10)
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	Methods (p.11)
20. Field notes	Were field notes made during and/or after the inter view or focus group?	Methods (p.11)
21. Duration	What was the duration of the inter views or focus group?	Methods (p.10)
22. Data saturation	Was data saturation discussed?	Discussion (p.20)
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Methods (p.11)
Domain 3: analysis and findings		
<i>Data analysis</i>		
24. Number of data coders	How many data coders coded the data?	Methods (p.10) and Contributors (p.23)
25. Description of the coding tree	Did authors provide a description of the coding tree?	N/A
26. Derivation of themes	Were themes identified in advance or derived from the data?	Results (p.15-18)
27. Software	What software, if applicable, was used to manage the data?	NA
28. Participant checking	Did participants provide feedback on the findings?	Strengths and Limitations (p.6) and Methods (p.11)
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Results (p.15-18)
30. Data and findings	Was there consistency between the data	Results (p.15-18)

consistent	presented and the findings?	and Discussion (p.19, 20)
31. Clarity of major themes	Were major themes clearly presented in the findings?	Results (p.15-18), Discussion (p.19, 20) and Conclusion (p.22)
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Results (p.15-18), Discussion (p.19, 20)

Once you have completed this checklist, please save a copy and upload it as part of your submission. When requested to do so as part of the upload process, please select the file type: *Checklist*. You will NOT be able to proceed with submission unless the checklist has been uploaded. Please DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

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