Long-term impact of adult WHO grade II or III gliomas on health-related quality of life: a systematic review

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Abstract

Background

Glioma diagnosis can be devastating and result in a range of symptoms. Relatively little is known about the long-term health-related quality of life (HRQOL) challenges faced by these patients. Establishing the impact of diagnosis on HRQOL could help positively tailor clinical decision making regarding patient support and treatment. The aim of this review is to identify the long-term HRQOL issues reported at least two years following diagnosis of WHO grade II/III glioma.

Method

Systematic literature searches were carried out using Medline, EMBASE, CINAHL, PsycINFO, and Web of Science Core Collection. Searches were designed to identify patient self-reports on HRQOL aspects defined as physical, mental or social issues. Quality assessment was conducted using the Mixed Methods Appraisal Tool (MMAT). Narrative synthesis was used to collate findings.

Results

The search returned 8923 articles. 278 titles remained after title and abstract screening, with twenty-one full text articles included in the final analysis. The majority of studies used quantitative methods, with three articles reporting mixed methodology. Negative emotional/psychological/cognitive changes were the most commonly reported. Physical complaints included fatigue, seizures and restricted daily activity. Social challenges included strained social relationships and financial problems. Patient coping strategies were suggested to influence patient's survival quality.

Conclusion

The consequences of a glioma diagnosis and treatment can have substantial implications for patients' long-term HRQOL and daily functioning. Findings from this review lay the groundwork for efforts to improve patient HRQOL in long-term survivorship.

Keywords: health-related quality of life, glioma, adult, long-term, survivorship

Introduction

Gliomas account for 78% of primary malignant brain tumours[1], with astrocytomas and oligodendrogliomas making up 16.7% and 4.5% of these respectively [2]. Gliomas and their treatment can result in noticeably impaired health-related quality of life (HRQOL)[3]. Patients often experience fatigue, cognitive deficits and mood disturbances [4]. The chosen treatment and prognosis of glioma depends largely on tumour histology and molecular profile [5].

While still burdensome, World Health Organisation (WHO) grade I brain tumours, typically have a good prognosis[2]. WHO grade IV brain tumours represent the other end of this spectrum of malignancy, with patients usually experiencing rapid disease progression and tumour recurrence. In this article, we will focus exclusively on WHO grade II or III gliomas, which are diffuse and malignant gliomas with intermediate prognosis. Survival ranges from 4-16 years following initial diagnosis [6], and patients receive multimodal treatments primarily with the aim of delaying disease progression and extending survival. Given this prognosis, consideration of HRQOL in long-term survival is of increasing importance in both clinical and social care settings for patients with WHO grade II and III gliomas.

Patients experience significant life changes immediately following diagnosis, such as the introduction of treatment and management of symptoms, changes in daily activities, and alterations to their social support system [7]. However, less is known about the longer-term experiences of these patients, when patients attempt to return to their day-to-day lives. Given that prognosis varies greatly between brain tumour groups, there is no clear or universal definition of 'long-term survival' in neuro-oncology. Here, we define 'long-term survival' in WHO grade II and III gliomas as ≥ 2 years since diagnosis. A period of this length following diagnosis will have allowed patients to adjust to living with their diagnosis, and patients will have completed first line treatment with potential late effects now starting to emerge. We anticipate that the long-term impact of the disease and treatment on their HRQOL will be clear from ≥ 2 years after diagnosis. We also expect that overall, HRQOL

impairments in long-term survival will be milder than in the acute phase, as there will have been physical and emotional recovery and adjustment [8].

Despite a growing interest in HRQOL within the field of oncology, the evidence-base within less common malignancies lags behind compared to their more prevalent counterparts such as breast or lung cancer. Similarly, in relation to neuro-oncology, grade II and III gliomas are relatively rare compared to the more common tumours e.g. glioblastoma (GBM). As a result, literature on long-term HRQOL in grade II and III gliomas exclusively is limited. Furthermore, existing literature in neuro-oncology commonly divides gliomas into low-grade (WHO I and II) and high-grade (WHO grade III and IV). These subgroups are becoming less relevant after the WHO 2016 tumour reclassification [9], which places greater emphasis on tumour behaviour. Yet, this can complicate assessing HRQOL in survivorship of WHO II and III glioma. To our knowledge, there has been no systematic review collating evidence to provide an overview of the long-term HRQOL issues faced by WHO grade II/III glioma patients.

Therefore, we performed a systematic review of quantitative, qualitative and mixed-methods evidence, to present an overview of HRQOL in survivors of grade II/III glioma. By identifying common experiences from patient self-reported HRQOL, this review will offer new insights into the impact of diagnosis and/or treatment on long-term survival. Through enhancing our understanding of these impacts, this review could be invaluable in tailoring clinical decision making to improve HRQOL in patients with grade II or III glioma.

Method

Search Methods

The following databases were searched: Medline (Ovid), Embase (Ovid), PsycInfo (Ovid), and PubMed and Web of Science Core Collection. Grey literature such as conference abstracts and theses were identified in Embase, PsycInfo and Web of Science. These searches were completed on 26th June 2020, and updated on 29th July 2021. The search terms and strategies were created with advice from an information specialist, specifically for the following concepts: brain tumours, adults,

quality of life and long-term survivorship. Search strategies were developed using a combination of free text terms and subject headings. Searches were limited to literature published in English. No limit was placed on time since publication. See supplementary material 1 for the complete search strategy. The protocol for this review was registered on PROSPERO (CRD42020207211). Literature titles found were exported to EndNote X9 software where the duplicate removal function was used, and title screening was carried out.

Selection Criteria

Primary, peer reviewed and grey literature was included according to the following criteria:

1. Human, adult participants (≥18 years old);
2. Diagnosis of a primary brain tumour/glioma;
3. Tumour pathology must be a histologically confirmed WHO grade II or III glioma. If the study had a mixed participant group, then reports were included if the majority of participants were eligible (≥ 50% WHO grade II/III);
4. Mean/median time since diagnosis (TSD) must have been ≥ 2 years. This cut-off allowed us to assess HRQOL after initial treatment(s), when patients start to resume their normal lives - hence providing the earliest indication of 'long-term' survival;
5. English language/translation.

Exclusion criteria were as follows:

1. Articles not published in English;
2. Reviews, case studies and case reports;
3. Reporting on WHO grade I, IV, or brain metastases/secondary brain tumours;
4. Studies using only non-self-reported measures of HRQOL e.g., performance outcomes or clinician- or proxy-reported outcomes.

In two stages (title/abstract and full text), articles were assessed for eligibility by the lead investigator (SF). A second reviewer (FB) independently screened a random sample (20%) at each

stage. Of these original libraries, we found a discrepancy of 14%. Discrepancies were discussed, and the lead reviewer (SF) revisited hits to ensure consistency in study selection.

