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[Intervention Review]

Early palliative interventions for improving outcomes in people with a primary malignant brain tumour and their carers

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ABSTRACT

Background

Primary malignant brain tumours can have an unpredictable course, but high-grade gliomas typically have a relentlessly progressive disease trajectory. They can cause profound symptom burden, affecting physical, neurocognitive, and social functioning from an early stage in the illness. This can significantly impact on role function and on the experiences and needs of informal caregivers. Access to specialist palliative and supportive care early in the disease trajectory, for those with high-grade tumours in particular, has the potential to improve patients' and caregivers' quality of life. However, provision of palliative and supportive care for people with primary brain tumours - and their informal caregivers - is historically ill-defined and ad hoc, and the benefits of early palliative interventions have not been confirmed. It is therefore important to define the role and effectiveness of early referral to specialist palliative care services and/or the effectiveness of other interventions focused on palliating disease impact on people and their informal caregivers. This would help guide improvement to service provision, by defining those interventions which are effective across a range of domains, and developing an evidence-based model of integrated supportive and palliative care for this population.

Objectives

To assess the evidence base for early palliative care interventions, including referral to specialist palliative care services compared to usual care, for improving outcomes in adults diagnosed with a primary brain tumour and their carers.

Search methods

We conducted searches of electronic databases, CENTRAL, MEDLINE, CINAHL, Web of Science, and PsycINFO (last searched 16 November 2021). We conducted searches to incorporate both qualitative and quantitative search terms. In addition to this, we searched for any currently recruiting trials in ClinicalTrials.gov and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal, and undertook citation tracking via Scopus. We also handsearched reference lists of potentially eligible systematic review articles to identify any other relevant studies, contacted experts in the field and searched key authors via Web of Science and searched SIGLE (System of Information on Grey Literature in Europe).

Selection criteria

We included studies looking at early referral to specialist palliative care services - or early targeted palliative interventions by other healthcare professionals - for improving quality of life, symptom control, psychological outcomes, or overall survival as a primary or secondary outcome measure. Studies included randomised controlled trials (RCTs), non-randomised studies (NRS), as well as qualitative and mixed-methods studies where both qualitative and quantitative data were included. Participants were adults with a confirmed radiological and/or histological diagnosis of a primary malignant brain tumour, and/or informal adult carers (either at individual or family level) of people with a primary malignant brain tumour.

Data collection and analysis

We followed standard Cochrane methodological procedures for data extraction, management, and analysis. We used GRADE to assess the certainty of the evidence for symptom control, i.e. cognitive function.

Main results

We identified 9748 references from the searches, with 8337 remaining after duplicates were removed. After full-text review, we included one trial. There were no studies of early specialist palliative care interventions or of early, co-ordinated generalist palliative care approaches.

The included randomised trial addressed a single symptom area, focusing on early cognitive rehabilitation, administered within two weeks of surgery in a mixed brain tumour population, of whom approximately half had a high-grade glioma. The intervention was administered individually as therapist-led computerised exercises over 16 one-hour sessions, four times/week for four weeks. Sessions addressed several cognitive domains including time orientation, spatial orientation, visual attention, logical reasoning, memory, and executive function.

There were no between-group differences in outcome for tests of logical-executive function, but differences were observed in the domains of visual attention and verbal memory. Risk of bias was assessed and stated as high for performance bias and attrition bias but for selective reporting it was unclear whether all outcomes were reported. We considered the certainty of the evidence, as assessed by GRADE, to be very low.

Authors' conclusions

Currently there is a lack of research focusing on the introduction of early palliative interventions specifically for people with primary brain tumours, either as co-ordinated specialist palliative care approaches or interventions focusing on a specific aspect of palliation. Future research should address the methodological shortcomings described in early palliative intervention studies in other cancers and chronic conditions. In particular, the specific population under investigation, the timing and the setting of the intervention should be clearly described and the standardised palliative care-specific components of the intervention should be defined in detail.

PLAIN LANGUAGE SUMMARY

Improving the outcome of people with primary brain tumours and their carers using early palliative interventions

Why this question is important

Brain tumours can have a significant impact on people and their carers. Brain tumours can impair people's physical, neurocognitive, and social functioning, which can affect the whole family, particularly informal caregivers, who often receive inadequate support. There is evidence in other cancers that providing access to palliative support in the early stages of a person's illness can help to improve their, and their caregivers', quality of life. However, it has not been confirmed that this is the case for people with brain tumours.

Objectives

We aimed to assess studies that included early palliative care interventions, including referral to specialist palliative care services compared to usual care, for improving outcomes in adults diagnosed with a primary brain tumour and their carers.

How we searched for evidence

We searched electronic medical literature databases for studies that included a range of different types of medical trials, both published and ongoing. We handsearched the reference lists of key papers and searched for key authors of research in the area. We included adults confirmed with a primary brain tumour and informal caregivers such as relatives.

What we found

We could not find any trials examining the impact of specialist palliative care teams on outcomes for patients or their carers. We included one trial which focused on a single symptom area - that of cognition - in a patient group of whom about half had a high-grade tumour. The trial randomised patients between a group receiving a structured cognitive rehabilitation intervention and a group receiving usual rehabilitation care of medications and physiotherapy. Cognitive rehabilitation consisted of supervised computer-based exercises, lasting 45 minutes at a time, four times a week, over a four-week period. There was no important difference between the two groups apart from some improvement in visual attention and verbal memory in those who received the cognitive rehabilitation intervention. However, we

assessed the certainty of the evidence as being very low, and we could find no evidence in this or other studies on any other aspect of palliative care.

What this means

Not enough research has been undertaken on early palliative care interventions which support people with primary brain tumours, and their caregivers. Research is needed which examines co-ordinated approaches to overall palliative care provision, and interventions which focus on specific aspects of palliation in this population.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of Findings

Cognitive training compared to usual care of physiotherapy and medication in early palliative care for participants with a primary brain tumour

Patient or population: patients with a primary brain tumour, within two weeks of surgical intervention

Setting: neurorehabilitation centre in Italy between November 2009 and October 2011

Intervention: cognitive training

Comparison: usual care of physiotherapy and medication

Outcomes	Impact	Nº of participants (studies)	Certainty of the evidence (GRADE)
Cognitive function using validated neuropsychological tests	Additional cognitive training did not have an impact on cognitive performance in the intervention group compared to controls, apart from the domains of visual attention and verbal memory.	53 (62 randomised, 53 analysed) (1 RCT)	⊕○○○ Very low ^{a,b}

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^aWe reported occasions of high risk of bias relating to attribute bias and other bias (i.e. description of statistical analysis missing).

^bThere was no ITT analysis – even in a modified form, no predefined primary outcome and no sample size; no confidence intervals and even the SDs for the two "significant domains" demonstrate a degree of overlap.

BACKGROUND

Description of the condition

Primary brain tumours account for an estimated 2% of malignancies worldwide (Ferlay 2015). Approximately 5500 people are diagnosed with a primary malignant brain tumour each year in the UK (Cancer Research UK 2019). Gliomas are the most common type of primary brain tumour, accounting for up to 80% of malignant brain tumours overall (Goodenberger 2012). Gliomas have traditionally been graded from 1 to 4 according to the World Health Organization (WHO) classification (Louis 2016). Grades 1 and 2 are described as low-grade slow-growing tumours. Grades 3 and 4 are described as high-grade fast-growing tumours. Glioblastoma, a high-grade glioma, occurs most commonly between the fifth and seventh decades (Stupp 2010). It is a particularly aggressive disease, with a median survival time of 12 to 15 months (Stupp 2009); the five-year survival rate is 12.2% (Cancer Research UK 2019). More recently, rapid developments in molecular diagnostics have suggested the need to further refine the nomenclature to better reflect clinical risk based on molecular markers of poor outcome, alongside histological features, for example independent biomarkers in IDH-mutant astrocytoma have been defined which reflect the poor clinical outcomes of high-grade glioma, even where histological appearances are of lower grade (Louis 2021).

The symptom burden for people diagnosed with a high-grade glioma in particular is substantial. People diagnosed with a primary brain tumour often experience significant disability early in their illness and before disease progression (Golla 2014). A wide range of physical symptoms have been reported in existing literature including fatigue, pain, seizures, and cognitive impairment (Armstrong 2016; Faithfull 2005; Ford 2012). Mood disorders are also common with a six-month prevalence of depression of up to 20%, and up to 90% describing at least some depressive symptoms in the early postoperative period (Batchelor 2006; Rooney 2011). There can be profound effects on physical, neurocognitive, and social functioning from an early stage in the illness (Long 2016; Moore 2013). These effects can be exacerbated by aggressive treatment regimens (Aziz 2003; Long 2016).

The disease trajectory can be unpredictable. It is often characterised by periods of sudden acute deterioration followed by a period where the clinical condition appears to plateau (Philip 2015). This makes prognostication difficult. People can become increasingly dependent and isolated, which combined with the symptom burden can result in a reduction in perceived quality of life.

