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Review

The level of reporting of neurocognitive outcomes in randomised controlled trials of brain tumour patients: A systematic review

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Abstract ***Background:*** Neurocognitive impairment is frequently present in brain tumour patients and is therefore considered an important outcome in brain tumour research. To use neurocognitive outcomes (NCO) in clinical decision-making, neurocognitive evidence should be of sufficiently high quality. We aimed to investigate the level of neurocognitive functioning reporting in randomised controlled trials (RCTs) in brain tumour patients.
Methods: We conducted a systematic literature search in several databases up to August 2017. Of the selected relevant RCTs, the following data were retrieved: basic trial demographics and NCO characteristics, quality of NCO reporting and risk of bias. We also analysed studies that should impact clinical decision-making based on their quality of reporting.
Results: We identified 65 RCTs, of which NCO was the primary end-point in 14 (22%). Important methodological limitations were related to the documentation of statistical approaches for dealing with missing data and to discussing limitations and generalisability issues uniquely related to the NCO components. Risk of bias was high regarding blinding of personnel and incomplete outcome data. Twenty RCTs (31%), eight with NCO as primary end-point and 12 as secondary end-point, satisfied a sufficient number of criteria to be classified as 'high-quality' NCO evidence. Most of these studies did contribute to clinical decision-making.

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Conclusion: Investigators involved in brain tumour research should give attention to methodological challenges related to NCO reporting as identified in this review, as 'high-quality' reporting of NCO evidence can be of value in clinical decision-making.

1. Introduction

Brain tumours can be classified as either primary, such as gliomas and meningiomas which originate in the brain, or secondary, in which systemic tumours metastasize to the brain. The incidence of primary brain tumours ranges from 5.6 for women to 7.8 for men per 100,000 [1]. With an incidence of cancer ranging between 306.3 and 429.9 per 100,000 persons and 9–45% of cancer patients developing brain metastases, secondary brain tumours far outnumber primary brain tumours [1,2]. Brain tumour patients often suffer from both generic symptoms as fatigue, and brain-specific symptoms as epilepsy, and neurological and neurocognitive impairments [3].

As neurocognitive functioning (NCF) is essential for human functioning, neurocognitive dysfunction has a profound impact on daily functioning and health-related quality of life (HRQoL) of brain tumour patients and their proxies [4]. This suggests that the negative impact of both the tumour and its treatment on NCF should be prevented as much as possible. Indeed, neurocognitive functioning has gained more attention in recent brain tumour research [5] and has been included as a secondary outcome in a growing number of randomised controlled trials (RCTs) in brain tumour patients. This is done both in patients with relatively good prognosis, for whom maintaining NCF over time is especially vital [6,7], and is also relevant in patients with fast growing tumours with poor prognosis. In clinical studies in brain metastases patients, NCF has been included even as a primary outcome [8,9]. This also holds true for studies on rehabilitation of neurocognitive disorders due to the tumour and its treatment [10,11].

To determine the net clinical benefit of a new treatment (i.e. weighing the benefits of a treatment against its side-effects), information on both survival and functioning (e.g. HRQoL and NCF) of patients is essential. Besides using standardised neurocognitive test batteries, instead of screening instruments, for which proposals have been published [12–15], study design and analysis of the outcome data are important for optimal evaluation of the net clinical benefit. Moreover, adequate reporting of neurocognitive data is critical. Without proper reporting, interpretation of neurocognitive outcome is hampered, thus limiting the evaluation of the net clinical benefit of the studied treatment. Therefore, in this systematic review, we investigated the level of neurocognitive functioning outcome (NCO) reporting in RCTs of brain tumour patients and assessed whether high level reporting RCTs did indeed impact clinical decision-making.

2. Methods

2.1. Search strategy

A literature search was conducted using the following electronic databases up to August 2017: PubMed/Medline, PsycINFO, Cochrane, CINAHL and Embase. The search strategy consisted of three search strings, related to 'neurocognitive assessment', 'brain tumours' and 'randomized controlled trials'. The complete search strategy is shown in Supplementary file 1.

All retrieved titles and abstracts were screened by two reviewers (E.H. and L.D.), and full texts of potential relevant articles were read. The reference lists of the selected full text articles were screened to identify additional relevant studies. Any uncertainty about the relevance of a study was resolved in consensus. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [16].

2.2. Inclusion and exclusion criteria

RCTs were included concerning adult (≥18 years) patients with an intracranial tumour, both those with brain tumours arising from the brain tissue as those abutting to the brain (i.e. glioma, brain metastasis, meningioma and primary central nervous system lymphoma), description of any objective neurocognitive assessment, and published in English in a peer-reviewed journal. Of note, we also included RCTs on brain-directed therapies such as prophylactic cranial irradiation (PCI) used in cancer patients without obvious and not yet visible brain metastases [17]. Any RCT comparing two or more treatments, including cognitive rehabilitation programs, were included. We included RCTs with NCO as either primary end-point ('primary NCO') or secondary end-point ('secondary NCO'). Exclusion criteria were RCTs including <10 patients; articles using subjective measures, such as questionnaires, to assess NCF; and RCTs in which both brain tumour patients and patients with other diagnoses were included because of possible difficulties in interpreting NCO results related specifically to brain tumour patients.