Data Extraction and Quality Assessment

Data extraction was carried out using a standardised template. Data extracted included study design, study outcomes, sample size and participant selection criteria, as well as the selected method used to report on HRQOL. Data was extracted in line with the themes derived from Hay & Reeves (2016)[10] definition of HRQOL - "*how well a person functions in their life and his or her perceived wellbeing in physical, mental & social domains of health*". Subcategories of HRQOL were added as appropriate (e.g., fatigue, emotional/psychological/cognitive functioning, coping), if necessary guided by domain definitions [11]. We used the Mixed Methods Appraisal Tool (MMAT) for quality assessment of included studies. This tool has been validated for use in reviews with mixed methods [12]. Following quality assessment, no studies were removed; however, studies of lower quality should be interpreted with caution and in consideration of their limitations. See supplementary material 2 for MMAT scores.

Narrative Synthesis

Narrative synthesis methodology was used to collate and interpret study findings. This type of synthesis was the most appropriate for this review due to the multiple methodology types and the variety of findings included. Figure 1 shows the process of narrative synthesis. Consequentially, evidence based on the themes of our chosen definition of HRQOL [10] were collated and synthesised into physical, mental, and social aspects affected by glioma diagnosis or treatment, with added domains where appropriate for e.g. fatigue, coping, positive changes.

Results

Search Results

The findings of this review were reported in accordance with PRISMA guidelines [13]. 8923 articles were returned in total. Upon removing duplicates, this left 2902 titles. 2624 articles were excluded based on title/abstract screening, as they did not meet the inclusion criteria. 278 articles were assessed in full for eligibility, removing 219 articles that did not meet the inclusion criteria. 41 articles appeared relevant; eight were excluded after full-text review with 14 lacking details needed to determine check against the inclusion/exclusion criteria. These were excluded after contacting the corresponding authors, see supplementary material 3. In total, 21 papers were included in the narrative synthesis. See figure 2 for search results.

Study characteristics

Sample sizes for the included studies ranged from 14 [14] - 477 [15]. Most of the studies published were from western countries, with over 50% of these studies originating from Europe. Included studies used a variety of study designs (cross sectional (n = 12), randomised controlled trial (n = 3), cohort (n = 2) pilot study (n = 1) & longitudinal (n = 3)). The majority of included studies (83%) had quantitative data, with three papers (17%) using mixed methodologies. Five studies used comparisons to either healthy or non-brain tumour control groups, with five of the remaining studies drawing direct comparisons between two brain tumour cohorts in treatment studies (24%). Studies reported on a variety of outcome measures. See table 1 for study characteristics and clinical cut-offs available.

Physical Functioning

12 articles reported issues relating to physical functioning aspects of HRQOL [14], [16], [17], [18], [19], [20], [21], [22], [23], [24] [25-27]. All of these studies measured HRQOL quantitatively through validated outcome measures (e.g. EORTC-C30, EORTC-BN20), and two studies also included qualitative measures [14], [22]. Apart from two from Japan [28] [17] these studies were from western countries. Four of these papers compared their respective sample to controls [25] [16], [18], [20]. These three control groups were two 'healthy population' groups, and two with non-CNS cancer group (diagnosed with non-Hodgkin's lymphoma and chronic lymphatic leukaemia). In these studies, glioma patients reported impaired physical functioning [16] [18], [20, 25].

Many of the commonly used, validated measures of HRQOL contain some assessment of physical functioning as part of their overall score. Several studies found overall physical functioning to be impaired in their sample [20], [23]. Two studies found that patients reported difficulties with motor functioning [17], [18], with one of these studies finding significantly higher levels of impairment compared to healthy controls [18]. Similarly, a mixed methods study found that in an open-ended feedback measure, patients reported difficulty with mobility in the form of issues maintaining daily routine [23]. Patients also reported other physical complaints such as epilepsy, headaches[25], loss of independence, hair loss, weight- gain and vision problems [21]. These reflect some of the long-term physical issues faced by glioma patients that can influence their HRQOL.

Fatigue

Increased levels of fatigue proved to be a common complaint [17], [19], [24] [28], and one study showed fatigue to be notably worse compared to controls [16] One study reported tiredness and sleep disturbances as affecting 50% of patients [24] Another study found that in examining factors related to quality of life measurements, insomnia had a statistically significant effect on patient's perceived global health status (GHS) [17]. It is important to note that of these studies reporting on fatigue, one examines the late effects of radiotherapy and adjuvant chemotherapy on HRQOL [19]. In this case,

conclusions are limited to patients undergoing those specific treatments, as opposed to general, long-term HRQOL for all glioma patients.

Mental Functioning

Psychological/Emotional Functioning (EF)

Impairments to psychological and/or emotional functioning (EF) were reported in 12 papers [14], [16], [29], [17], [30], [31], [32], [21], [33], [22], [23], [24] [34] [28]. This was measured across various HRQOL measures that include EF as a subscale, as well as other validated scales specifically for other psychological or emotional impairment (e.g. HADS [35], POMS [36], PANAS [37], ABS [38], CES-D [39]). 10 of these articles originated from western countries, with the remaining study occurring in Japan [17]. Three of these studies included qualitative methods alongside their validated scale measures [14], [16], [22].

Multiple studies found evidence of glioma patients' depressive symptoms [14], [16], [17], [31], [32], [21]. These studies had reports of depression [16], [30], [31], anxiety [29], [31] as well as anger, tension [14], future uncertainty [17], impaired emotional functioning [33] and increased levels of psychological distress [21], [22], [23], [16, 24] and negative affect [32]. Three studies [14], [16], [31] found clinically significant levels of depressive symptoms as measured by screening instruments (i.e. POMS [36], HADS [35], BDI [40]) by a small margin relative to the clinical cut-offs displayed in table 1. Another three studies [29], [32], [21] also found elevated scores of depressive symptoms, which did not reach clinically or statistically significant differences compared to controls. Similarly, samples did not surpass their respective clinical cut-offs. One finding of note is that patients reported high levels of both positive and negative affect, indicating higher emotional reactivity than the reference 'healthy' population [32]. Interestingly, one study assessing the quality of life of brain tumour patients in the context of the COVID-19 pandemic found that across the first nationally imposed lockdown in Germany, patients showed significant levels of distress, anxiety and depression, with around 23% of patients reporting elevated levels of depression symptom load.[41] Overall, studies appear to suggest that while differing across measures, glioma patients clearly endure some level of mood/emotional disturbance.

In the qualitative strands of the three mixed methodology studies, evidence of emotional disturbance was reported [22], [23]. Negative affect was also reported to increase in patients, with one of these studies finding that half of the patients complained of mood disturbances (56%), with a smaller percentage reporting difficulties dealing with change (26%) [22]. Another of these studies found that negative outcomes relating to psychological well-being included fear of recurrence and distress over treatment and initial diagnosis [23]. However, this same study also found that part of this distress could be attributed to lack of information and support from medical staff, particularly in regards to coping with their cancer diagnosis [23].

Coping styles

Patients' self-efficacy for coping with cancer (SECC) also influenced their chosen coping strategy, and determined how heavily they relied on external sources of support. Subsequently, this study found that patients with greater SECC reported lower unmet psychological needs [21]. Interestingly this article also found that patients with greater SECC reported lower unmet needs in regards to their respective healthcare services, the amount of information provided as well as the support and patient care [21]. This aligns with findings described above, suggesting the link between patient distress and lack of information and support provided by medical staff [23].