Informal care providers of people with high-grade glioma are also reported to experience significant burden and distress (Jacobs 2014; Wasner 2013). Collins 2014 reported significant needs in relation to the challenge of caring, the lack of support available to carers, and the suffering of caregivers. The neurocognitive effects of the disease, coupled with the increased dependency and social isolation, can result in changes to relationships with family members/care providers, which are not so commonly observed in the context of other malignancies (Ford 2012; Lipsman 2007).

A systematic, multidisciplinary approach to assessment and management of patient and caregiver needs would therefore have the potential to improve physical, social and mental health outcomes, as well as better use of health and social

care resources. For a number of chronic conditions and cancer diagnoses other than brain tumours, there is already evidence from meta-analyses that specialist palliative care service interventions can improve symptom burden, health-related quality of life and acute healthcare resource use (Kavalieratos 2016; Quinn 2020). To this end, a Lancet Oncology Commission on integration of oncology and palliative care (Kaasa 2018), proposes a move away from the dualistic approach of disease-focused and host-focused approaches to care towards integrated, multiprofessional and patient-focused care delivery from the point of diagnosis onwards. It also recognises the need for research to highlight optimal models of integration, and evidence of effectiveness for specific interventions across domains, such as symptom control, cognitive and physical functioning and shared decision making.

The importance of effective and efficient palliation for people with gliomas is reflected in the European Association of Neuro-Oncology guidelines (Pace 2017), which nonetheless identifies evidence gaps across a range of clinical domains and service models, with the provision of palliative and supportive care for this patient population historically ill-defined and ad hoc (Faithfull 2005; Moore 2013). The National Institute for Health and Clinical Excellence (NICE) additionally recommends that people with a primary brain tumour could benefit from specialist palliative and supportive care early in the process, at diagnosis, if possible, with continued integration of services throughout the course of the patient's illness (NICE 2018).

Description of the intervention

The emphasis of palliative care is on dealing with the whole person; identifying and managing the challenges of a life-threatening illness and addressing the physical, psychological, and spiritual symptoms that profoundly affect quality of life. It also focuses on assistance with decision making, including advance care planning and addressing issues of relevance to significant others in terms of caregiver burden and well-being (Radbruch 2009; Rietjens 2017; WHO 2020).

Palliative care interventions may be initiated individually by the oncologist, neurosurgeon, or primary care team; by members of the wider supportive care team in a co-ordinated care approach; or be provided by specialist palliative care teams as part of an integrated model. A specialist palliative care service is defined as one delivered by a multiprofessional team, usually comprising of doctors, nurses, and psychosocial workers with higher training in palliative care provision, possibly commissioned to provide palliative care at a specialist level.

The concept of 'early' palliative care has been introduced more recently to differentiate palliative interventions delivered earlier in the disease trajectory from those in the terminal phase or last days of life. There is, however, no universally accepted definition, with significant heterogeneity in description of what constitutes 'early' in reported studies in cancer and in other serious illnesses. This has ranged from definitions based on time since diagnosis or recurrence (Bakitas 2015), likely prognosis (Zimmermann 2014), in tandem with oncological review (Temel 2010), or based on symptom burden (Groenvold 2017). The American Society of Clinical Oncology practice guidelines suggest a definition of 'early' as "within 8 weeks of diagnosis" (Ferrell 2017).

This Cochrane Review focused on palliative care interventions, either in the form of a specialist palliative care service or interventions undertaken by other healthcare professionals, with the specific intent of palliation. The review included interventions delivered to both the person with the brain tumour and the carer, or either alone. It included interventions delivered in both community and secondary care settings. The timing, nature, and duration of the intervention had to be clearly stipulated. Trials included in this review contained an explicit intent to provide 'early palliative care' or provide a clear trial definition of 'early' in relation to time since diagnosis or provision during ongoing active anticancer intervention.

How the intervention might work

A systematic review of the qualitative literature by [Moore 2013](#) examining the palliative and supportive care needs of people with high-grade glioma and their carers demonstrated the need for consistent, well-delivered information around disease sequelae and treatment effects. It specifically highlighted unmet needs in terms of care co-ordination, and the need for psychological and social support. [Golla 2014](#) has demonstrated increasing symptom burden and unmet psychosocial needs over time from diagnosis onwards, with increasing care dependency for those with high-grade glioma. [Sterckx 2015](#) has identified a delay in people seeking psychosocial and palliative care support, whilst [Triebel 2009](#) suggests that about half of people with glioma have difficulty understanding and processing treatment and care choices, although there is some evidence that they are keen to be aware of palliative care options earlier in their illness ([Vierhout 2017](#)).

A systematised, multidisciplinary service intervention, as typified by the specialist palliative care model described above, therefore, has the potential to benefit people with brain tumours and caregivers across a range of needs. In the wider literature, there is increasing evidence that specialist palliative care service interventions are associated with improved patient outcomes in both malignant and non-malignant life-limiting conditions ([Bakitas 2015](#); [Harding 2010](#); [Higginson 2010](#); [Kristjanson 2006](#); [Temel 2010](#); [Temel 2017](#); [Zimmermann 2014](#)), although not all studies demonstrate consistent benefit ([Davis 2015](#); [Groenvold 2017](#)). A review of trials by [Davis 2015](#) highlighted significant heterogeneity in patient populations, intervention types, settings, and outcome measurements, making comparisons difficult. Nonetheless, a 2016 random-effects meta-analysis of palliative care interventions on patient and carer outcomes included 43 studies across a range of conditions and demonstrated improvements in patient quality of life and symptom burden ([Kavalieratos 2016](#)). [Quinn 2020](#) has undertaken a similar meta-analysis confined to people with chronic non-cancer illness and has again found evidence of benefit, with palliative care intervention, compared to control, resulting in less healthcare resource use and moderate improvements in symptom burden.

[Haun 2017](#) specifically examined the timing of palliative care intervention in a Cochrane Review, which compared early intervention by professional palliative care services compared to standard cancer care alone in advanced cancer (but not specifically brain cancer). There was evidence of modest improvements in health-related quality of life and symptom burden in patients receiving palliative care shortly after diagnosis. An unexpected finding in some studies has been the presence of a survival

advantage in those receiving early palliative care intervention ([Bakitas 2015](#); [Temel 2010](#)). Although this has not been replicated in the [Kavalieratos 2016](#) or [Haun 2017](#) reviews, the importance of assessing for survival, and exploration of potential underlying reasons, has been highlighted.

Why it is important to do this review

People diagnosed with a primary brain tumour experience a high symptom burden, uncertain prognosis, and unpredictable disease trajectory. Specialist palliative care services are well-placed to be able to support the complex needs of this population, and based on the evidence described above, early palliative care involvement for people with cancer is advocated by the American Society for Clinical Oncology ([Ferrell 2017](#)), and European Society for Medical Oncology ([Jordan 2017](#)). However, there are currently no systematic reviews that have looked specifically at the evidence base for early referral to specialist palliative care services or other designated early palliative care interventions for improving quality of life, carer outcome, and overall survival in people diagnosed with a primary brain tumour. The systematic review evidence already described in relation to cancer and non-cancer diagnoses has identified challenges for interpretation on the basis of heterogeneity in settings, methodological diversity and a lack of consistency in trial outcomes. The diversity in the palliative care-specific component of interventions and trial populations makes it difficult to equate the benefits suggested in those studies, with the specific needs of people with a brain tumour.

Previous studies that have looked at the supportive and palliative care needs of people diagnosed with a high-grade glioma have also consistently concluded that the quality of evidence remains limited ([Catt 2008](#); [Collins 2014](#); [Lin 2012](#); [Moore 2013](#)). In particular, there has been a lack of studies conducted on specialist palliative care provision or co-ordination of care, and a need for more evidence on specific palliative care interventions for domains, such as fatigue, mood disorders and carer support ([McConigley 2012](#); [Pace 2017](#)). Defining the nature of effective interventions in this context will help develop a more collaborative, needs-based model of care.

The importance of this topic is recognised at a UK national level. NICE recommends that people with brain tumours receive specialist palliative and supportive care early in the process, at diagnosis if possible, with continued integration throughout the course of the person's illness ([NICE 2018](#)). NICE also commend earlier palliative care referral for improving quality of life and overall survival and its benefit to "managing the distress associated with reduced life expectancy" ([NICE 2018](#); p.41). In doing so, NICE anticipates that not only will communication be improved, but service provision will be more responsive to patients' needs, with more timely transfer of patients to services and treatments as a result. Patients and their families/caregivers will be more satisfied, and people may be able to stay in their preferred place of care through improved continuity of care. The recent James Lind Alliance Neuro-Oncology Priority Setting Partnership Report gives context to the priority of research in this area ([MacDonald 2015](#)).

Therefore, understanding the effectiveness of early referral to specialist palliative care services or other palliative care interventions would help guide improvement to service provision, and the development of an evidence-based model of supportive and palliative care for this patient population.

