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Treatment of cognitive deficits in brain tumour patients: current status and future directions

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Purpose of review
Increased life expectancy in brain tumour patients had led to the need for strategies that preserve and improve cognitive functioning, as many patients suffer from cognitive deficits. The tumour itself, as well as antitumor treatment including surgery, radiotherapy and chemotherapy, supportive treatment and individual patient factors are associated with cognitive problems. Here, we review the recent literature on approaches that preserve and improve cognitive functioning, including pharmacological agents and rehabilitation programs.

Recent findings
Minimizing cognitive dysfunction and improving cognitive functioning in brain tumour patients may be achieved both by preserving cognitive functioning during antitumor treatment, including techniques such as awake brain surgery, less invasive radiation therapies such as stereotactic radiotherapy and proton therapy, as well as with interventions including cognitive rehabilitation programmes. Novel rehabilitation programs including computer-based cognitive rehabilitation therapy (CRT) programmes that can be adjusted to the specific patient needs and can be administered at home are promising. Furthermore, personalized/precision medicine approaches to identify patients who are at risk for cognitive decline may facilitate effective treatment strategies in the future.

Summary
Cognitive functioning has gained greater awareness in the neuro-oncological community, and methods to preserve and improve cognitive functioning have been explored. Rehabilitation programmes for brain tumour patients should be further developed and referred to in clinical practice.

Keywords
brain tumour, cognitive deficits, rehabilitation, treatment

INTRODUCTION
Cognitive functioning refers to mental processes such as attention, perception, thinking, reasoning and remembering, the so-called ‘higher’ cerebral functions. Intact cognitive functioning is important, as it enables to function autonomously within society. In patients with a brain tumour, the presence of the tumour directly threatens cognitive functioning. This is the case in patients with primary brain tumours such as meningiomas and malignant gliomas, as well as in patients with brain metastases, the most prevalent brain tumours. As even mild cognitive deficits can have functional and psychosocial consequences, preserving and improving cognitive functioning in these patients is important to maintain functioning and wellbeing through the disease course.

Many brain tumour patients exhibit cognitive impairment at some point during the disease course, and cognitive deficits are already present in over 90% of the patients with a primary brain tumour and brain metastases before treatment [1,2]. Tumour characteristics such as location, size, histology and growth rate as well as patients characteristics, including age, cardiovascular risk and cognitive

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In clinical trials, cognitive outcomes should be implemented to gain information on the positive and negative effects of novel (cognition-sparing) treatment strategies on cognition on the short and long term.

In clinical practice, cognitive impairment should be screened for, and eligible patients should be informed about and informed on/referred to intervention programmes.

Computer-based cognitive rehabilitation programmes provide access to large patient populations and enable patients to follow rehabilitation in their own environment and at their own pace.

Future studies should further unravel the association between genetic and cognitive factors to clinically screen for patients who are most vulnerable to cognitive decline.

Preservation of cognitive functioning
Treatment options for tumour patients often include a combination of surgery, radiotherapy, chemotherapy and supportive treatment.

Surgery
Extensive surgical resection has shown to confer survival benefit in primary brain tumours including gliomas [7], and in general, brain tumour patients experience less seizures, headache and signs of intracranial pressure after surgery. Maximal well tolerated resection while avoiding severe disabling neurological and cognitive deficits is the main challenge in brain tumour patients. Identifying acquired cognitive problems after surgery may be difficult, as presurgery cognitive testing is not always embedded in clinical care, complicating prepost comparison, and deficits are often subtle and may be overshadowed by pronounced and mostly transient speech and motor deficits [8]. In glioma patients, studies showed that patients experienced cognitive deficits after surgery [9,10]; however, these were partly transient, and at the individual patient level, postoperative improvement was seen as well [11]. In patients with meningioma, cognitive functioning frequently improves after surgery, but remains significantly lower than in healthy controls [12,13]. Postoperatively, the most affected cognitive domains are memory and executive function [13].

Awake surgery with intraoperative electrical stimulation and real-time monitoring aims to identify brain circuits crucial for cognitive functioning. It allows for more precise resection of the tumour without damaging surrounding tissue, and is thereby assumed to preserve cognitive functioning in glioma patients [14–16]. However, most studies only included follow-up of a few months, and studies on long-term cognitive outcomes after awake surgery are lacking. Also, nowadays, testing during awake tumour resection is mainly focused on the domains of language and motor function in patients with left-hemispheric tumours. More recently, a few explorative studies in brain tumour patients evaluated the feasibility and effects of monitoring other cognitive functions during awake surgery, for example executive functioning (that is inhibition) and working memory [17,18].