One study found on average, patients under-utilised the coping strategies available to them [29], with confrontative and optimistic styles reported most frequently. In this study, there was only evidence of depression in 13% of the sample (full sample: n = 46), in line with previous findings in brain tumour patients [42]. These findings could suggest that the chosen coping strategy could have significant impact on patient wellbeing. However, the aim of this study was to examine the reliability of caregiver ratings of emotional concerns and coping strategies, therefore we are unable to conclude any link between the effectiveness of these different coping styles alongside ratings of depression.

Positive Change

While there are many negative effects of glioma diagnosis on HRQOL, patients can also experience positive changes in outlook because of their diagnosis. Patients can also experience greater acceptance of changes, increased perceptions of hope and importance [22]. Another study found that despite experiencing increased negative affect, that patients were satisfied with their lives overall, and perceived greater maturity and greater sense of self [32].

Self-reported Cognitive Functioning (CF)

Impaired cognitive function is a common concern in glioma patients, and an important aspect of HRQOL. We selected studies based on their use of self-reported measures; therefore, results from studies only reporting on objectively measured CF (using performance outcomes) were not included. In this literature sample, CF was often a sub-scale of the utilised HRQOL measures. However, it was also a common complaint reported in the qualitative strands of the mixed method studies [14], [16], [17], [18], [28], [33], [23].

Reports of impaired cognitive functioning included communication difficulties [17], impairment of memory and problems with concentration [16]. One qualitative report from a mixed methods study reported the frustration felt as a result of impaired communication – one patient described how they had "words in my head but I can't get them out", subsequently making daily communication difficult [23]. Findings suggest the degree to which glioma patients might experience impaired CF could be dependent on the tumour pathology, treatment strategy as well as whether there is tumour recurrence [28], [33]. For example, one quantitative study found that there was a larger number of reports of impairment to memory, cognition and intellectual functions in patients having undergone radiation therapy alongside neurosurgery than those who had undergone neurosurgery alone [31]. Overall, the present review found that glioma patients' self-reported cognitive issues are of considerable importance across their long-term survival.

Social Functioning (SF)

Changes to lifestyle and social relationships were reported by five articles [14], [18], [22], [23], [24]. This includes issues related to work and finance. Several articles reported patients experiencing financial difficulties following diagnosis [14], [17] and [18] and frustration with resultant impaired abilities to work [23]. Given the inclusion criteria for this review ≥ 18 years, we can assume that a high proportion of the samples included were of working age, so disruptions to working life could be significantly impactful. Patients' social relationships can also suffer because of glioma diagnosis [22], [33], [24]. A mixed methods study described that altered body image concerns as a result of a glioma or treatment can put strain on both existing social relationships as well act as a hindrance to meeting new people [22]. Two articles reported that strained personal and familial relationships could have a notable negative impact on patient HRQOL [23], [24]. Findings also suggested that positive outcomes of HRQOL were associated with greater levels of communication, support and acceptance from family members [22], [23]. Indeed, during the COVID-19 pandemic lockdown, the number of social interactions per week was associated positively with patient HRQOL, demonstrating the interdependent relationship between psychological, emotional, and social functioning [41].

Discussion

Despite HRQOL and long-term survivorship research becoming a prominent part of oncology research over the past several decades, our searches only returned 21 studies. The reported issues that patients face were mapped across the domains outlined by the WHO definition of HRQOL – those of *'physical, mental and social wellbeing*' [10]. This broad definition allowed us to report on the wide variety of issues. We collated evidence from both quantitative and mixed methods studies. The rich data available suggests there are various links between these domains, all of which contribute to patients' overall reported HRQOL. By employing few exclusion criteria, we ensured that the full breadth of available evidence could be included and assessed.

During long-term survival, WHO grade II/III glioma patients experience a variety of physical impairments. These include issues with motor functioning, pain and changes in appearance. These were most commonly reported in studies with samples categorised as '2-5 years since diagnosis' suggesting that physical impairments are more marked in the earlier phases of long-term survivorship. This suggests that support aimed at improving physical functioning or helping patients adjust to physical changes, is best offered earlier in survivorship. Fatigue was also a frequent complaint. This is in line with previous findings - van Coevorden-van Loon, Coomans, Heijenbrok-Kal, Ribbers & van den Bent (2017) found fatigue to be a prevalent side effect of treatment in low-grade glioma patients [43]. Peters et al., (2014), examined the impact of fatigue and HRQOL on survival in patients with high-grade glioma (WHO grade III/IV)[44]. This paper was not included in our review due to the high proportion of grade IV tumours included. However, their findings suggest that the greater the number of symptoms of fatigue, the poorer the quality of patients' survival. Our findings confirm that WHO grade II/III patients also experience the debilitating effect of fatigue, even years after diagnosis.

Given the nature of the disease and treatment strategies employed, it is perhaps unsurprising that impaired physical functioning is a relevant factor in HRQOL of these patients. Still, the evidence suggests that more prevalent and persistent issues were found in the domains of psychological/emotional and cognitive functioning. Psychological, emotional and cognitive functioning issues were the most common complaints reported, and were reported across all three survivorship groups (2-5; 5-10; 10+ years), suggesting that the emotional burden experienced by patient persists across long-term survivorship. Investigations covered changes in body image perception [22], prevalence of depression and/or anxiety symptoms [16], [29], [17], [30], [31], declines in mental wellbeing [32], [21], and increased levels of cognitive and communication difficulties [23]. The severity of these issues varied across studies due to the different constructs measured with the various outcome measures, as well as differences in clinical cut offs. In this review, we did not aim to cover cognitive performance outcomes, thus we excluded studies that only reported results of neurocognitive tests. We focused on including studies that used self-reported cognitive functioning. This arguably provides

greater insight into patient experience of cognitive functioning and HRQOL as the correlations between HRQOL and neurocognitive functioning are not straightforward [45].

We defined long-term survival as ≥ 2 years since diagnosis as this period would have allowed patients to adapt to their diagnosis and to return to some version of their 'normal' lives. Adaptation and coping impacts upon HRQOL with two studies [12], [31] suggesting that severity of emotional difficulty faced by patients could be heavily dependent on their employed coping style. This is in line with Nip et al., (2016), which found that in a study of lung cancer patients, coping strategies and emotional support correlated with mood and ratings of HRQOL [46]. Those that utilised acceptance coping styles reported better HRQOL and mood than those that employed more styles of self-blame and denial. Hack & Degner (2004) also found that in breast cancer patients, their long-term psychological adjustment depended on their employed coping strategy [47]. While these samples are not directly comparable for this review, they provide important perspective in the wider context of the experience of long-term survival in cancer patients. It may be useful to establish the importance of coping styles in glioma patients, particularly given the added cognitive difficulties they experience alongside their cancer-related disease burden. There were also reports of changes in perspective to adopt a more positive outlook and appreciation for life following diagnosis [22]. One mixed methods study suggested a positive correlation between spiritual well-being and HRQOL outcomes [23]. This demonstrates the complexity of patients' response to their diagnosis and/or treatment, and highlights an important area, which should be investigated further using qualitative study designs.