OBJECTIVES

To assess the evidence base for early palliative care interventions, including referral to specialist palliative care services compared to usual care, for improving outcomes in adults diagnosed with a primary brain tumour and their carers.

METHODS

Criteria for considering studies for this review

Types of studies

Our inclusion criteria included randomised controlled trials (RCTs) and non-randomised intervention studies. It also included qualitative studies and mixed-methods studies, where both qualitative and quantitative data were included. We intended to include trials looking at early referral to specialist palliative care services, or early targeted palliative interventions by other healthcare professionals for improving quality of life, symptom control, carer outcomes, or overall survival as a primary or secondary outcome measure.

Types of participants

Inclusion criteria

- Adults (aged 18 years and older) who have a confirmed radiological or histological diagnosis, or both, of a primary malignant brain tumour
- Informal adult carers of people with a confirmed diagnosis of a primary malignant brain tumour. This is usually at an individual level, but we also included family level.

Exclusion criteria

- Participants who have a diagnosis of a benign brain tumour
- Participants who have metastatic disease from an extracranial primary

Types of interventions

We included studies where there was explicit intent to provide 'early palliative care' or where there is a clear trial definition of 'early' in relation to time since diagnosis or ongoing active anticancer intervention. We included studies reporting specialist and non-specialist palliative care interventions, defined as any intervention by a healthcare professional that addresses palliation in any or all of the following areas.

- Symptom control
- Physical function
- Cognitive function
- Psychological support
- Information giving
- Advance or future care planning

A specialist palliative care service is defined as one delivered by member(s) of a multiprofessional team with higher training in palliative care provision or commissioned to provide palliative care at a specialist level, or both.

We included interventions delivered in community and secondary care settings, and interventions delivered to both participant and carer, or either alone. We only included interventions where the

specific components of an intervention were described, and the timing (commencement) and duration of the intervention were clearly stipulated.

The comparators of interest were usual care, including as part of a waiting list control. Usual care is defined as that normally provided by the neuro-oncology team. It might include provision of generalist or specialist palliative care support, but not intentionally activated for all people at the time of diagnosis or initiation of anticancer treatment.

Types of outcome measures

Primary outcomes

- Quality of life
- Symptom control
- Psychological outcomes
- Overall survival

We planned to report outcomes separately for participants and, where appropriate, carers in a summary of findings table using [GRADEpro GDT](#) software ([GRADEpro GDT](#)). Further details on the outcome measures that we accepted, where reported by included studies, are shown below.

Participants

- Survival from time of enrolment, to include one-year and overall survival
- Quality of life, using validated quality of life tools, e.g. FACT-G ([Cella 1993](#)), FACT- Br ([Weitzner 1995](#)), EORTC QLQ C30 and BCM 20 ([Osoba 1996](#)), McGill Quality of Life Questionnaire ([Cohen 1995](#)), 36-Item Short Form Health Survey (SF-36) ([Ware 1992](#)), 46-item Functional Assessment of Chronic Illness Therapy–Palliative Care (FACIT-Pal) ([Lyons 2009](#)); qualitative analysis of participant experience using validated and clearly described methodologies
- Symptom control, using validated symptom assessment tools, e.g. Edmonton Symptom Assessment Scale (ESAS) ([Bruera 1991](#)), Palliative Outcomes Scale (POS) ([Hearn 1999](#)), Quality of Life at the End of Life (QUAL-E) ([Steinhauser 2004](#)), Symptom Experience Scale (SES) ([Samarel 1996](#)), physical and cognitive function using validated assessment tools.
- Psychological outcomes, including anxiety and depression, using validated assessment tools, e.g. Beck Depression Inventory (BDI) ([Beck 1961](#)), Hamilton Rating Scale for Depression (HAM-D) ([Hamilton 1960](#)), Hospital Anxiety and Depression Scale (HADS) ([Zigmond 1983](#))

Informal carer(s)

- Psychological outcomes, including anxiety and depression, using validated assessment tools (as mentioned above; carer burden, using validated assessment tools, e.g. Caregiver Strain Index (CSI) ([Robinson 1983](#)), Supportive Care Needs Survey for Partners & Caregivers (SCNS-P&C) ([Girgis 2011](#)), the Carer Experience Scale (CES) ([Al-Janabi 2008](#)), Quality of Life During Serious Illness-Family Carers (QOLLI-F) ([Cohen 2006](#)), Zarit Burden Inventory ([Seng 2010](#)), and FAMCARE ([Kristjanson 1993](#)))

Secondary outcomes

- Care co-ordination and information giving by participants and carers
- Receipt of planned anticancer treatment for participants
- Bereavement outcomes for informal carers
- Carer experience
- Resource use and costs

Further details on the outcome measures that we accepted, where reported by included studies, are shown below.

Participants

- Care co-ordination and information giving, based on qualitative assessment of participant feedback, or objective measures of satisfaction, or both
- Receipt of planned anticancer treatment: completion of initial neuro-oncology multidisciplinary team (MDT) treatment
- Resource use to include hospital and hospice utilisation, measured in length of inpatient stay in days, number of outpatient appointments

Informal carer(s)

- Care co-ordination and information giving, based on qualitative assessment of carer feedback, or objective measures of satisfaction, or both
- Qualitative analysis of carer experience, using clearly described and validated methodologies
- Bereavement outcomes, using validated measures
- Resource use and costs; to include opportune costs of loss of income

Important information on participants and carer experience of interventions may be published as part of a controlled trial or separately.

Search methods for identification of studies

Electronic searches

We identified relevant studies by conducting searches of electronic databases, which included:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 11) ([Appendix 1](#));
- MEDLINE via Ovid (1946 to November week 2, 2021) ([Appendix 2](#));

- Embase via Ovid (1980 to November 2021) ([Appendix 3](#));
- Cumulative Index to Nursing and Allied Health Literature (CINAHL from 1982 to 16 November 2021) ([Appendix 4](#));
- Web of Science (1900 to November 2021) ([Appendix 5](#));
- PsychInfo (1806 to November 2021) ([Appendix 6](#)).

We conducted searches to incorporate both qualitative and quantitative search terms. The search strategies were developed by the Information Specialist for Cochrane Gynaecological, Neuro-oncology and Orphan Cancers, and the most recent search was executed by the author team to ensure that the search was as up-to-date as feasible.

We searched for any currently recruiting trials in ClinicalTrials.gov (clinicaltrials.gov), and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch).

Searching other resources

We handsearched the reference lists of potentially eligible systematic review articles to identify any other relevant studies. We contacted experts in the field to suggest any relevant unidentified studies (published or unpublished). In addition, we searched for the included articles and authors using citation tracking via Scopus. We handsearched the most relevant journals and sourced dissertations and theses, searching key authors via Web of Science and searched SIGLE – System for Information on Grey Literature in Europe. Specific search terms used are shown in [Appendix 7](#).

