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REVIEW

Life beyond a diagnosis of glioblastoma: a systematic review of the literature

L Gately[1] · SA McLachlan[1] · A Dowling[1] · J Philip[2]

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Abstract
Background The median survival of glioblastoma is 12–14 months with less than 10% of patients surviving at least 2 years from diagnosis. Patients diagnosed with glioblastoma face poor prognosis, significant symptom burden, and high care needs. The aim of this study is to undertake a literature review to document the issues encountered by long-term survivors of glioblastoma, a small but important subset of patients.
Methods MEDLINE, PsychInfo, and EMBASE were searched with core concepts: (1) glioblastoma, (2) survivor, and (3) terms pertaining to survivorship issues. A thematic analysis was undertaken of the three included studies.
Results Long-term survivors of glioblastoma encounter neurologic deficits, impairment in cognition, psychological distress, reduced social function, and future uncertainty. These issues result in the inability to return to work and financial difficulties. Independence in activities of daily living, working memory, and overall quality of life appears to be preserved.
Conclusions Long-term survivors of glioblastoma continue to have significant symptom burden and care needs. There is currently a paucity of literature surrounding this topic. Further research is required to accurately describe these issues in order for improved supportive care to be implemented in the community and the outpatient setting.
Implications for Cancer Survivors Understanding the issues faced by long-term survivor of glioblastoma will provide insight into the care needs of patients as well as support networks required for patients and their carers.

Keywords Glioblastoma · Survivor · Quality of life

Introduction

Glioblastoma is the most common primary brain tumor in adults, with incidence increasing by 3% per year [1]. Historically, treatment with radiotherapy alone following surgery resulted in dismal 3- and 5-year survival rates of 4.4 and 1.9%, respectively [2].

In 2005, the National Cancer Institute of Canada and European Organization for Research and Treatment of Cancer published seminal results showing an improvement in overall survival with the addition of concurrent oral temozolomide to standard radiotherapy [3]. This resulted in temozolomide being approved by the Food and Drug Administration and subsequently other drug regulatory authorities around the world, as well as establishing combined therapy as standard treatment for this condition (Stupp protocol). After a median of 5 years follow-up, chemoradiation resulted in a 3-year survival of 16% and 5-year survival of 9.8% [2]. The prospect of longer term survival was now a small but distinct possibility.

Long-term survivors (LTS) of glioblastoma have been defined as patients alive 18 months to 5 years following diagnosis [4, 5], without clear consensus on an appropriate definition. The Central Brain Tumor Registry of the United States (CBTRUS) suggested that 4.7% of all patients diagnosed with glioblastoma survive longer than 5 years [6]. This is in line with previously published population studies [7].

Functional independence and neurocognitive ability are significant predictors of quality of life for patients with brain tumors [8, 9]. Many patients diagnosed with brain tumors

✉ L Gately
lucyjgately@hotmail.com

[1] Department of Medical Oncology, St Vincent's Hospital, Melbourne, Australia

[2] Centre for Palliative Care, St Vincent's Hospital, Melbourne, Australia

develop impairment in neurocognition, which results in behavioral, emotional, and cognitive difficulties [10]. This deteriorates over time and may eventually compromise their ability to be independent [11]. In addition, psychological well-being can adversely affect a patient's cognitive and functional ability, as well as their quality of life, and may be both under-recognized and under-treated in LTS.

There is a growing body of information regarding the functional independence, psychological well-being, and neurocognitive function of patients with lower-grade gliomas. However, there remains little information about the issues encountered by LTS of glioblastoma during survivorship. With the advent of improved surgical and radiotherapy techniques and the discovery of immunomodulatory agents, LTS of glioblastoma are likely to be a growing cohort. As patients live longer, their ability to function independently, and as a part of society, becomes increasingly important.

The aims of this review was to examine the current literature regarding the survivorship issues encountered by LTS of glioblastoma, with a view to understanding the care needs and supports required by these patients. By understanding the current knowledge, gaps will be identified to direct future research.

Method

Research question

What issues are experienced by long-term survivors of glioblastoma?

Search strategy

A search strategy was developed using a systematic approach to identify studies with terms relating to (1) glioblastoma and (2) survivor. Further search terms relating to an aspect of survivorship (quality of life, neurologic, cognitive, physical, depression, distress, etc.) were also added. The search was carried out in May 2016 and focused on studies published in the last 30 years (1 May 1986–1 May 2016).