Social relationships and functioning were highlighted as important aspects of HRQOL across all three survival-time categories. Studies reported lifestyle changes, difficulty forming [22] and maintaining social relationships [23] It is clear that maintaining positive social relationships is important for patient HRQOL [46], [48] yet impaired social functioning as measured with European Organisation for Research into Treatment of Cancer Quality of Life Questionnaire -C30 (EORTC QLQ-C30), Short-Form 36 (SF-36) was not highly prevalent in this review. Although this was not a direct aim of this review, our findings are in line with previous literature, which highlights that a

glioma diagnosis can carry a significant burden not just for patients, but also for their family and friends [49].

Strengths and Limitations

This systematic review is, to our knowledge, the first to look at long-term survival and HRQOL in WHO grade II/III glioma patients, with few exclusion criteria in terms of study design or methodology, ensuring that we capture the full breadth of existing evidence. We looked exclusively at patient self-reported outcomes of HRQOL, allowing direct insight into patient experience of long-term survivorship. By including evidence from mixed-methods studies, we could identify similar HRQOL themes regardless of methods used, including those HRQOL aspects that are not typically captured with validated questionnaires. The context provided by qualitative dimensions of the mixed-methods studies are particularly useful and may highlight potential avenues where interventions could be offered to patients.

However, this review has some limitations. Firstly, because there is no universal definition of 'long-term' survival in neuro-oncology, we chose a pragmatic cut-off of ≥ 2 years after diagnosis (mean or median) as from a clinical viewpoint, these patients will have completed treatment and entered a period of follow-up. Included studies reported on mixed samples, and not all potentially eligible studies included information on time since diagnosis (see supplementary material 3). Subsequently we may have excluded potentially relevant studies based on this lack of information. Furthermore, by using the mean/median average time since diagnosis, studies could include patients who were assessed < 2 years after diagnosis. This means that some of the included studies' results may include patient experiences earlier after diagnosis, so conclusions for long-term quality of life should be interpreted with caution. We acknowledge that many studies included in this review recruited participants before the 2016 WHO tumour reclassification, which is likely to have influenced the samples included before and after this point, making it more difficult to draw conclusions on HRQOL for WHO grade II/III glioma. Our decision to include literature if the sample had at least 50% grade II/III tumours, may have introduced some level of bias for studies with greatly mixed samples. Thirdly, the inclusion of only English published/translation of papers could account

for the lack of diversity in the locations of included studies, introducing a potential for cultural bias to our findings. The studies included also used a wide range of outcome measures (e.g. EORTC QLQ-C30, Hospital Anxiety and Depression Scale (HADS)[35], Profile of Mood States (POMS)[36], etc.). Some of these are better validated within the glioma population, or have clearer cut-off scores for clinical relevance than others. Therefore, it was not possible to add information on statistical as well as clinical relevance for all HRQOL outcomes in this review. Due to the nature of the samples included, we were unable to infer the effect of the different treatments used in the various tumour groups, and the influence this might have had on the HRQOL outcomes. Finally, the MMAT quality assessment indicates the quality of the studies varied, emphasising conclusions should be assumed with caution – see supplementary material 2.

Future Research

In future studies, consideration should be given to the importance of coping mechanisms, self-efficacy, and resilience in managing the quality of patients' survival. This could help inform clinical practise and allow tailoring of support services for long-term survivors of glioma. A previous review looked at identifying supportive care interventions to improve HRQOL in brain tumour patients [50]. Across ten RCTs included in said review, only two interventions were found to improve HRQOL (home-based psychosocial interventions and acupuncture with rehabilitation). Further intervention studies are needed to improve the evidence-base for effectiveness of support. Particularly, as our review findings suggest that even years after diagnosis, glioma patients experience HRQOL issues. Observational studies should include age at diagnosis as well as details on treatments received to allow investigation of these factors on long-term HRQOL in WHO grade II/III glioma patients. While the studies included originated from a variety of different countries (e.g. Italy, USA, Sweden, Denmark, Japan, France, Netherlands, Germany & Norway etc.), there was a significant lack of studies included from non-westernised countries. This could have introduced a level of cultural bias to this review due to variations in perceptions of health and wellbeing [51] as well as financial affluence across cultures. This also applies to the potential impact of spirituality and religion. Future studies

could explore the influence of wealth, culture, spirituality and religion on glioma survivors' HRQOL using qualitative methods.

Conclusions

This systematic review presents an up-to-date overview of the state of the evidence around HRQOL in glioma survivorship – a population confronted not just with the diagnosis and treatment of cancer, but also with a neurological condition. While physical and social issues can persist for years after diagnosis, the impact on mental functioning (psychological, emotional, and cognitive) is much more prominent. Evidence suggests that patients' capacity to cope with long-term survivorship issues could be indicative of HRQOL, however further research is needed to establish any causal link. Findings from this review aids understanding of the impact that glioma diagnosis and treatment can have on patient HRQOL. This could help to facilitate the development of interventions aimed at improving glioma patients' quality of survival, and help in streamlining existing resources and support for patients in clinical practice

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References

1. Surgeons, A.A.o.N. *Types of Brain Tumours*. 2021 [cited 2021 19.08]; Available from: https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Brain-Tumors#:~:text=Gliomas%20are%20the%20most%20prevalent,percent%20of%20malignant%20brain%20tumors.
2. Ostrom QT, Cioffi G, Gittleman H, et al., *CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016.* Neuro-Oncology, 2019. **21**(Supplement5): p. V1-V100.
3. IJzerman-Korevaar M, Snijders TJ, de Graeff A, Teunissen SCCM, de Vos FYF., *Prevalence of symptoms in glioma patients throughout the disease trajectory: a systematic review.* Journal of Neuro-Oncology, 2018. **140**(3): p. 485-496.
4. Osoba D, Brada M, Prados MD, et al. *Effect of disease burden on health-related quality of life in patients with malignant gliomas.* Neuro-oncology, 2000. **2**(4): p. 221-228.
5. Liang J, Lv X, Lu C, et al. *Prognostic factors of patients with Gliomas - an analysis on 335 patients with Glioblastoma and other forms of Gliomas.* BMC Cancer. **20**(1): p. 35.
6. Claus EB, Walsh KM, Wiencke, et al. *Survival and low-grade glioma: the emergence of genetic information.* Neurosurgical focus, 2015. **38**(1): p. E6.
7. Liu R, Solheim K, Polley M-Y, et al. *Quality of life in low-grade glioma patients receiving temozolomide.* Neuro-oncology, 2009. **11**(1): p. 59-68.
8. Liu R, Page M, Solheim K, et al. *Quality of life in adults with brain tumors: Current knowledge and future directions.* Neuro-Oncology, 2009. **11**(3): p. 330-339.
9. Louis DN, Perry A, Reifenberger G, et al. *The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary.* Acta Neuropathologica, 2016. **131**(6): p. 803-820.
10. Hays RD, Reeve BB. *Measurement and Modeling of Health-Related Quality of Life*. 2017, Elsevier. p. 570-578.
11. Bosc M. *Assessment of social functioning in depression.* Compr Psychiatry, 2000. **41**(1): p. 63-9.
12. Hong QN, Fabregues S, Bartlett G, et al. *The Mixed Methods Appraisal Tool (MMAT) version 2018 for information professionals and researchers.* Education for Information, 2018. **34**(4): p. 285-291.
13. Page MJ, McKenzie JE, Bossuyt PM, et al., *The PRISMA 2020 statement: An updated guideline for reporting systematic reviews.* International journal of surgery (London, England), 2021. **88**: p. 105906.