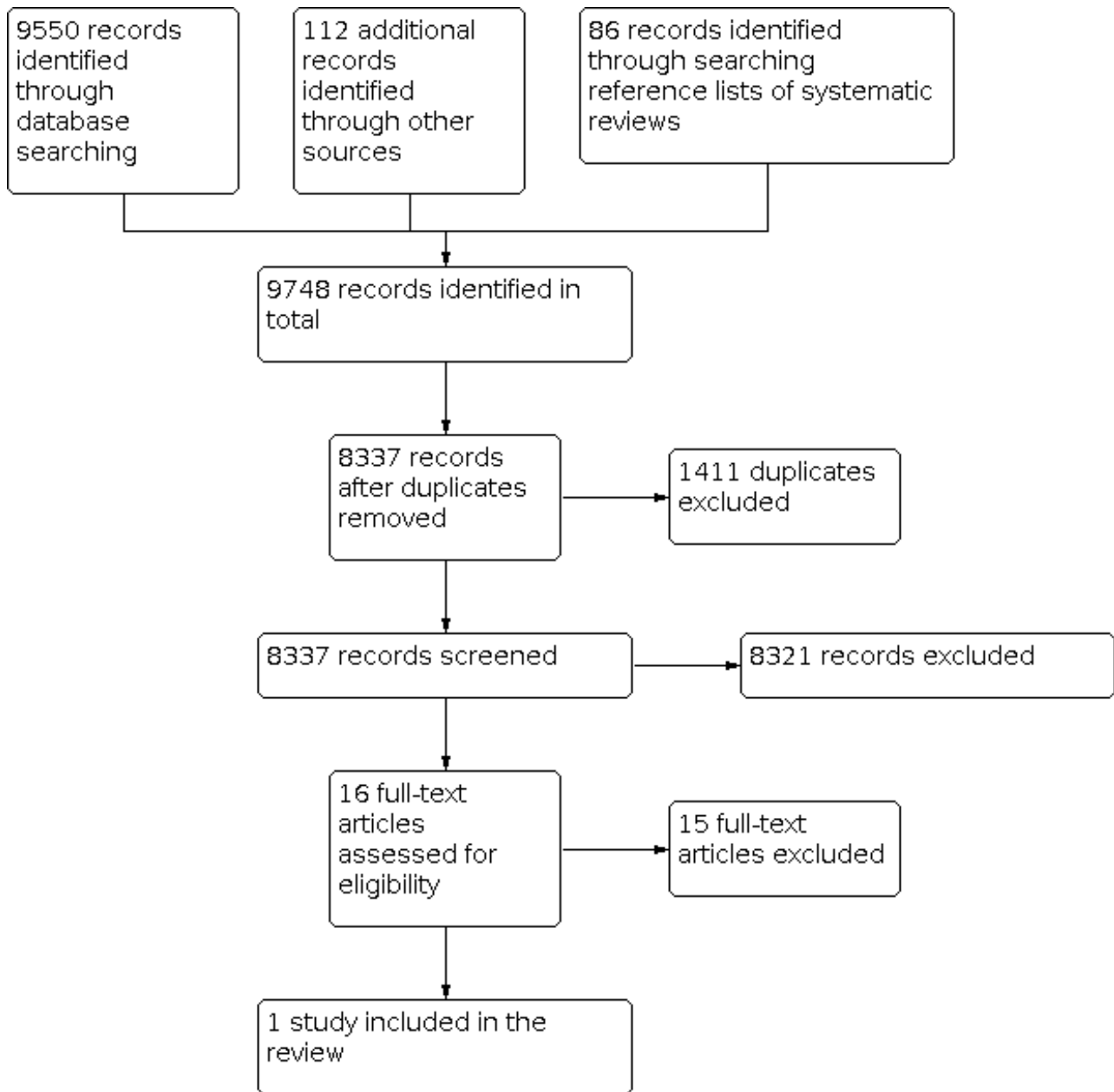
Data collection and analysis

We followed the protocol for this review for the collection and analysis of data ([Byrne 2019](#)).

Selection of studies

We imported the records from all searches into Covidence review software ([Covidence 2021](#)), and removed duplicate references before screening. Two review authors (AB, ATB) independently screened and shortlisted all abstracts and trial titles identified by the search strategy to assess eligibility against the inclusion criteria. We obtained full-text copies of all papers considered as potentially eligible for further assessment. A second review author (AB or ATB) independently checked these identified papers were potentially eligible to include for further review. A third review author (from, ATB, AB, SS) independently checked and resolved any disagreements relating to which references to include or exclude. We illustrate the trial selection process in a PRISMA diagram ([Figure 1](#)).

Figure 1. PRISMA flow diagram of studies identified for the review



Data extraction and management

We developed an electronic data extraction form which was piloted against the checklist provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Three review authors (AB, ATB, SS) independently extracted the following data items, if available.

- Publication details
- Trial design
- Participant number and details, including age and sex and condition
- Description of the intervention(s) and control
- Methods and timing of data collection

- Outcomes, including quality of life, symptom control, psychological outcomes, survival in each case, including assessment tools and units of measurement
- Methods of addressing missing data
- Risk of bias for RCTs (RoB 1 tool)
- Risk of bias for non-RCTs (ROBINS-I tool)

All review authors were given the opportunity to provide feedback on the included items.

Assessment of risk of bias in included studies

Two review authors (ATB, AB) independently assessed the risk of bias using the criteria and guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which a third

review author (from ATB, AB, or SS) independently checked. We reported the following seven domains.

- Sequence generation (checking method of generating allocation sequence)
- Allocation concealment (checking if allocation methods could be foreseen)
- Blinding (participants and personnel, i.e. methods to blind participants' knowledge of which intervention were given)
- Blinding (outcome assessment, i.e. blinding assessors from which intervention given to the participant)
- Incomplete outcome data (checking differences between intervention and control groups)
- Selective outcome reporting (checking how outcomes are reported)
- Other bias (including recruitment bias, stopping early for benefit, carry-over effects in cross-over studies, and non-validated outcome measures)

We gave each domain a judgement of 'low risk', 'high risk', or 'unclear risk' if insufficient details were provided in the trial. This was accompanied with a 'support for judgement' statement summarising how we made risk judgements to ensure transparency of the decisions made. We considered studies to be of high methodological quality ('high-quality' studies) if the risk of bias for all domains was low. We considered studies to be of low methodological quality ('low-quality' studies) if the risk of bias was high or unclear in one or more domains. Any disagreement on the judgement of bias was resolved by discussions between the review authors.

For non-randomised studies we intended to employ the ROBINS-I tool which shares many features of RoB 1, but specifically addresses areas of particular concern for bias in non-randomised studies, including confounding, selection and information (Sterne 2021). However, we did not include any non-randomised trials.

Measures of treatment effect

Where possible, we planned to calculate risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous data, and mean differences (MDs) or standardised mean differences (SMDs) with 95% CIs for continuous data where different scales are used across trials. For time-to-event data for survival, we planned to analyse as death hazard ratios (HRs) under the assumption that the HR is consistent across the follow-up period. Data aggregation was not possible, therefore we presented the results of the individual trial in table format and described the primary findings narratively.

Unit of analysis issues

We anticipated that the appropriate unit of analysis would be by type, timing, and duration of specialist palliative intervention for improving quality of life, carer outcomes, and survival in people diagnosed with a primary brain tumour. We anticipated a limited number of RCTs and non-randomised intervention studies.

Dealing with missing data

The included trial did not describe methods used for dealing with missing data, and we did not impute missing data for any of the outcomes.

Assessment of heterogeneity

We would have followed the statistical analysis method as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021). We expected heterogeneity due to differences in participant populations, types and timing of interventions, and differences in outcome scales used. We planned to assess for the presence of variation in effects observed across studies using a Chi² test. To quantify the degree of heterogeneity we would have employed the I² statistic, which reflects the percentage of variability in effect estimates that is due to heterogeneity rather than to chance (Deeks 2021). We would have considered a 0% to 40% threshold to be a low level of heterogeneity, 30% to 60% to be a moderate level of heterogeneity, and 50% to 90% to be a substantial level of heterogeneity (Deeks 2021). We would also have described, where possible, the potential sources of heterogeneity, rather than simply quantify its existence. Non-randomised studies would have been expected to be more heterogeneous compared to randomised trials, and the most effective method of observing variation being through the visual inspection of the forest plot.

Assessment of reporting biases

We aimed to minimise publication bias by sourcing unpublished data, where possible. If we identified an individual meta-analysis containing at least 10 studies, we planned to assess publication bias using funnel plots and by Egger's test (Egger 1998).

Data synthesis

We summarised included studies using the *Characteristics of included studies* table provided by the Review Manager 5 software (Review Manager 2020). For substantial and unexplained heterogeneity ($P < 0.10$), we would have considered pooling data using the random-effects model. Where studies compare more than one intervention or a combination of interventions, we planned to analyse each comparison separately. If possible, we planned to calculate a weighted treatment effect using Review Manager 5 software. We would have expressed the results as RRs with 95% CIs for dichotomous outcomes and MDs and 95% CIs for continuous outcomes. Qualitative data would have been described alongside the quantitative data, and where appropriate we would have correlated findings, for example in terms of possible domains of impact and explorations of heterogeneity.

Subgroup analysis and investigation of heterogeneity

Where sufficient studies and data existed, we planned to undertake the following subgroup analyses.

- Tumour type
- Age group (18 to 70 years and over 70 years)
- Type of intervention (individual versus group), frequency of intervention (less than once a week, once a week, 2 to 3 times a week), and duration of specialist palliative care intervention
- Time from definitive treatment (surgery, radiotherapy, or chemotherapy) to specialist palliative care intervention
- Type of treatment received; surgery and adjuvant chemotherapy or radiotherapy, or both; surgery alone; chemotherapy alone; radiotherapy alone; combined chemotherapy and radiotherapy with no surgery

We planned to investigate whether the results of subgroups were significantly different by performing the test for subgroup differences available in Review Manager 5 ([Review Manager 2020](#)).

Sensitivity analysis

If we had identified heterogeneity across the included studies, we would have undertaken sensitivity analyses to determine the effect of excluding studies at high risk of bias. In addition, we planned to use sensitivity analyses to explore the effect of the primary outcomes of the trial (early referral to specialist palliative care to improve quality of life, carer outcomes, and overall survival for people diagnosed with a primary brain tumour).

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for the trial outcome in [Summary of findings 1](#) according to the GRADE approach using GRADEpro GDT software ([GRADEpro GDT](#)), which considers issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results, to assess the certainty of the evidence related to each of the key outcome measure ([Langendam 2013](#); [Schünemann 2021](#)).

We used the GRADE checklist and GRADE Working Group certainty of evidence definitions ([Meader 2014](#)). We downgraded the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each trial limitation.

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Description of studies

The trial included in this review is summarised in the [Characteristics of included studies](#) table.