Searches were conducted in three databases (Medline, PsychInfo, EMBASE). Search terms were applied to "key word," "title," and "abstract" and were chosen individually for each database according to their system of indexing. Hand searches of citations and reference lists of articles identified from this search strategy supplemented the electronic search. Search was completed independently by two authors (LG, AD).

Study selection

All articles identified by the search strategy were assessed for eligibility as outlined in Fig. 1. The following inclusion criteria were used: adult patients diagnosed with glioblastoma

Inclusion criteria
Median survival > 2 years
Adult patients diagnosed with glioblastoma

Exclusion criteria
Focus on treatment, molecular, cell-biology or prognostication
Review papers, case studies and case series

Fig. 1 Inclusion and exclusion criteria

(glioma WHO grade IV) who survived more than 2 years from diagnosis. Given the lack of consensus on a definition of "long-term survivor," patients who had survived more than 2 years from diagnosis were used as this is twice the median survival for patients with glioblastoma and corresponds with a halving of the cumulative relative survival rate [12]. Qualitative, quantitative, and mixed methodology studies were included with endpoints relating to survivorship such as physical function, neurocognitive function, psychological function, and quality of life.

Studies were excluded if the primary focus was on molecular characteristics, prognostication, or cell biology. Case reports and case series were also excluded.

Figure 2 illustrates the search process for this review. Articles were identified as per the search strategy and screened by title and abstract for survivorship endpoints and definition of long-term survivor. Remaining articles or those unclear from the abstract review underwent full text review to assess quality of data and survivorship endpoints. Duplicates were removed.

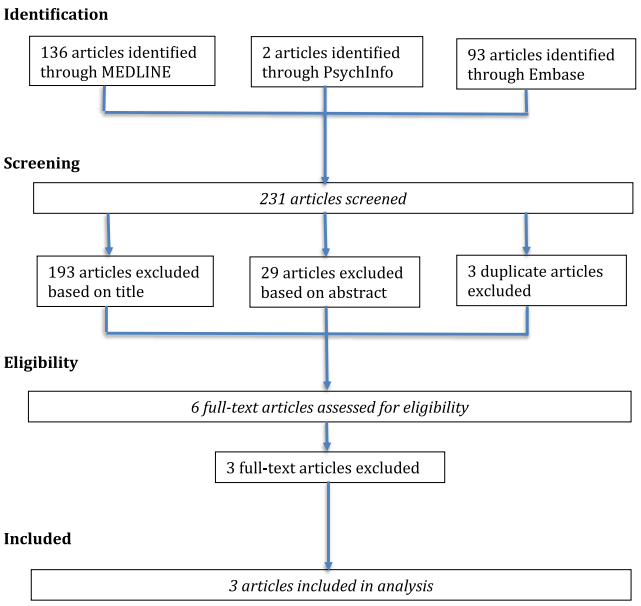

Fig. 2 Search strategy for review

Data extraction and analysis

Preliminary synthesis was performed by tabulating the specific details of the included studies, such as population, study design, outcomes, and conclusions. Data extraction and synthesis were thematic. Themes were identified and extracted to form a comprehensive picture of survivorship issues encountered by long-term survivors of glioblastoma. This allowed conclusions to be drawn based on common elements across otherwise heterogeneous studies. A narrative summary technique was used to aid interpretation of study results.

Results

There were just three studies identified that provided insights into the survivorship issues faced by long-term survivors of glioblastoma (Table 1). These were all quantitative studies and involved a total of 66 patients across all the studies, surviving a minimum of 3 years. Median survival was not consistently reported and majority of patients were alive at the time each article reported. Outcomes were tested at a single time point with no follow-up. All patients underwent surgery; however, further oncological treatment varied amongst the studies. The themes emerging from this literature could be broadly understood within the following categories: functional independence, neurocognitive function, psychological well-being, and patient reported quality of life (Table 2).

Functional independence

All three studies examined the neurologic function and functional independence of long-term survivors of glioblastoma.

Significant neurologic deficits were reported in up to 85% of patients [13]. This ranged from a reduction in manual dexterity to hemiparesis [13, 15]. Impairments in communication were present in 30%, mainly verbal fluency and dysphasia [15]. Neurologic deficits appeared to influence a patient's ability to remain functionally independent. This is supported by a reduction in performance status over time, particularly with relapses [5, 13], and at least 35% of patients required some assistance with activities of daily living [13, 15].