14. Taphoorn MJB, Heimans JJ, Snoek FJ, et al., *Assessment of quality of life in patients treated for low-grade glioma: A preliminary report.* Journal of Neurology Neurosurgery and Psychiatry, 1992. **55**(5): p. 372-376.
15. Reijneveld JC, Taphoorn MJB, Coens C, et al. *Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study.* The Lancet Oncology, 2016. **17**(11): p. 1533-1542.
16. Taphoorn MJB, Schiphorst AK, Snoek FJ, et al. *Cognitive functions and quality of life in patients with low-grade gliomas: The impact of radiotherapy.* Annals of Neurology, 1994. **36**(1): p. 48-54.
17. Umezaki S, Shinoda Y, Mukasa A, et al., *Factors associated with health-related quality of life in patients with glioma: impact of symptoms and implications for rehabilitation.* Japanese Journal of Clinical Oncology, 2020. **50**(9): p. 990-998.
18. Habets EJ, Taphoorn MJB, Nederend S, et al. *Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors.* J Neurooncol, 2014. **116**(1): p. 161-8.
19. Taphoorn MJB, van den Bent MJ, Mauer MEL, et al. *Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: Results of a European Organisation for Research and Treatment of Cancer randomized clinical trial.* Journal of Clinical Oncology, 2007. **25**(36): p. 5723-5730.
20. Boele FW, Douw L, Reijneveld JC, et al. *Health-related quality of life in stable, long-term survivors of low-grade glioma.* Journal of Clinical Oncology, 2015. **33**(9): p. 1023-1029.
21. Kohlmann K Janko M, Ringel F, et al. *Self-efficacy for coping with cancer in glioma patients measured by the Cancer Behavior Inventory Brief Version.* Psycho-Oncology, 2020. **29**(3): p. 582-585.
22. Rowe L, Vera E, Acquye A, et al. *The prevalence of altered body image in patients with primary brain tumors: an understudied population.* Journal of Neuro-Oncology, 2020. **147**(2): p. 397-404.
23. Munoz C, Juarez G, Munoz ML, et al. *The quality of life of patients with malignant gliomas and their caregivers.* Social work in health care, 2008. **47**(4): p. 455-478.
24. Gustafsson M, Edvardsson T, Ahlstrom G. *The relationship between function, quality of life and coping in patients with low-grade gliomas.* Supportive Care in Cancer, 2006. **14**(12): p. 1205-1212.
25. Aaronson NK. et al., *Compromised Health-Related Quality of Life in Patients With Low-Grade Glioma.* Journal of Clinical Oncology, 2011. **29**(33): p. 4430-4435.
26. Weitzner MA. *Psychosocial and neuropsychiatric aspects of patients with primary brain tumors.* Cancer Investigation, 1999. **17**(4): p. 285-291.

27. Weitzner MA, Meyers CA, Byrne K. *Psychosocial functioning and quality of life in patients with primary brain tumors.* Journal of Neurosurgery. **84**(1): p. 29-34.
28. Okita Y, Narita Y, Miyahara R, et al. *Health-related quality of life in long-term survivors with Grade II gliomas: The contribution of disease recurrence and Karnofsky Performance Status.* Japanese Journal of Clinical Oncology, 2015. **45**(10): p. 906-913.
29. Moreale R, Campanella F, Marin F, Skrap M, Palese A, et al. *Emotional concerns and coping strategies in Low Grade Glioma patients and reliability of their caregivers in reporting these concerns: Findings from a cross-sectional study.* European journal of oncology nursing : the official journal of European Oncology Nursing Society, 2017. **30**: p. 113-119.
30. Boele FW, Klein M, Verdonck-de Leeuw IM, Cuijpers P, et al. *Internet-based guided self-help for glioma patients with depressive symptoms: a randomized controlled trial.* Journal of Neuro-Oncology, 2018. **137**(1): p. 191-203.
31. Haldbo-Classen L, Amidi A, Wu LM, et al. *Long-term cognitive dysfunction after radiation therapy for primary brain tumors.* Acta Oncologica, 2019. **58**(5): p. 745-752.
32. Campanella F, Palese A, Missier DF, et al, *Long-Term Cognitive Functioning and Psychological Well-Being in Surgically Treated Patients with Low-Grade Glioma.* World Neurosurgery, 2017. **103**: p. 799-808.e9.
33. Jakola AS, Unsgard G, Myrmel SK, et al. *Surgical strategies in low-grade gliomas and implications for long-term quality of life.* Journal of Clinical Neuroscience, 2014. **21**(8): p. 1304-1309.
34. Tabrizi S, Yeap YB, Sherman JC, et al. *Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma.* Radiotherapy and Oncology, 2019. **137**: p. 95-101.
35. Zigmond AS, Snaith RP. *The Hospital Anxiety and Depression Scale.* Acta Psychiatrica Scandinavica, 1983. **67**(6): p. 361-370.
36. Searight HR, Montone K. *Profile of Mood States*, in *Encyclopedia of Personality and Individual Differences*, V. Zeigler-Hill and T.K. Shackelford, Editors. 2017, Springer International Publishing: Cham. p. 1-6.
37. TranV. *Positive Affect Negative Affect Scale (PANAS)*, in *Encyclopedia of Behavioral Medicine*, M.D. Gellman and J.R. Turner, Editors Editors. 2013, Springer New York: New York, NY. p. 1508-1509.
38. Glatzer W and Gulyas J. *Affect Balance Scale*, in *Encyclopedia of Quality of Life and Well-Being Research*, A.C. Michalos, Editor. 2014, Springer Netherlands: Dordrecht. p. 78-80.
39. Radloff LS. *The CES-D Scale.* Applied Psychological Measurement, 1977. **1**(3): p. 385-401.
40. Upton J. *Beck Depression Inventory (BDI)*, in *Encyclopedia of Behavioral Medicine*, M.D. Gellman and J.R. Turner, Editors. 2013, Springer New York: New York, NY. p. 178-179.