Results of the search

We identified a total of 9748 references from electronic databases and other sources. After duplicates were removed, we screened 8337 references and identified 16 for retrieving the full-text paper (see [Figure 1](#)). Following full-text assessment, we excluded 15 studies following independent review by two review authors, and independent assessment by a third review author if there was uncertainty or disagreement. We contacted two authors of two individual papers to obtain further information on data relating to our inclusion criteria in order to clarify whether they were eligible for inclusion in the review ([Boele 2013](#); [El Jawahri 2010](#)).

Included studies

We identified one randomised control trial (RCT) in this review ([Zucchella 2013](#)).

Participants

Trial participants were adults with a primary brain tumour diagnosed on brain imaging, with subsequent histopathological confirmation, who were treated with maximal feasible tumour resection, and who demonstrated evidence of cognitive impairment following admission to a single neuro rehabilitation centre within two weeks of surgery. Cognitive impairment was defined as test scores below population-based norms on at least three neuropsychological tests at baseline. Of 109 consecutive participants tested, 79 demonstrated evidence of cognitive impairment and, from those meeting the inclusion criteria, 62 were randomised. These participants were randomised using a computerised random number generator into the intervention group (N = 30) or the control group (N = 32). There were five and four dropouts in the intervention and control groups, respectively, during the trial and 25 and 28 in the intervention and control groups, respectively, were included in the final analysis. Demographics were reported from the final total of participants. Within the intervention group, the mean age was 58 years with 14 males and 11 females. Within the control group, the mean age was 52 years with 13 males and 15 females.

Setting

Participants were recruited post-neurosurgery and referred to a neuro rehabilitation centre in Italy between November 2009 and October 2011.

Intervention and comparator

The intervention consisted of a battery of neuropsychological tests which the participants performed within 16 individual one-hour sessions, four sessions per week for four weeks. The battery of tests was administered from a computerised programme. Each exercise lasted 45 minutes, varied between levels of difficulty and aimed to address a variety of cognitive functions, including time orientation, spatial orientation, visual attention, logical reasoning, memory, and executive function. These areas of cognitive functioning have previously been demonstrated to display deficits in people with brain tumours ([Taphoon 2004](#) as cited by [Zucchella 2013](#)). The intervention sessions also included a 15-minute discussion after the cognitive exercises around the difficulties participants faced during task performance and providing strategies of how to deal with similar situations in everyday life.

The control group consisted of usual care of physiotherapy and medication without the addition of cognitive training.

'Early' aspect

The intervention was provided within two weeks of surgery, which the authors specify as being 'early rehabilitation treatment'.

Excluded studies

We listed the studies from the final stage of assessment and reasons for their exclusion (see [Characteristics of excluded studies](#)). We excluded studies for not explicitly stating an 'early' definition for the intervention, or at least identifying when in disease trajectory the intervention was given, so therefore could not meet the 'early'

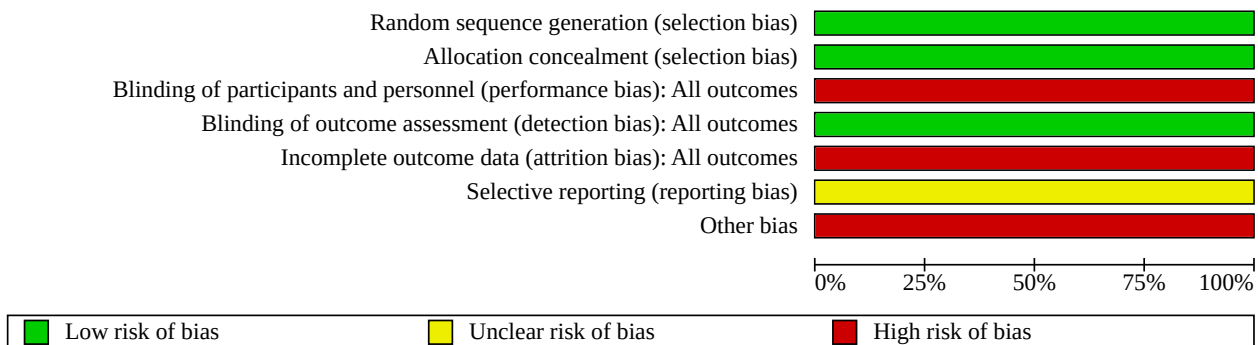
intervention criteria (Boele 2013; El Jawahri 2010; Gehring 2009; Keir 2011; Ownsworth 2015; Reblin 2018), the type of trial design not meeting the 'type of intervention' inclusion criteria (Keir 2011; Ozier 2016; Tabibian 2019), or unable to separate intracranial from other central nervous system (CNS) tumour in the results and inadequate information to describe the intervention (Baski 2017). In three studies, brain tumour patients could not be identified in the participant population (Cherrier 2013; Goedendrop 2014; Lowe 2009), and in three studies, brain tumour patients were identified as

participants in a wider cancer cohort, but their results could not be identified separately within the main results (Clark 2013; Oh 2012; Rummans 2006).

Risk of bias in included studies

Summary of all bias assessment is presented in the risk of bias graph (Figure 2), with justifications for each decision presented in the risk of bias table (see below Characteristics of included studies).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We judged the risk as low as the authors state that participant allocation methods were randomised using a computerised random number generator. These numbers were put into envelopes and randomly assigned to the participants: it was randomly determined whether the even or odd number would enter the experimental group.

Blinding

We judged the risk of performance bias as high as participants were not blinded. However, we judged outcome assessment (detection bias) to be low as it was reported that the pre- and post-treatment assessments were completed by a psychologist blind to participant randomisation and not involved in the direct care of the participants.

Incomplete outcome data

We judged this as a high risk due to the lack of reporting of missing data or how it would be handled, and the decision to exclude participants from the analysis who did not complete the intervention: no intention-to-treat (ITT) analysis was reported.

Selective reporting

Data were provided for each of the cognitive battery tests described, but it was unclear whether any other outcomes were measured and unreported.

Other potential sources of bias

The authors did not provide a statistical analysis plan. They did not describe a priori what the primary outcome was or effect size of interest was, nor did they detail a priori what the secondary outcomes were; therefore we judged this a high risk of bias.

Effects of interventions

See: [Summary of findings 1 Summary of Findings](#)

See [Summary of findings 1](#).

Cognitive training versus usual rehabilitative care

Cognitive function

Within-group analysis of 62 randomised participants compared cognitive performance at baseline (T0) and post-treatment of four weeks (T1) and showed that in the intervention group there was improvement in performance for all neuropsychological measures at the end of the treatment period compared to baseline. In the control group, there were also trends towards improvement across domains from T0 to T1.

Between-group analysis compared cognitive performance between the intervention group and the control group. No difference was observed between the intervention and control groups in any of the tests of logical-executive function. Only in the domains of verbal memory and visual attention were improvements seen in performance in the intervention group compared to controls. A difference in test scores (total correct recall) was observed between participants in the intervention group compared to controls for the Rey Auditory Verbal Learning Test (RAVLT) - delayed recall (mean score 6.1 with SD of 3.1 for the intervention group, mean score 3.6 with SD of 2.5 for the control group; P = 0.004). Improvement in recall was observed in the intervention group compared to controls for the logical memory test for both immediate recall (mean score 5.3 with SD of 1.6 for the intervention group, mean score 3.6 with SD of 1.3 for the control group; P < 0.001), and for delayed recall (mean score of 5.0 with SD of 2.0 for the intervention group, mean score 2.8 with SD of 1.7 for the control group ; P < 0.001). A difference in performance was observed in the intervention group compared to

controls for the Attentive Matrices Test (mean score 36.0 with SD of 12.9 for the intervention group, mean score 25.3 with SD of 9.4 for the control group; $P = 0.005$).

The intervention group also differed compared to controls in time taken to complete the Trail Making Test, both part A (mean time 87.1 seconds with SD of 48.9 in the intervention group, mean time 112.2 seconds with SD of 38.8 for the control group; $P = 0.015$) and part B (mean time 216.2 seconds with SD of 102 in the intervention group, mean time 296.1 seconds with SD of 87.7 for the control group; $P = 0.009$).

The certainty of the evidence, as assessed by GRADE, was considered to be very low.

DISCUSSION

Summary of main results

We were unable to identify any studies of early, systematic specialist palliative care team interventions for people with brain tumours or other generalist provider-led approaches to palliative care provision. We were only able to include one trial of an early intervention with potential impact on a domain of interest: a RCT comprising a cognitive rehabilitation intervention compared to usual rehabilitation care of medications and physiotherapy post-surgery for inpatients with a primary brain tumour (Zucchella 2013). The trial did not report on any of the other palliative outcomes of interest for this review. We excluded 15 studies at full-text stage (see [Characteristics of excluded studies](#) table for reasons).