Radiation therapy
Radiation may lead to significant, but mostly transient, cognitive disability in 50–90% of the patients, occurring in the acute phase (during radiation),...
early-delayed (in the first months after radiation) and late-delayed (up to years after radiation) [19]. Acute side effects include inflammation and injury to neuronal structures, causing oedema that leads to symptoms such as headache, nausea and dizziness and cognitive deficits. Early-delayed effects are associated with demyelination and oedema, which may affect cognitive functioning as well [20]. Although acute and early-delayed side effects are thought to be transient, late-delayed damage is of the greatest concern, because the related cognitive impairments can be irreversible and progressive. Late-delayed complications may lead to focal deficits (radiation necrosis), and more importantly, to chronic diffuse encephalopathy, which may even result in dementia [21]. In severe cases of late-delayed radiation injury, imaging studies demonstrated diffuse leukoencephalopathy and progressive atrophy [22], while histopathology may show small vessel necrosis in the white matter and depletion of stem cells in the hippocampal area and subventricular zone. However, a larger subgroup of patients experience mild-to-moderate, though persistent cognitive impairment following radiation therapy [22].

Less invasive radiation techniques such as limited fraction dose, stereotactic radiotherapy instead of whole brain radiotherapy [23–25], and sparing the hippocampus during radiation may possibly result in less cognitive problems in patients with primary brain tumours and brain metastases [24]. In addition, proton radiation therapy, which reduces entrance dose and eliminates exit dose, is also expected to contribute to preservation of cognitive functioning by sparing normal tissue to a larger extent [26].

**Chemotherapy**

Compared with radiation therapy, the adverse effects of chemotherapy on cognitive functioning in brain tumour patients have gained less attention. Distinguishing cognitive deficits caused by chemotherapy is challenging in primary brain tumour patients, as most patients who underwent chemotherapy also underwent surgical resection and radiotherapy. However, late cognitive deficits have been demonstrated in glioma patients, years after radiation and Procarbazine, lomustine and vincristine chemotherapy [27]. In contrast, a systematic review in patients with primary central nervous system (CNS) lymphoma without previous surgery or radiotherapy suggested that cognition improved after induction chemotherapy compared with baseline, presumably also partly due to corticosteroids [28]. For patients with systemic cancer, even without CNS metastases, there is an emerging body of research demonstrating that chemotherapeutic agents may cause cognitive deficits both on the short and long term [29]. Common cognitive domains affected by systemic chemotherapy include learning, memory, information processing speed and executive functioning [30], which has been described as the ‘chemo brain’ [22] or ‘cancer-related cognitive impairment’ (CRCI) [31]. With regard to long-term deficits in these patients, imaging studies have demonstrated structural changes in the brain, including volume reduction and altered white matter integrity [32], which are associated with long-term cognitive problems [29].

There has been little evidence on neuroprotective strategies to prevent chemotherapy-related cognitive impairment in brain tumour patients. Animal studies suggested the possibility of preserving cognitive decline by administration of preventing agents while undergoing chemotherapy [33–36], or exercise to assist in preventing cognitive dysfunction during or after chemotherapy by increasing neurogenesis [36–38], but there are no clinical data.

**Targeted therapy and immunotherapy**

Angiogenesis inhibitors, such as bevacizumab, have been successful in the treatment of various systemic cancers. However, in glioma patients, there is no evidence for overall survival benefit, nor for decline in (cognitive) functioning [39,40]. Results of trials investigating immunotherapy and their impact on cognitive functioning in patients with glioma [41], CNS lymphoma [42] and meningioma [43] are still to be expected.

**Supportive treatment**

Factors such as epilepsy, antiepileptic drugs (AEDs) and corticosteroids may affect cognition and behaviour as well. AEDs have a significant negative effect on attention and information processing speed [44], though second-generation AEDs such as levetiracetam and oxcarbazepine seem to minimize the negative impact of seizures on health-related quality of life (HRQoL) and cognition [45,46]. Perioperative corticosteroids improve cognition because of diminishing oedema, but there is otherwise evidence of detrimental (cognitive) effects of long-term corticosteroid use [6].

**Interventions to preserve and improve cognitive functioning**

Two approaches are often distinguished when looking at interventions that aim to improve cognitive functioning: pharmacological treatment and cognitive rehabilitation therapy (CRT).
Pharmacological treatment

Pharmacological agents that have been studied in brain tumour patients include amongst others donepezil, armodafinil and modafinil. Table 1 includes trials on pharmacological agents in brain tumour patients, including more than 10 patients [47–55]. In a large randomized controlled trial, the efficacy of memantine, a NMDA receptor antagonist also used in Alzheimer’s disease, was found to delay cognitive decline in patients with brain metastases during whole-brain radiotherapy [47], although the trial lacked statistical significance due to patient loss. There has also been interest in donepezil, an acetylcholinesterase inhibitor also used in patients with Alzheimer’s disease, and results of three studies in brain tumour patients suggested that donepezil improved some aspects of cognitive functioning, including attention, memory and motor speed [48–50]. Other trials that aimed to investigate methylphenidate [56] and combined levothyroxine/liothyronine supplementation [57] were terminated because of accrual issues. Thus, although some studies reported small successes of pharmacological treatment, limitations including limited sample size, recruitment issues and the lack of a control group to account for practice effects hamper conclusions.