41. Troschel FM, Ahndorf F, Wille L-M, et al. *Quality of Life in Brain Tumor Patients and Their Relatives Heavily Depends on Social Support Factors during the COVID-19 Pandemic.* Cancers, 2021. **13**(6): p. 1276.
42. Rooney AG, Carson A, and Grant R. *Depression in Cerebral Glioma Patients: A Systematic Review of Observational Studies.* JNCI Journal of the National Cancer Institute, 2011. **103**(1): p. 61-76.
43. van Coevorden-van Loon EMP, Coomans MB, Heijenbrok-Kal MH, Ribbers GM, van den Bent MJ. *Fatigue in patients with low grade glioma: systematic evaluation of assessment and prevalence.* Journal of Neuro-Oncology, 2017. **133**(2): p. 237-246.
44. Peters KB, West MJ, Hornsby WE, et al. *Impact of health-related quality of life and fatigue on survival of recurrent high-grade glioma patients.* Journal of Neuro-Oncology, 2014. **120**(3): p. 499-506.
45. Habets EJJ, Dirven L, Wiggenraad RG, et al. *Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: A prospective study.* Neuro-Oncology, 2016. **18**(3): p. 435-444.
46. Nipp RD, El-Jawahri A, Fishbein NJ, et al. *The relationship between coping strategies, quality of life, and mood in patients with incurable cancer.* Cancer, 2016. **122**(13): p. 2110-2116.
47. Hack TF, Degner LF. *Coping responses following breast cancer diagnosis predict psychological adjustment three years later.* Psycho-Oncology, 2004. **13**(4): p. 235-247.
48. Kroenke K, Outcalt S, Krebs E, et al. *Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain.* General Hospital Psychiatry, 2013. **35**(4): p. 359-365.
49. Renovanz M, Maurer D, Lahr H, et al. *Supportive Care Needs in Glioma Patients and Their Caregivers in Clinical Practice: Results of a Multicenter Cross-Sectional Study.* Frontiers in Neurology, 2018. **9**.
50. Pan-Weisz TM, Kryza-Lacombe M, Burkeen J, Hattangadi-Gluth J, Malcarne VL, McDonald CR, et al. *Patient-reported health-related quality of life outcomes in supportive-care interventions for adults with brain tumors: A systematic review.* Psycho-Oncology, 2019. **28**(1): p. 11-21.
51. Schmidt S, Bullinger M. *Current issues in cross-cultural quality of life instrument development.* Archives of Physical Medicine and Rehabilitation, 2003. **84**(4 SUPPL. 2): p. S29-S34.

Table 1 – Study Characteristics

Reference Number	TSD Category	Title	Year	Author	TSD (years)	Location	Sample style (n =)	Molecular Markers	Age at diagnosis	Controls/Comparison Sample	Study Aims	Instrument	Clinical Cut-off
[14]	2-5 years	Assessment of quality of life in patients treated for low-grade glioma: a preliminary report	1992	Taphoorn, Heimans, Snoek, Lindeboom, Oosterink, Wolbers Karim	2 years	Netherlands	Adult low grade glioma-patients, treated with surgery and radiotherapy at least 1 year previously (n = 14)	Not reported	Not reported	N/A	Evaluate the utility of the instruments and assess quality of life.	Affect Balance Scale (ABS) Profile of Mood States (POMS) Interview	N/A 7 [52]
[16]	2-5 years	Cognitive functions and quality of life in patients with low-grade glioma – the impact of radiotherapy	1994	Taphoorn, Klein Schiphorst , Snoek Lindeboom , Wolbers , Karim, Huilgens, Heimans	3.5 years	Netherlands	Adult patients >18 years with low grade supratentorial glioma without clinical or CT signs of recurrence (+ or – surgery and radiotherapy at least 1 year previously	Not reported	Not reported	Patients treated with radiotherapy (LGG/RT+) vs those without (LGG/RT-) Control – Patients with non-Hodgkin's lymphoma, chronic lymphatic leukaemia ((NHL/CLL)	Do the severe disturbances observed in LGG patients are related to the tumour, the radiotherapy or the malignancy caused psychological problems	Profile of Mood States (POMS)	7 [52]
[19]	2-5 years	Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of an EORTC	2007	Taphoorn, van den Bent, Mauer, Coens, Delattre, Brandes, Smitt, Bernsen, Frenay,	2 years +	Multi-country	Anaplastic oligodendroglioma, treated with RT +/- adjuvant chemotherapy (combined Procarbazine, Lomustine, Vincristine	Not reported	Not reported	RT+ vs RT- adjuvant chemotherapy	Impact of adjuvant chemotherapy on HRQOL	EORTC QLQ-C30 EORTC QLQ-BN20	9 (functioning domains) 5-10[53] (symptom domains) [53] N/A

		randomised controlled trial		Tijssen, Lacombe, Allgeier, Bottomley			(n = 50)						
[33]	2-5 years	Surgical strategies in low-grade gliomas and implications for long-term quality of life	2014	Jakola, Unsgard, Myrmel, Kloster, Torp, Sagberg, Lindal, Solheim	≥ 2 years	Sweden	18 years, diagnosis of grade I or II low-grade glioma, biopsy & watchful waiting; early resection (n = 153)	Not reported	Not reported	Comparison of those that favoured biopsy vs resection	Compare the long-term HRQOL in two hospital cohorts with different surgical strategies	Euro-Qol 5D (EQ-5D) EORTC QLQ-C30 EORTC QLQ-BN20	0.10 [54] 90 (functioning domains) 5-10[53] (symptom domains) [53] N/A
[17]	2-5 years	Factors associated with health related quality of life in patients with glioma: impact of symptoms and implications for rehab	2020	Umezaki, Shinoda, Mukasa, Tanaka, Takayanagi, Oka, Tagawa, Haga Yashino	2.9 years	Japan	WHO Grade II-IV glioma (n = 66)	**Grade II** Diffuse astrocytoma (IDH mutant/wildtype or NOS*) *(n = 8)* IDH-mutant, 1p19q-codeleted Oligodendroglioma NOS/Oligoastrocytom a NOS *(n = 7, n = 3)* Diffuse glioma, IDH-wildtype, NES *c* **Grade III** IDH-mutant Anaplastic astrocytoma *(n=9)* IDH – wildtype Anaplastic astrocytoma . NOS *(n = 2)* Anaplastic	Not reported	N/A	Investigate the impact of symptoms on quality of life – focussed on social participation because many patients with glioma are of working age	EORTC– QLQ C30 EORTC QLQ-BN20	90 (functioning domains) 5-10[53] (symptom domains) [53] N/A

								oligodendroglioma *(n = 7)* IDH-mutant, 1p19 codeleted Anaplastic glioma, IDH wildtype NES *(n = 1)*					
[29]	2-5 years	Emotional concerns and coping strategies in low-grade glioma patients	2017	Moreale, Campanella, Marin, Skrap, Pales	3.2 years	Italy	Surgically treated WHO low-grade glioma (n = 36)	Not reported	Not reported	Caregivers – capable of responding to a face-to-face interview	Advance knowledge in the field of depression, anxiety and coping strategies enacted by LGG patients by measuring their prevalence in their post-surgical period. To establish whether caregivers can reliably report these concerns as surrogate informants.	Beck Depression Inventory (BDI) State-Trait Anxiety Inventory (STAI) Jaloweic Coping Strategy (JCS)	0-9 indicate no or minimal depression, 10-19 indicate mild to moderate depression etc. [55] 40 [56] N/A
[32]	2-5 years	Long-term cognitive functioning and psychological wellbeing in surgically treated patients with low-grade glioma	2017	Campanella, Palese, Del Missier, Moreale, Lus, Shallice, Fabbro, Skrap`	3.35 years	Italy	Surgically treated patients with radiologically stable low-grade glioma, fluent in Italian with no sign of tumour progression (n=50)	Not reported	Not reported	N/A	Investigation of long-term cognitive and affective functioning and psychological wellbeing	State Trait Anxiety Inventory (STAI) Beck Depression Inventory (BDI)	40 [56] 0-9 indicate no or minimal depression, 10-19 indicate mild to moderate