In the Zucchella 2013 trial, participants in the intervention group were admitted for neurorehabilitation within two weeks of surgery for their brain tumour, and were subsequently randomised to a cognitive rehabilitation intervention or control, meeting the criteria for an early intervention aimed at palliating cognitive decline. The intervention itself was well-described and comprised of therapist-guided computerised exercises, to address cognitive domains of time orientation, spatial orientation, visual attention, logical reasoning, memory, and executive function. Sixteen individual one-hour sessions, four sessions/week, for four weeks were conducted by two experienced neuropsychologists.

Participants in both the intervention and control groups were found to have an improvement in all cognitive domains targeted and assessed in the trial, compared to baseline. Between-group analysis showed no difference in outcomes apart from the cognitive domains of visual attention and verbal memory, where there was very low-certainty evidence of improvement in the intervention group.

Overall completeness and applicability of evidence

There were several limitations to the included trial. Methodological limitations included a lack of definition for primary and secondary outcomes, no reporting of sample size estimation and exclusion of randomised participants from the analysis. Participants who did not complete the intervention and control periods were excluded and there was no discussion of the extent or management of missing data. There was also a lack of follow-up at the end of the trial to determine whether the improvements were maintained over time, and a lack of assessment of overall quality of life, and of other behavioural and mood domains, including anxiety and depression. There was no health economic analysis.

Only completed data were included in the analysis, however the extent of missing data were unclear. Furthermore, the trial population included a mix of glioma and meningioma diagnoses, with approximately half described as having high-grade glioma; the number of patients with higher-grade, more aggressive brain tumours was not specified, which may impact on the relevance to this review. Also, many of the primary outcomes of interest for our review were not included in the Zucchella 2013 trial.

Quality of the evidence

Overall, we assessed the certainty (quality) of the evidence using GRADE as very low; the trial cannot provide a reliable indication of any likely effect across the outcomes measured. We identified high risk for attrition bias due to the lack of reporting of missing data or how it would be handled, and the decision to exclude participants from the analysis who did not complete the intervention; no ITT analysis was reported. We judged the risk of performance bias as high, as participants were not blinded. However, we judged the risk of detection bias (outcome assessment) to be low, as pre- and post-treatment assessments were completed by a psychologist blind to participant randomisation. Data were provided for each of the cognitive battery tests described, but units of measurements were unclear; it was also unclear as to whether any other outcomes were measured and unreported. Additionally, the authors did not provide a statistical analysis plan and did not describe a priori what the primary outcome was or effect size of interest was, nor did they detail a priori what the secondary outcomes were.

Potential biases in the review process

We took recognised steps to minimise bias in the review process. Two review authors independently screened all abstracts and the resulting full-text papers. We also ensured two review authors independently completed the data extraction forms. For both screening and data extraction, a third review author independently screened, and extracted any conflicting views and all three review authors discussed and agreed on the final decisions. We also ensured that we updated the search to ensure the final set of included studies was as up-to-date as feasible; the date of the last search completed was 16 November 2021. We also attempted to obtain additional data from authors of studies during screening, which we eventually excluded. We aimed to minimise publication bias by sourcing unpublished data where possible, although bias relating to the size of the trial and the positive outcomes may also be indicative of publication bias.

Agreements and disagreements with other studies or reviews

There is systematic review evidence of the effectiveness of early specialist palliative care intervention in a range of chronic conditions and cancer (Haun 2017; Quinn 2020). However, none of the included trials have been specific to brain tumour patients or included significant numbers of brain tumour participants. Additionally, methodological quality has been variable and heterogeneity in trial populations, settings, and outcomes has made cross-trial comparison challenging. In particular, the diversity of intervention content and the description of palliative care-specific components are problematic in allowing a reliable interpretation of relevance to brain tumour populations who have symptom burdens, cognitive changes and health and social needs which often differ from other cancer groups.

In response to these challenges, [Golla 2020](#) has published a protocol for a phase III, multicentre RCT of early palliative care intervention for patients with glioblastoma multiforme. The population is well-defined and the protocol describes a systematic, manualised early palliative care service intervention – within four weeks of diagnosis – and includes a clear description of the usual care group intervention. The primary outcome is a quality of life outcome, measured using a widely used and well-validated tool: the FACT-Br. The trial is due to complete recruitment in 2023. A randomised, controlled parallel group single-centre trial on the effect of early palliative care on the management of brain tumour patients has also been registered (May 2021) on the WHO International Clinical Trials Registry Platform (ICTRP) ([CTRI/2021/05/033855](#)). The primary outcome will be a quality of life measure. Recruitment had not commenced as of September 2021.

There is also emerging evidence of effectiveness for some domain-specific palliative and supportive interventions for brain tumour patients, but outside of the ‘early intervention’ context. [Boele 2013](#) and [Gehring 2009](#) for example, are excluded from the review based on the definition of ‘early palliative interventions’, but their results are noteworthy. Like the [Zucchella 2013](#) trial, [Gehring 2009](#) reported on a multifaceted cognitive rehabilitation programme evaluating the impact on both cognitive abilities and quality of life. However, in contrast patients were recruited at a later phase of illness: at least six months following diagnosis. Like the [Zucchella 2013](#) trial, the intervention was individually delivered and neuropsychologist supervised, and the authors reported a positive impact of the intervention on short-term cognitive impairments and continuing improvements in cognitive functioning and mental fatigue in the longer-term (6 months follow-up).

[Boele 2013](#) focused specifically on supporting the caregivers of high-grade glioma patients. The trial was open to patient-caregiver dyads but was not designed as an early intervention trial. The intervention comprised a caregiver attending six one-hour sessions, every other week with a psychologist to provide education around symptoms of the disease and day-to-day problems, along with the option of cognitive behavioural therapy to help the caregivers support the patient. They reported improvements in carer health-related quality of life, sustained over time (8-month period reported).

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence to date on the impact of early specialist palliative care service interventions to support people with primary

brain tumours. Similarly, there is a lack of evidence of benefit for early palliative interventions targeted at specific symptoms, such as fatigue, pain control, cognition and mood disorders, which might contribute to a wider systems approach to palliation. However the nature of brain tumour patients’ and their carers’ unmet needs mandates for future research specific to brain tumours that explores early integrated approaches to palliative care and oncology provision, and which can inform international guidance on such a dualistic approach ([Ferrell 2017](#); [Jordan 2017](#)).

Implications for research

Further research - specific to the brain tumour population - is needed to confirm the benefit seen in other cancers of early integration of palliative service interventions and oncology. Studies are also required to assess early palliative interventions for specific domains, such as fatigue, mood disorder, carer needs, and shared decision making, as defined by [Pace 2017](#) and others.

In designing future studies, researchers must address the methodological shortcomings previously described, with particular attention to clear description of settings and patient populations. Clear definition of intervention content will be crucial, with a need to better define the component parts of palliative care models to understand the core domains of benefit ([Firth 2019](#); [Luckett 2014](#)). Golla’s phase III RCT has been designed to address many of these issues ([Golla 2020](#)). The development of core outcome sets, including patient-reported outcomes, for brain tumour research will also help minimise the heterogeneity of outcome reporting, which has hampered comparison between brain tumour trials in the past.

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CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Zucchella 2013
Study characteristics

Methods	RCT
Participants	<p>62 participants were randomised to the intervention (N = 30) and control group (N = 32). 53 participants completed the trial and were included in the final analysis: 25 in the intervention group (mean age 58.7 ± 13.9; 44% female) and 28 controls (mean age 52.7 ± 17; 53% female).</p> <p>Inclusion criteria: 18 years of age, a diagnosis of a primary brain tumour, defined as the presence of a primary lesion using CT or MRI, and confirmed by histopathological examination.</p> <p>Exclusion criteria: experience of neglect, aphasia, concomitant neurological or psychiatric disorders, severe disturbances in consciousness preventing examination, motor impairment.</p> <p>Setting: neurorehabilitation unit of the IRCCS Neurological Mediterranean Institute NEUROMED, Italy between November 2009 and October 2011.</p>
Interventions	<p>Intervention group: cognitive rehabilitation programme. Computerised exercises of 45 minutes addressing cognitive domains:</p> <ul style="list-style-type: none"> • time orientation • spatial orientation • visual attention • logical reasoning • memory and executive function <p>The final 15 minutes consisted of discussions with the psychologist relating to concerns or difficulties with the cognitive exercises. Participants conducted 16 individual one-hour sessions, four sessions/week for four weeks.</p> <p>Control group: participants received usual rehabilitation care of medications and physiotherapy; no cognitive training given.</p> <p>Follow-up: baseline, 4 weeks</p>
Outcomes	<p>Cognitive domains measured were:</p> <ul style="list-style-type: none"> • time orientation • spatial orientation • visual attention • logical reasoning • memory and executive functioning

Zucchella 2013 (Continued)

A validated neuropsychological test battery measured these different areas of cognitive function:

- Mini Mental State Exam (global cognitive functioning)
- Digit Span and Corsi's Test (verbal and spatial immediate memory span)
- Rey Auditory Verbal Learning Test: verbal memory, immediate and delayed recall)
- Logical memory (verbal memory, immediate and delayed recall)
- Raven's Coloured Progressive Matrices 47 (non-verbal reasoning)
- Frontal Assessment Battery (frontal functionality)
- Trail Making Test A and B (simple speed processing and complex attention)
- Attentive Matrices (visual selective attention)
- Phonological fluency (verbal fluency)
- Semantic fluency (verbal fluency)
- Rey-Osterrieth complex figure copy (Visuo-constructional abilities)

Notes	109 participants initially enrolled; 47 excluded after initial cognitive screening. From the 62 randomised participants, 5 from the intervention group and 4 from control dropped out due to worsening of clinical conditions.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As stated in the trial design (quote): 'The randomisation schedule was computer generated using a basic random number generator.'
Allocation concealment (selection bias)	Low risk	Participant allocation used random numbers in envelopes assigned to participants. Experimental group allocation determined by randomly assigning odd or even numbers.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants unblinded despite trial personnel blinded to allocation, which may lead to possible bias in participant performance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments performed by a single-blinded psychologist.
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing data unclear and whether an ITT analysis performed was also unclear. Incomplete data reporting may result in incorrect interpretation of significant results.
Selective reporting (reporting bias)	Unclear risk	Unclear if other outcomes sought and not reported.
Other bias	High risk	No statistical analysis plan included; no a priori difference in outcomes or trial powering described

CT: computed tomography
 MRI: magnetic resonance imaging
 RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baski 2017	Quasi-experimental research design but insufficient detail to be able to describe the content and administration of the intervention. A mixture of CNS tumour types, including extracranial CNS tumours and unable to distinguish between patient types in results.
Boele 2013	Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Cherrier 2013	Brain tumour patients could not be identified in the participant population.
Clark 2013	Brain tumour patients were identified as participants in a wider cancer cohort, but their results could not be identified separately within the main results.
El Jawahri 2010	Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Gehring 2009	Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Goedendrop 2014	Brain tumour patients could not be identified in the participant population.
Keir 2011	A single-arm pilot trial, therefore the type of trial design did not meet the 'type of intervention' inclusion criteria. Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Lowe 2009	Brain tumour patients could not be identified in the participant population.
Oh 2012	Brain tumour patients were identified as participants in a wider cancer cohort, but their results could not be identified separately within the main results.
Ownsworth 2015	Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Ozier 2016	A non-randomised single-arm pilot trial, therefore the type of trial design did not meet the 'type of intervention' inclusion criteria.
Reblin 2018	Not explicitly stating an 'early' definition for the intervention, or at least identifying when in the disease trajectory the intervention was given, so therefore could not meet the 'early' intervention criteria.
Rummans 2006	Brain tumour patients were identified as participants in a wider cancer cohort, but their results could not be identified separately within the main results.
Tabibian 2019	A retrospective cohort trial design, therefore the type of trial design did not meet the 'type of intervention' inclusion criteria.

CNS: central nervous system

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2021/05/033855

Study name	Effect of early palliative care on management of brain tumour patients
Methods	Randomized, Parallel Group Trial
Participants	Patients with primary brain tumours (N = 110)
Interventions	Patients will be randomly assigned to either the intervention group (proactive specialist palliative care in the form of symptomatic management at 1 month, 3 month and 6 months of initial visit) or the control group (palliative care provided when the treating physician considers it necessary).
Outcomes	Primary outcome is QoL assessed at 1 month, 3 and 6 months of follow up
Starting date	28/05/2021
Contact information	Dr Vinod Kumar: drvinodkr912@gmail.com
Notes	

Golla 2020

Study name	Effect of early palliative care for patients with glioblastoma (EPCOG)
Methods	Randomised phase III clinical trial protocol
Participants	Patients with glioblastoma multiforme (GBM) (N = 214)
Interventions	GBM patients and their caregivers will be randomly assigned to either the intervention group (receiving proactive EIPC on a monthly basis) or the control group (receiving treatment according to international standards and additional, regular assessment of QoL ('optimised' standard care)).
Outcomes	The primary outcome is QoL assessed by subscales of the Functional Assessment of Cancer Therapy for brain tumour (FACT-Br)
Starting date	10/05/2019
Contact information	Dr Heidrun Golla: heidrun.golla@uk-koeln.de
Notes	

DATA AND ANALYSES
Comparison 1. Cognitive training versus usual rehabilitative care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cognitive function	1		Other data	No numeric data

Analysis 1.1. Comparison 1: Cognitive training versus usual rehabilitative care, Outcome 1: Cognitive function

Cognitive function

Study	Cognitive test	Intervention group (mean, SD)	Control group (mean, SD)
Zucchella 2013	RAVLT—delayed recall (score)	6.1 ± 3.1	3.6 ± 2.5
	Logical memory—immediate recall (score)	5.3 ± 1.6	3.6 ± 1.3
	Logical memory—delayed recall (score)	5 ± 2	2.8 ± 1.7
	Trail Making Test Part A (seconds)	87.1 ± 48.9	112.2 ± 38.8
	TMTB Trail Making Test Part B (seconds)	216.2 ± 102	296.1 ± 87.7
	Attentive matrices (score)	36 ± 12.9	25.3 ± 9.4

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Palliative Care] explode all trees
- #2 MeSH descriptor: [Terminal Care] explode all trees
- #3 MeSH descriptor: [Terminally Ill] explode all trees
- #4 MeSH descriptor: [Hospices] explode all trees
- #5 MeSH descriptor: [Hospice Care] explode all trees
- #6 MeSH descriptor: [Hospice and Palliative Care Nursing] explode all trees
- #7 "last year of life" or LYOL or "life's end"
- #8 (macmillan or marie curie or district) near nurs*
- #9 hospice* or (nursing near/3 home*)
- #10 MeSH descriptor: [Palliative Medicine] explode all trees
- #11 MeSH descriptor: [Advance Care Planning] explode all trees
- #12 advance* near/5 care plan*
- #13 future near/5 care plan*
- #14 MeSH descriptor: [Caregivers] explode all trees
- #15 (early or specialist or general or primary) near/5 palliat*
- #16 support* near/3 care
- #17 palliat*
- #18 "advanced disease**"
- #19 "end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"
- #20 end near/6 life
- #21 terminal* near/6 (disease* or ill* or care*)
- #22 "terminal-stage*" or dying
- #23 close near/6 death
- #24 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
- #25 (home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) near/2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)
- #26 self near/3 (help* or care)
- #27 (psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) adj3 (car* or service* or plan* or interven* or support* or assist* or prog*)
- #28 symptom* near/3 (care or manag* or support* or modif* or control* or assess*)
- #29 #25 or #26 or #27 or #28
- #30 MeSH descriptor: [Brain Neoplasms] explode all trees
- #31 MeSH descriptor: [Glioma] explode all trees
- #32 brain near/3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)
- #33 glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r**"
- #34 #30 or #31 or #32 or #33
- #35 early or advance* or forward or simultaneous
- #36 #24 or #29
- #37 #35 and #36
- #3. #34 and #37

Appendix 2. MEDLINE search strategy

1. exp Palliative Care/
2. exp Terminal Care/
3. exp Terminally Ill/
4. exp Hospices/
5. exp Hospice Care/
6. exp "Hospice and Palliative Care Nursing"/
7. ("last year of life" or LYOL or "life's end").ti,ab.
8. ((macmillan or marie curie or district) adj nurs*).mp.
9. (hospice* or (nursing adj3 home*)).mp.
10. exp Palliative Medicine/
11. exp Advance Care Planning/
12. (advance* adj5 care plan*).ti,ab.
13. (future adj5 care plan*).ti,ab.
14. exp Caregivers/
15. ((early or specialist or general or primary) adj5 palliat*).ti,ab.
16. (support* adj3 care).ti,ab.
17. palliat*.tw.
18. "advanced disease*".tw.
19. ("end-stage disease*" or "end stage disease*" or end-stage illness" or "end stage").tw.
20. (end adj6 life).tw.
21. (terminal* adj6 (disease* or ill* or care*)).ti,ab.
22. ("terminal-stage*" or dying).ti,ab.
23. (close adj6 death).tw.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. ((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) adj2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)).ti,ab.
26. (self adj3 (help* or care)).ti,ab.
27. ((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) adj3 (car* or service* or plan* or interven* or support* or assist* or prog*)).ti,ab.
28. (symptom* adj3 (care or manag* or support* or modif* or control* or assess*)).ti,ab.
29. 25 or 26 or 27 or 28
30. exp Brain Neoplasms/
31. exp Glioma/
32. (brain adj3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).ti,ab.
33. (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r*").ti,ab.
34. 30 or 31 or 32 or 33
35. (early or advance* or forward or simultaneous).ti,ab.
36. 24 or 29
37. 35 and 36
38. 34 and 37

Appendix 3. Embase search strategy

1. exp palliative therapy/
2. exp terminal care/
3. exp terminally ill patient/
4. exp hospice/
5. exp hospice care/
6. exp "Hospice and Palliative Care Nursing"/
7. ("last year of life" or LYOL or "life's end").ti,ab.
8. ((macmillan or marie curie or district) adj nurs*).mp.
9. (hospice* or (nursing adj3 home*)).mp.
10. exp palliative nursing/
11. exp cancer palliative therapy/
12. exp advance care planning/
13. (advance* adj5 care plan*).ti,ab.
14. (future adj5 care plan*).ti,ab.
15. exp caregiver/
16. ((early or specialist or general or primary) adj5 palliat*).ti,ab.