The ability to maintain employment is also a key component in functional independence. Less than 30% of patients

Table 1 Analysis of studies identified for review

Paper	Population	Study design	Outcomes	Conclusions
Steinbach et al. [5] Surviving glioblastoma for more than 5 years: the patient's perspective Neurology (2006)	Sample: 10 patients surviving more than 5 years since diagnosis (median survival not specified) Grade: glioblastoma Location: Germany	Quantitative Cross-sectional	Neurocognitive function Psychosocial function Patient reported quality of life	Depression/anxiety present in 30% Cognitive deficits present in all with impairment of attention, construction, and arithmetic most common Memory preserved Good quality of life perceived, however reductions in role and physical functioning 70% neurologic deficit (mild-moderate in 40%, severe in 30%) 60% unable to work
Hottinger et al. [13] Neurological outcome of long-term glioblastoma survivors Journal of Neurooncology (2009)	Sample: 39 patients surviving at least 3 years from diagnosis (median survival 9.2 years) Grade: primary glioblastoma Location: USA	Quantitative Retrospective case review	Disease control Neurocognitive function Treatment-related toxicity Patient reported symptom burden	Continuous remission in 31% Neurologic disability present in 85% 20% wheelchair bound 38% with cognitive deficits Nearly 50% require at least some assistance in activities of daily living 43% unemployed Clinically significant treatment-related complications in 46%
Flechl et al. [14] Neurocognitive and sociodemographic functioning of glioblastoma long-term survivors Journal of Neurooncology (2012)	Sample: 17 patients surviving at least 3 years (median survival not specified) Grade: primary glioblastoma Place: Austria	Quantitative Cross-sectional	Patient reported quality of life Neurocognitive function Psychosocial function Symptom burden	Nearly 50% reported moderate-severe impairment in cognitive function Psychological distress reported by 35% Global quality of life was unaffected but cognition and social functioning reduced Fatigue, financial difficulties, and future uncertainty were common Manual dexterity was impaired in nearly half of patients 35% required at least some assistance in activities of daily living

Table 2 Themes emerging from current literature

Functional independence	Neurocognitive	Psychological well-being	Patient reported quality of life
Neurologic deficits are common and impacts on a patient's ability to live independently [5, 13, 15] A significant proportion are unable to work [5, 13]	Cognitive deficits are present in the majority of patients [5, 13, 15]	Psychological symptoms and distress present in up to one third of patients [5, 15]	Global quality of life appears unaffected [5, 15] Fatigue, financial difficulties and future uncertainty are common [5] Social functioning and role functioning reduced [5, 15].

returned to work following diagnosis [5, 13, 15]. The remaining patients retired or were unable to return to work due to their deficits [13], and a proportion of these patients is supported by the disability pension [15].

Neurocognitive function

Each of the studies examined the cognitive function of long-term survivors of glioblastoma and impairments were frequently reported. Rates of cognitive impairment ranged from 40 to 100% [5, 13, 15]. Neurocognitive testing was undertaken by two studies [5, 15] and assessed memory (verbal, figural, and working), attention, language, construction, and arithmetic domains. This was tested via either neuropsychological evaluation [5] or a computerized instrument, NeuroCog FX [15]. In the study by Hottinger, there was no prospective testing and cognitive symptoms were taken from the patient's medical record [13].

Patients frequently reported cognitive slowing and distractibility [13]. Objective neurocognitive testing supported this and showed impairment in attention in the majority of patients, as well as a reduction in arithmetic and constructional abilities [5, 15]. Deficits were seen even in patients who presented clinically asymptomatic with normal MMSE [5].

Patients often reported difficulties with recent memory [13]; however, neurocognitive testing showed the domains of working memory and recall to remain surprisingly conserved [5, 15].

Approximately 50% of patients were being treated with an anti-convulsant due to a history of seizures [5, 15]. There was no further information on the severity or duration of seizures or medication use.

Psychological well-being

Two studies examined the psychological well-being of long-term survivors of glioblastoma via either the European Organisation for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire [5] or the Hospital Anxiety and Distress Scale [15]. Psychological symptoms consistent with anxiety, depression, or distress were reported in 30–35% of patients [5, 15].