													depression etc. [55]
	2-5 years	The Quality of Life of Patents with Malignant Gliomas and Their Caregivers	2008	Muñoz Juarez, Muñoz Portno, Fineman Badie Mamela, Ferrell	2.86	USA	Age 18 or older, no tumor recurrence or progressionafter initial diagnosis, life expectancy ≥3 months, KPS ≥ 70 (n = 20)	Not reported	Not reported	Caregiver ratings	What aspects of QOL disruption are reported by patients with malignant gliomas? What positive aspects of the experience of glioma are reported bypatients	FACT—Br QOLCS N/A	N/A N/A
[30]	2-5 years	Internet-based guided self-help for glioma patients with depressive symptoms: a randomised controlled trial	2018	Boele, Klein, Verdonck-de Leeuw, Cuijpers, Heimans, Snijders, Vos, Bosma, Tijssen, Reijneveld	3.44 years	Netherlands	Adult glioma patients, grade II, III, IV, at least mild depressive symptoms (n= 89)	Not reported	45 years (mean)	Patients with aematological malignancies	Levels of depressive symptoms by means of a low-intensity form of CBT, delivered online to increase accessibility	Center for Epidemiological Studies-Depression(CES-D) Short-Form 36 (SF-36)	≥ 16 [57] N/A
[15]	2-5 years years	Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised open label phase 3 intergroup study	2016	Reijneveld, Taphoorn, Coens, Bromberg, Mason, Hoang-Xuan, Ryan, Hassel, Enting, Brandes, Wick, Chinot, Reni,	5.6 months since diagnosis to treatment – follow up to 36 months	Multi-country (Europe (Austria, Belgium, France, Germany, Hungary, Italy, Netherlands, Portugal, Spain, Sweden, and Switzerland,	Adult patients 18+, WHO histologically confirmed diffuse grade II astrocytoma, oligodendroglioma, oligoastrocytoma, WHO performance status ≥ 2,	1p status (deleted vs non-deleted vs indeterminate)	40 years (mean)	Radiotherapy vs Chemotherapy	Determine whether temozolomide compromises HRQOL and global cognitive functioning to a lesser extent than does radiotherapy	EORTC QLQ-C30 EORTC QLQ-BN20	90 (functioning domains) 5-10[53] (symptom domains) [53] N/A

				Kantor, Thiessen, Klein, Verger, Barchers, Hau, Bock, Smits, Galfnopoulos Garlia, Bottomley, Stupp, Baumert		United Kingdom), Asia and Oceania (Australia, New Zealand, and Singapore), North America (Canada [NCIC group]), the Middle East (Egypt and Israel),	without previous chemotherapy who needed active treatment other than surgery (n = 477)						
[27]	2-5 years	Psychosocial functioning and quality of life in patients with primary brain tumors	1996	Weitzner, Meyers, Byrne	2.5 years	USA	Primary brain tumour patients undergoing treatment (n = 50)	Not reported	Not reporter	N/A	Evaluate the multidimensional aspects of QOL of patients with primary brain tumours.	Ferrans and Powers Quality of Life Index for Cancer (FP-QLI) Psychosocial Adjustment to Illness Scale–Self Report (PAIS-SR)	N/A N/A
[22]	5-10 years	The prevalence of altered body image inpatients with primary brain tumours: an understudied population	2020	Rowe, Vera, Acquaye, Crandon, Shah, Bryla, Wu, Wall, Siegel, Reyes, Penas-Prado, Leggiero, Cordova, Burton, Antony, Boris,	5 years (median)	USA	≥ 18 years old) patients with histologically confirmed PBT, with intracranial only disease	Not reported	Not reported	N/A	Address the prevalence of body image concerns in PBT patients using validated questionnaires and explore contributing psychological, disease and treatment related factors	Body Image Concerns (BIS) Appearance Schemas Inventory–Revised MD Ander-son Symptom Inventory-Brain Tumor Module (MDASI-BT)	≥ 10 N/A N/A

				Aboud, Vyas, Mathen, Gilbert, Capmhausen, Mendoza, Armstrong								Patient Reported Outcomes Measurement Information System (PROMIS®)	N/A
[25]	5-10 years	Compromised health-related quality of life in patients with low-grade glioma	2011	Aaronson, Taphoorn, Heimans, Postma, Gundy, Beute, Slotman, Klein	5.6 years	Netherlands	Low-grade glioma patients with no clinical signs of tumour recurrence for >1 year after histologic diagnosis and primary treatment, and no radiologic signs of recurrence within 3 months before participation (n=195).	Not reported	Not reported	Patients with non-Hodgkin's lymphoma, chronic lymphatic leukaemia ((NHL/CLL) Health Controls Group – general population normative sample	Reporting on the prevalence of generic and brain-cancer specific HRQOL problems among patients with LGG a	Short Form -36 (SF-36) (Dutch)	N/A
[21]	5-10 years	Self-Efficacy for coping with cancer in glioma patients measured by the CBI-B	2019	Kohlmann, Janko, Ringel, Renovanz	5.7 years	Germany	Diagnosis of a glial cerebral tumor (n = 37)	Not reported	49 years (mean)	N/A	Impact of self-efficacy for coping with cancer on distress and supportive care needs	Cancer Behaviour Inventory – Brief (CBI-B) Distress Thermometer (DT)	N/A ≥ 3 [58]

[20]	5-10 years	Health related quality of life in long-term survivors with grade II gliomas: the contribution of disease recurrence and KPS	2015	Okita, Narita, Miyahara, Miyaluta, Ohno, Shibiu	5.8 years	Japan	Long-term survivors of grade II gliomas (n = 80)	Not reported	33 years (median)	N/A	Relationship between HRQOL & time since treatment, KPS, history of recurrence & radiotherapy	EORTC-QLQ C30 EORTC-QLQ BN20	90 (functioning domains) 5-10 (symptom domains) [53] N/A
[59]	5-10 years	Quality of life in brain tumor patients and their relatives heavily depends on social support factors during the covid-19 pandemic	2021	Troschel, Ahndorf, Wille, Brandt, Jost, Eich, Stummer, Wiewrodt, Jetschke, and Wiewrodt	6 years	Germany	Adult brain tumour patients (n = 63)	Not reported	Not reported	Comparison to relatives	Assess QOL in brain tumour patients and their relatives across a twelves week timespan during the first COVID-19 related lockdown	HADS Distress Thermometer WHO5 well-being score	**≥8** ≥ 3 [58] **≤28[60]**
[31]	5-10 years	Long-term cognitive dysfunction after radiation therapy for gliomas	2019	Halbo-Classen, Amidi, Wu, Lukacova, von Oettingen, Gottrup, Zachariae & Høyer	7.3 years	Denmark	Adult patients with glioma or medulloblastoma (n =110)	Confirmed tumours grades I-III according to WHO 2016 guidelines	54.9 years	Neurosurgery + RT vs neurosurgery alone	Compared cognitive functioning in brain tumour patients	Patient Assessment of Own Functioning (PAOFI)	10.78. [61]
[34]	5-10 years	Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma	2019	Tibrizi, Yeap, Sherman, Nachtigal, Colvin, Dworkin, Fullerton, Daartz, Royce, Oh, Batchelor, Curry,	6.8 years (median)	USA	LGG patients if they had an indication for radiation therapy, age >18 yers, KPS score >70 (n=120)	IDHI1-R132H mutation status was available for 17 tumours -71% carried the mutation. 1p19q co-deletion status was available for a different set of 17 tumours – 29% carried this codeletion	Not reported	N/A	Examine the long-term morbidity following proton therapy in this update prospective cohort of patients with LGG	FACT-G FACT-Br FACT-fatigue	N/A N/A N/A