17. (support* adj3 care).ti,ab.
18. palliat*.tw.
19. "advanced disease*".tw.
20. ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.
21. (end adj6 life).tw.
22. (terminal* adj6 (disease* or ill* or care*)).ti,ab.
23. ("terminal-stage*" or dying).ti,ab.
24. (close adj6 death).tw.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. ((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) adj2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)).ti,ab.
27. (self adj3 (help* or care)).ti,ab.
28. ((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) adj3 (car* or service* or plan* or interven* or support* or assist* or prog*)).ti,ab.
29. (symptom* adj3 (care or manag* or support* or modif* or control* or assess*)).ti,ab.
30. 26 or 27 or 28 or 29
31. exp brain tumor/
32. exp glioma/
33. (brain adj3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).ti,ab.
34. (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r*").ti,ab.
35. 31 or 32 or 33 or 34
36. (early or advance* or forward or simultaneous).ti,ab.
37. 25 or 30
38. 36 and 37
39. 35 and 38

Appendix 4. CINAHL search strategy

- 1 (MH "Palliative Care")
- 2 (MH "Terminal Care+")
- 3 (MH "Terminally Ill Patients+")
- 4 (MH "Hospices")
- 5 (MH "Hospice Care")
- 6 (MH "Hospice and Palliative Nursing")
- 7 TX ("last year of life" OR LYOL OR "life's end")
- 8 TX((macmillan or "marie curie" or district) N nurs*)
- 9 TX (hospice* or (nursing N3 home*))
- 10 TX "Palliative Medicine"
- 11 TX "Advance Care Planning"
- 12 TX (advance* N5 care plan*)
- 13 TX (future N5 care plan*)
- 14 TX "Caregivers"
- 15 TX (((early or specialist or general or primary) N5 palliat*)
- 16 TX (support* N3 care)
- 17 TX palliat*
- 18 TX "advanced disease*"
- 19 TX ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage")
- 20 TX (end N6 life)
- 21 TX (terminal* N6 (disease* or ill* or care*))
- 22 TX ("terminal-stage*" or dying)
- 23 TX (close N6 death)
- 24 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
- 25 TX ((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) N2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*))
- 26 TX (self N3 (help* or care))
- 27 TX ((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) N3 (car* or service* or plan* or interven* or support* or assist* or prog*))
- 28 TX (symptom* N3 (care or manag* or support* or modif* or control* or assess*))

29 S25 or S26 or S27 or S28
 30 (MH "Brain Neoplasms+")
 31 (MH "Glioma")
 32 TX (brain N3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*))
 33 TX (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumor*")
 34 S30 or S31 or S32 or S33
 35 TX (early or advance* or forward or simultaneous)
 36 S24 or S29
 37 S35 and S36
 38 S34 and S37

Appendix 5. Web of Science search strategy

TOPIC: ("Palliative Care")
 TOPIC: ("Terminal Care")
 TOPIC: ("Terminally Ill")
 TOPIC: ("Hospices")
 TOPIC: ("Hospice Care")
 TOPIC: ("Hospice and Palliative Care Nursing")
 TOPIC: (("last year of life" OR LYOL OR "life's end"))
 TOPIC: (((macmillan or marie curie or district) and nurs*))
 TOPIC: ((hospice* or (nursing NEAR/3 home*)))
 TOPIC: ("Palliative Medicine")
 TOPIC: ("Advance Care Planning")
 TOPIC: ((advance* near/5 care plan*))
 TOPIC: ((future near/5 care plan*))
 TOPIC: ("Caregivers")
 TOPIC: (((early or specialist or general or primary) NEAR/5 palliat*))
 TOPIC: ((support* NEAR/3 care))
 TOPIC: (palliat*)
 TOPIC: ("advanced disease*")
 TOPIC: (("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"))
 TOPIC: (end NEAR/6 life)
 TOPIC: ((terminal* Near/6 (disease* or ill* or care*)))
 TOPIC: ("terminal-stage*" or dying)
 TOPIC: (close Near/6 death)
 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
 TS=(((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) N2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)))
 TOPIC: ((self NEAR/3 (help* or care)))
 TOPIC: (((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) NEAR/3 (car* or service* or plan* or interven* or support* or assist* or prog*)))
 TOPIC: ((symptom* NEAR/3 (care or manag* or support* or modif* or control* or assess*)))
 #25 or #26 or #27 or #28
 TOPIC: ("Brain Neoplasms")
 TOPIC: ("Glioma")
 TOPIC: ((brain near/3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)))
 TOPIC: ((glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r*"))
 #30 or #31 or #32 or #33
 TOPIC: ((early or advance* or forward or simultaneous))
 #24 or #29
 #35 and #36
 #34 and #37

Appendix 6. PsychInfo search strategy

1. exp Palliative Care/
2. Terminal Care.mp
3. exp Terminally Ill patient/
4. exp Hospice/

5. Hospice Care.mp.
6. ((hospice or palliative) adj3 nursing).tw.
7. ("last year of life" or LYOL or "life's end").ti,ab.
8. ((macmillan or marie curie or district) adj nurs*).mp.
9. (hospice* or (nursing adj3 home*)).mp.
- 10 Palliative Medicine.mp
11. exp Advance Directives/
12. (advance* adj5 care plan*).ti,ab
13. (future adj5 care plan*).ti,ab.
14. exp Caregivers/
15. ((early or specialist or general or primary) adj5 palliat*).ti,ab.
16. (support* adj3 care).ti,ab.
17. palliat*.tw.
18. "advanced disease*".tw.
19. ("end-stage disease*" or "end stage disease*" or end-stage illness" or "end stage").tw.
20. (end adj6 life).tw.
21. (terminal* adj6 (disease* or ill* or care*)).ti,ab.
22. ("terminal-stage*" or dying).ti,ab.
23. (close adj6 death).tw.
24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. ((home* or in-home* or domicile or outreach or residential or housing or posthospital or post-hospital or communit* or moblie or ambulatory or door to door) adj2 (team* or centre* or center* or treat* or care or interven* or therap* or manag* or model* or program* or service* or nurs* or support or plan or assist*)).ti,ab.
26. (self adj3 (help* or care)).ti,ab.
27. ((psycholog* or pharmacolog* or psychiat* or social* or emotion* or spiritual* or relig* or faith or bereavement or grief or complement* or alternative) adj3 (car* or service* or plan* or interven* or support* or assist* or prog*)).ti,ab.
28. (symptom* adj3 (care or manag* or support* or modif* or control* or assess*)).ti,ab.
29. 25 or 26 or 27 or 28
30. exp Brain Neoplasms/
31. exp Glioma/
32. (brain adj3 (tumor* or tumour* or neoplas* or malignan* or cancer* or carcinoma*)).ti,ab.
33. (glioma* or astrocytoma* or meningioma* or oligodendroglioma* or oligoastrocytoma* or glioblastoma* or GBM* or Glioblastoma multiforme or "Primary brain tumo?r").ti,ab.
34. 30 or 31 or 32 or 33
35. (early or advance* or forward or simultaneous).ti,ab.
36. 24 or 29
37. 35 and 36
38. 34 and 37

Appendix 7. Search terms for clinical trials, grey literature and journals

ClinicalTrials.gov (completed trials only): 'Brain Tumour & Palliatve'

WHO ICTRP (completed trials only with results): 'Brain Tumour & Palliatve'

SIGLE: 'Brain tumour and care'

EthOs: 'Brain tumour and palliative care'

Open Access Theses & Dissertations: (brain AND tumour) AND (palliative OR care) AND language:(en OR eng OR english)

Journals: 'brain tumo?r and palliative care'

'brain tumour and palliative care'

'brain tumour'

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AB drafted the final review

ATB drafted the final review

SS drafted the final review

FM contributed to drafting the final review
HB contributed to drafting the final review
MB contributed to drafting the final review
AN contributed to drafting the final review
HF contributed to drafting the final review
All authors agreed on the final version of the review for publication.

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Anthony Byrne has no known conflicts of interest.
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- None, Other

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We edited the background information sections to include updated literature and references. We were unable to conduct much of the analysis, as described in the protocol (i.e. analysis of heterogeneity, measures of treatment effect, subgroup analysis and sensitivity analysis) and instead we provided a narrative summary. This difference was due to identifying only a single trial eligible for inclusion within the review. We did not use the ROBINS-I tool for non-randomised study bias, as planned within the protocol, since we did not identify any non-randomised studies for inclusion in this review.