Table 1. Pharmacological agents for the management of cognitive impairment in brain tumour patients

| Ref.          | Pharmacological agent | Study design                          | Population (n)                  | Timing                                      | Relevant results                                                                 |
|---------------|-----------------------|---------------------------------------|---------------------------------|---------------------------------------------|--------------------------------------------------------------------------------|
| Boele et al. [51] | Modafinil            | Double-blind, placebo controlled cross-over trial | Primary brain tumour (n = 37)   | At baseline, after 6 weeks of modafinil/placebo and 6 weeks after opposite treatment | Modafinil did not exceed the effects of placebo                                  |
| Brown et al. [47] | Memantine            | Double-blind, placebo controlled RCT | Brain metastases (n = 508)       | At baseline, and at 8, 16, 24 and 52 weeks after the start of WBRT | Memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function and processing speed |
| Butler et al. [52] | Methylphenidate HCI  | Double-blind, placebo controlled RCT | Primary and metastatic brain tumours (n = 68) | At baseline, during and 4, 8 and 12 weeks after RT | No difference in MMSE score between the groups                                   |
| Correa et al. [48] | Donepezil            | Pilot                                 | Primary brain tumour (n = 15)    | After treatment with RT + CT or CT          | A significant postbaseline improvement in attention, motor speed, visual memory |
| Gehring et al. [53] | Methylphenidate and modafinil | Open-label, randomized pilot trial | Primary brain tumour (n = 24)  | At baseline and 4 weeks thereafter          | Improvement in processing speed and executive functioning                        |
| Meyers et al. [54] | Methylphenidate      | Open-label without control group       | High-grade gliomas (n = 30)     | At baseline, week 4, 8, 12 thereafter       | Improvement in various tests, mood, subjective improvement in 20/26 patients after 4 weeks |
| Rapp et al. [50] | Donepezil            | RCT                                   | Primary and metastatic brain tumours (n = 198) | After partial RT or WBRT                     | Modest improvement in memory and motor speed                                      |
| Page et al. [55] | Armodafinil          | Double-blind, placebo-controlled RCT | Meningioma and glioma (n = 54)  | At the end of RT and 4 weeks after RT       | No difference between the treatment arms on any of the cognitive tests           |
| Shaw et al. [49]  | Donepezil            | Open-label without control group       | Primary brain tumours, one metastatic (n = 35) | 6 months post RT                           | Improvement in various cognitive tests after 24 weeks                           |

CT, chemotherapy; RCT, randomized controlled trial; RT, radiotherapy; WBRT, whole-brain radiation therapy.
Cognitive rehabilitation

CRT refers to neuropsychological interventions aimed at preventing or treating cognitive deficits, and is based on the principles of neuroplasticity (i.e. learning) and designed to improve cognitive abilities through compensation or retraining. Retraining includes repeated practice of tasks that aim to strengthen impaired cognitive functions. Compensation training focuses on learning new strategies and alternative means to improve daily functioning and achieve goals, for example pacing, breaking down complex tasks into smaller steps and using mnemonics. The two are often studied in combination. CRT can be provided to individual patients or in groups, at home or in rehabilitation centres and with traditional face-to-face approaches as well as through computerized programmes. In other patient populations, such as stroke patients and traumatic brain injury patients, CRT has shown to be effective and is often incorporated in the standard of care [58,59]. In brain tumour patients, a number of cognitive intervention programmes have been developed (see Table 2) [60–67]. Although often hampered by methodological issues, for example not all studies included a control group to rule out effects of practice and natural recovery [60], most programmes reported some improvements in cognitive test-performance [61–65] and also with regard to subjective cognitive functioning [66]. Similar to the pharmaceutical trials, problems with accrual have been reported in several trials, especially when CRT was offered in the early disease stage. There is no consensus on the optimal timing for CRT. If the aim is to minimize or prevent cognitive problems due to adjuvant treatment and to make the most use of still intact skills, CRT should start as early as possible [6,64,68]. An early cognitive training programme for early postsurgery primary brain tumour patients showed that cognitive functioning already improved after a few weeks [64]. Conversely, as patients with newly diagnosed brain tumours often undergo multiple time-consuming and intensive treatment regimens that may also cause cognitive problems, offering