				Loeffler, Shish									
[20]	10+ years	Health-related quality of life in stable, long-term survivors of low-grade glioma	2015	Boele, Douw, Reijneveld, Robben, Taphoorn, Aaronson, Heimans, Klein	6 years (mid-term), 12 years (long-term)	Netherlands	Histologically confirmed oligodendroglioma, astrocytoma and oligoastrocytoma, diagnosed at least 1 year before study start, clinically stable for at least 1 year (long-term n = 67) (mid-term n = 65)	Not reported	32 years (mean)	Individually matched healthy controls	Changes in HRQOL in long-term survivors of grade I or II astrocytoma, oligodendroglioma or oligoastrocytoma, evaluate severity of compromised HRQOL at mid and long term assessment.	Short Form-36 (SF-36) EORTC QLQ-BN20	N/A N/A
[24]	10+ years	The relationship between function, quality of life and coping in patients with low-grade glioma	2006	Gustafsson, Edvardsson, Ahlström	10 years (median)	Sweden	LGG patients aged 18 and older, living in Örebro (n=39)	Not reported	Not reported	N/A	Describe function, quality of life and coping with illness-related problems in patients	EORTC QLQ-C30 Ways of Coping Questionnaire	90 (functioning domains) 5-10[53]

[18]	**10+ years**	**Health-related quality of life and cognitive functioning in long term anaplastic oligodendroglioma & oligoastrocytoma**	**2013**	**Habets, Taphoorn, Nederend, Klein, Delgadillo, Hoang-Xuan, Bottomley, Allgeier, Seute, Gijtenbeek, Gans, Enting, Tijssen, van den Bent, Reijneveld**	**12.1 years**	**Netherlands**	**Long-term survivors of WHO grade III gliomas (n = 32)**	**1p/19q codeletion and non-1p/19q deletion**	**Not reported**	**Healthy controls**	**Examine the long-term functioning of anaplastic glioma patients and the HRQOL & cognitive functioning**	**EORTC-QLQ C30** **EORTC-QLQ BN20**	**90 (functioning domains) 5-10[53] (symptom domains) [53]** **N/A**

Figure 1 - Flow Chart of Review Process

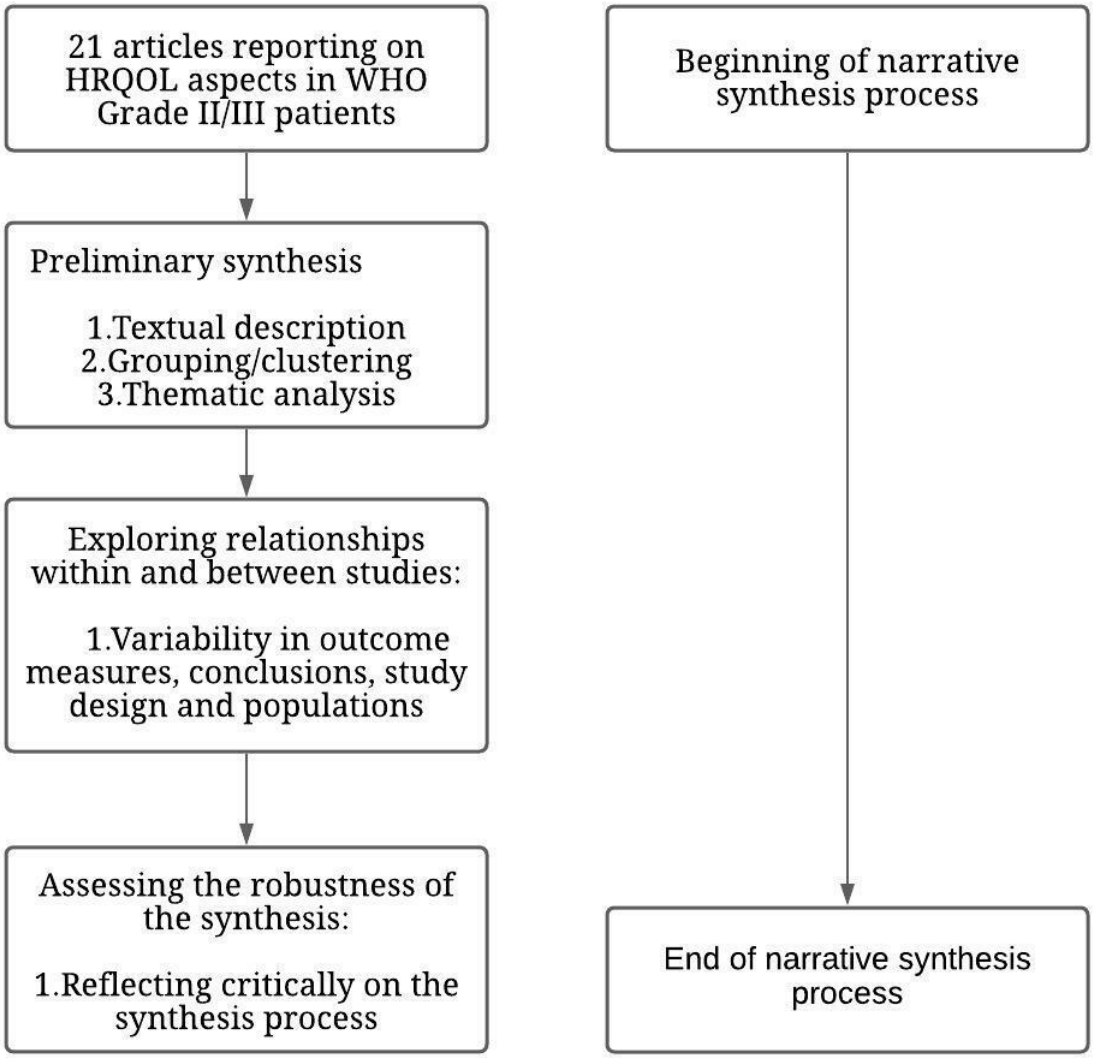

Figure 2 - Flow Chart of Search Process