Patient reported quality of life domains

Two studies specifically examined the quality of life of long-term survivors of glioblastoma. Both studies used the EORTC QLQ-C30 instrument [5, 15], and one study expanded on this using the EORTC QLQ-BN20 instrument specifically designed for brain tumors [15]. Global health and overall quality of life appeared to be unaffected despite the frequency of deficits on objective testing [5, 15]. Fatigue and drowsiness were the most frequently reported symptoms [15]. Patients also identified a reduction in social functioning, role functioning, and physical functioning [5, 15]. Future uncertainty was frequently reported as a specific concern [15]. Financial difficulties were more likely reported by patients with a reduced cognition and those on the disability pension [15]. Carer perspectives were not reported.

Discussion

To our knowledge, this paper is the first to review literature pertaining to issues in survivorship amongst long-term survivors of glioblastoma. The results most strikingly highlight the paucity of studies investigating these issues in this cohort. The consistency of findings across the three studies included suggests importantly that these themes are present in this population, highlighting that a significant proportion of patients may have deficits that are under-appreciated and that further in-depth qualification of these issues is required.

There is a volume of literature describing the issues faced by long-term survivors of low-grade glioma. Low-grade gliomas, such as oligodendrogliomas and diffuse astrocytomas, have a different natural history, tumor biology, and management strategy when compared with glioblastoma and have a more favorable prognosis with 5-year survival of 79.1 and 47.3%, respectively (c.w. 4.7% in glioblastoma) [6]. Given this, extrapolation of data may not provide a holistic representation for long-term survivors of glioblastoma. Currently, there is no literature directly comparing the issues faced by long-term survivors of high-grade versus low-grade gliomas.

Neurocognitive testing has demonstrated that patients with a history of glioblastoma have deficits, even in the absence of

symptoms or with normal Mini Mental State Examination scores [12]. Whilst dedicated neurocognitive testing can be lengthy, this suggests that thorough history taking and screening tests may not be sufficient to recognize cognitive impairment and, as such, raises the possibility of under-recognition. This demonstrates the importance of undertaking dedicated testing of long-term survivors to identify impairments early and provide sufficient support.

The cause of cognitive impairment remains unknown. Whilst the tumor itself may have an impact, radiation-induced complications are also thought to be implicated. Leukoencephalopathy was present radiologically in all patients [5, 13], and one quarter developed symptoms of cognitive impairment in the absence of active tumor [13]. This suggests that treatments for glioblastoma may also play a role in the development of cognitive impairment.

Long-term survivors of low-grade glioma have also been shown to have cognitive deficits compared with healthy controls at 6 and 12 years post diagnosis, particularly if radiotherapy was received as part of initial treatment [15, 16]. In a study of 65 patients, the most common deficits were in attention, executive functioning, and information processing speed [16]. These domains are similar to those reported to be impaired in glioblastoma survivors [5, 13, 15], albeit at a later time.

Mental health issues are often under-recognized and under-reported by survivors [17]. This may be due to a lack of insight on a patient's behalf and as such, self-reporting may be unreliable. As psychological symptoms can have important implications on quality of life, dedicated anxiety/depression/distress assessments should be undertaken at clinical encounters.

Long-term survivors of glioblastoma often perceive their overall quality of life to be preserved [5, 15]. This is despite the detection of functional and neurocognitive impairments, and psychological symptoms. Long-term survivors of low-grade glioma also report health-related quality of life to be relatively intact [18, 19]. Dedicated cognitive, psychological, and quality of life testing is rarely performed routinely at outpatient clinic appointments, and clinicians often rely on patients reporting symptoms, which could lead to under-reporting and under-recognition.

Additionally, the implications of the presence of seizures, use of anti-convulsants, or chronic steroid treatment have not been well documented but are likely important factors in long-term survivors of glioblastoma.

These studies provide some insight into the survivorship issues encountered by long-term survivors of glioblastoma. As most patients with glioblastoma cannot be cured, maintaining functional independence and health-related quality of life becomes a top priority. As new treatments become available with the potential for increased survival, it is essential to understand the possible deficits and to allow for increased support within the medical system and the community. Future research could aim to expand on the current literature with qualitative interviews to identify key themes addressing the needs of these patients, the correlation between self-reporting during clinics to dedicated testing, and the feasibility of incorporating a specifically designed questionnaire to assist with patient reporting of symptoms.