| Ref. | Intervention outline | Study design | Population (n) | Timing | Effect on cognition |
|------|---------------------|--------------|----------------|--------|---------------------|
| Gehring et al [66] | Weekly individual supervised compensation training and computerized retraining | RCT | Low-grade and anaplastic gliomas (n = 140) | At least 6 months postsurgery | Improvement in short-term cognitive complaints, long-term cognitive functioning and mental fatigue |
| Hassler et al [65] | Compensatory training. Weekly group training sessions for attention, verbal and memory skills | RCT | Grade III and IV glioma patients (n = 11) | Postsurgery, RT and CT | Modest improvement in memory and attention |
| Maschio et al [63] | Cognitive rehabilitation training (RehabTR). Weekly sessions using computerized retraining | Pilot study | Patients with brain tumour related epilepsy (n = 16) | Post surgery | Improvements in short-term verbal memory, episodic memory, fluidity and long-term visuospatial memory improved immediately and at 6-month follow-up |
| Sacks-Zimmerman et al [67] | CogMed Computer-based cognitive remediation therapy (CRT) | Prospective pilot study | Low-grade glioma patients (n = 3) | Post surgery | Results of only three patients have been published |
| Richard et al [61] | Goal Management Training (GMT): Behavioural intervention combining mindfulness and strategy training | Pilot randomized trial (three groups) | Primary brain tumour patients (n = 26) | Postsurgery and >3 months post possible RT and/or CT | Executive functioning improved at 4-month follow-up |
| Van der Linden et al [60] | ReMind: iPad-based psycho-education, strategy training and retraining | Feasibility study | Low-grade glioma and meningioma (n = 15) | Before surgery or other treatment | Intervention was found to be feasible, results of the RCT are expected |
| Yang et al [62] | Virtual reality: Computer-based cognitive rehabilitation program | Trial comparing VR and computerized retraining with computerized retraining | Primary brain tumour patients (n = 38) | After surgery, and further treatment with RT/CT | Improvement in visual and auditory attention, short-term visual spatial memory |
| Zucchella et al [64] | Compensation training and computerized training | RCT | Primary brain tumour patients [62] | Postsurgery | Improvement of visual attention and verbal memory |

CT, chemotherapy; RCT, randomized controlled trial; RT, radiotherapy; VR, virtual reality.
rehabilitation after antitumour treatment may be fit best for patients with a longer prognosis both in terms of timing and in terms of effectiveness. At this time, patients also attempt to resume their normal daily activities and return to work and then start to experience cognitive problems. Consequently, flexible computer-based CRT programmes that can be adjusted to the specific patient needs and can be administered at home may especially be suitable.

Other interventions

Given the overlapping impact of both cognitive and emotional problems, intervention programmes that address outcomes as HRQoL, fatigue, mood or a combination of these may have indirect positive effects on cognitive functioning as well. Several uncontrolled studies that investigated psychological/psychosocial interventions [69,70] and yoga [71] in brain tumour patients showed to be feasible, reported some successes with regard to various HRQoL outcomes and were highly appreciated by patients. In addition, several exercise programmes in glioma patients similarly showed to be feasible, improved functional outcome [72,73] and suggested to have positive outcomes with respect to HRQoL outcomes [74,75,76]. In meningioma patients, uncontrolled studies on exercise programmes found decreased symptoms of depression and insomnia [77], and improved functional outcome [78].

CONCLUSION AND FUTURE OPPORTUNITIES

During the past years, cognitive functioning has gained greater awareness in the neurooncological community. More clinical trials have included cognitive performance as an endpoint, and methods to preserve and improve cognitive functioning have been explored. Important long-term data with regard to novel cognition-sparing treatment strategies such as awake surgery, hippocampal sparing and proton therapy are awaited.

The implementation of the so-called personalized or precision medicine into clinical practice allows optimization of therapy based on the patients’ individual (genetic) profile, in order to maximize the therapeutic effect and minimalize side effects. More specifically, patients vulnerable to cognitive decline might be identified at an early stage, which allows for personalized and timely intervention. Recent studies have highlighted the importance of molecular markers in neurooncology, and their link with cognitive functioning. Glioma patients with isocitrate dehydrogenase 1 (IDH1) mutant gene may exhibit less cognitive impairment than their wild-type counterparts [5,79]. With regard to germline genetic characteristics, studies have suggested that the APOE ε4 allele, a known risk factor for Alzheimer’s disease [80], single nucleotide polymorphisms in the catechol-O-methyl transferase (COMT), brain-derived neurotrophic factor (BDNF) and dystrophia-binding protein one (DTNBP1) genes are associated with (impaired) cognitive functioning in brain tumour patients as well [81]. The evidence so far is, however, insufficient to implement formally testing of these genetic polymorphisms in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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