Limitations

Studies were only included in this review if they analyzed patients who had survived at least 2 years following diagnosis of glioblastoma. At this stage, there is no set definition of long-term survivors of glioblastoma, with time from diagnosis ranging from 18 months to 5 years. Smoll et al. proposed that long-term survivors should be defined as patients alive at 2.5 years following diagnosis, as this corresponds with a halving of the cumulative relative survival [12]. As such, a cutoff of at least 2 years was used to improve the capture rate.

In all three studies, patients were identified by outpatient clinic documentation. Patients must therefore have been able to attend an appointment, leading to a potential bias of only including patients of a relatively good performance status. This impacts the generalizability of the findings and may result in under-estimation of the level of deficits and burden of long-term survivors of glioblastoma. Nevertheless, we believe that the collation of these data has enabled a baseline understanding of the issues facing this growing cohort, from which future investigation can be developed.

Conclusion and practice implications

Long-term survivors of glioblastoma develop neurocognitive deficits, which affect their functional independence, and are at risk of developing significant psychological symptoms. Despite this, patients often perceive their overall quality of life to be preserved.

The literature as a whole suggested some interesting findings and direction for future research. Overall, there is a paucity of literature surrounding this subject. As new treatments become available and the numbers of long-term survivors grow, understanding the issues faced in survivorship becomes increasingly important. This understanding will provide insight into the care needs of patients as well as support networks required for patients and their carers. Future research with a particular focus upon qualitative testing and improving the detection of issues is required.

Compliance with ethical standards

Funding Nil.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dobes M, Khurana V, Shadbolt B, et al. Increasing incidence of glioblastoma multiforme and meningioma, and decreasing incidence of schwannoma (2000-2008): findings of a multicentre Australian study. Surg Neurol Int. 2011;2:176.
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459–66.
3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
4. Schmidinger M, Linzmayer L, Becherer A, et al. Psychometric- and quality-of-life assessment in long-term glioblastoma survivors. J Neuro-Oncol. 2003;63(1):55–61.
5. Steinbach JP, Blaicher HP, Herrlinger U, et al. Surviving glioblastoma for more than 5 years: the patient's perspective. Neurology. 2006;66:239–42.
6. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. Neuro-Oncology. 2013;15(Suppl 2): ii1–ii56.
7. Krex D, Klink B, Hartmann C et al. Long-term survival with glioblastoma multiforme. First published online: 4 September 2007;2596–2606. doi:10.1093/brain/awm204.
8. Sacko A, Hou MM, Temgoua M, et al. Evolution of the Karnosky Performance Status throughout life in glioblastoma patients. J Neuro-Oncol. 2015;122(3):567–73.
9. Giovagnoli AR, Silvani A, Colombo E, et al. Facets and determinants of quality of life in patients with recurrent high grade glioma. J Neurol Neurosurg Psychiatry. 2005;76:562–8.
10. Meyers C, Boake C. Neurobehavioral disorders experienced by brain tumor patients: rehabilitation strategies. Cancer Bull. 1993;45:362–4.
11. Sizoo E, Dirven L, Reijneveld J, et al. Measuring health-related quality of life in high-grade glioma patients at the end of life using a proxy-reported retrospective questionnaire. J Neuroonc. 2014;116(2):283–90.
12. Smoll NR, Schaller K, Gautschi OP. Long-term survival of patients with glioblastoma multiforme (GBM). J Clin Neurosci. 2013;20(5): 670–5.
13. Hottinger A, Yoon H, DeAngelis L, et al. Neurological outcome of long-term glioblastoma survivors. J Neuro-Oncol. 2009;95:301–5.
14. Flechl B, Ackerl M, Sax C, et al. Neurocognitive and sociodemographic functioning of glioblastoma long-term survivors. J Neuro-Oncol. 2012;109:331–9.
15. Forst DA, Nahed BV, Loeffler JS, Batchelor TT. Low-grade gliomas. Oncologist. 2014;19(4):403–13.
16. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol. 2009;8(9):810–8.
17. Ford E, Catt S, Chalmers A, et al. Systematic review of supportive care needs in patients with primary malignant brain tumors. Neuro-Oncology. 2012;14(4):392–404.
18. Boele FW, Douw L, Reijneveld JC, et al. Health-related quality of life in stable, long-term survivors of low-grade glioma. JCO. 2015;33(9):1023–9.
19. Kiebert GM, Curran D, Aaronson NK, et al. Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: results of a randomized phase III trial on dose response (EORTC trial 22844). EORTC Radiotherapy Co-operative Group. Eur J Cancer. 1998;34(12):1902–9.