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Neurocognitive functioning and health-related quality of life in patients with brain tumors: impact of tumor- and treatment-related factors

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Citation

Habets, E. J. J. (2020, February 6). *Neurocognitive functioning and health-related quality of life in patients with brain tumors: impact of tumor- and treatment-related factors*. Retrieved from <https://hdl.handle.net/1887/84582>

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Cover Page



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Author: Habets, E.J.J.

Title: Neurocognitive functioning and health-related quality of life in patients with brain tumors: impact of tumor- and treatment-related factors

Issue Date: 2020-02-06

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Impact of tumor- and treatment-related factors



Esther Habetts

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The studies described in this thesis were funded by

St. Jacobusstichting Den Haag, Netherlands Organisation for Scientific Research (NWO, project number: 10-10400-96-14003), and Dutch Cancer Society (grant number: VU2014-7113).

Printing of this thesis was kindly supported by

St. Jacobusstichting Den Haag.

Bookdesign & illustration

Ilse Schrauwers – www.isontwerp.nl

Printed by

Gildeprint, Enschede

ISBN/EAN

978 9492 3033 01

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Neurocognitive functioning and health-related quality of life in patients with brain tumors. Impact of tumor- and treatment-related factors.

Thesis, Leiden University, The Netherlands 2019

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Neurocognitive functioning and health-related quality of life in patients with brain tumors

Impact of tumor- and treatment-related factors

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 6 februari 2020
klokke 15.00 uur

door

Esther Johanna Jacobus Habets

geboren te Vianen
in 1983

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Prof. dr. M.J.B. Taphoorn

Prof. dr. M. Klein, Vrije Universiteit Amsterdam

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Leden promotiecommissie

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Prof. dr. M.J. van den Bent, Erasmus Universiteit Rotterdam

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Part I

Introduction

1

General introduction and outline



Introduction

Epidemiology and classification of brain tumors

Brain tumors can be classified as either primary, such as gliomas which originate from the glial cells in the brain, or as secondary, in which case systemic tumors (mainly from lung, melanoma, renal cell, breast, and colorectal cancer) metastasize to the brain.

In the Netherlands, gliomas have an incidence of 5.9 per 100,000 persons,¹ resulting in approximately 1000 new cases per year. Traditionally gliomas were divided into either of four grades, primarily based on their histopathology (World Health Organization (WHO) 2007 classification of gliomas). Grade I and II gliomas are classified as low-grade glioma, and grade III (anaplastic glioma) and grade IV (glioblastoma multiforme) as high-grade glioma.² Standard treatment for grade I glioma, which are often pediatric tumors, consists of surgery. Although most of these patients are cured after treatment, a substantial number suffers from late effects such as depression and social difficulties, and performs on an intelligence level below average³. Grade II gliomas are often slowly-growing but infiltrate the surrounding brain tissue. Despite treatment with (early) surgery, increasingly followed by adjuvant radiotherapy and/or chemotherapy, these tumors do recur and can eventually evolve into grade III or IV glioma. These high-grade gliomas, with glioblastoma as the most prominent and aggressive subtype, are rapidly growing tumors infiltrating the surrounding brain tissue. Treatment for grade III glioma consists of surgery (often) followed by radiotherapy and chemotherapy.⁴ For glioblastoma multiforme, standard treatment is surgery, followed by radiotherapy with concomitant and six cycles of adjuvant chemotherapy⁵. In 2016 the WHO classification of gliomas has been updated by the additional inclusion of molecular genetics, which resulted in major adjustments in classification and, consequently, treatment of specific glioma patients^{6,7}. For patient groups presented in this thesis, the WHO 2007 classification was used, categorizing patients based on tumor histopathology.

Median overall survival for grade II glioma ranges from 4.7 to 9.8 years,⁸ for anaplastic gliomas from 19 to 42 months,^{9,10} and for glioblastoma patients from only 9 to 15 months.^{1,5}

With an incidence of cancer ranging between 306.3 to 429.9 per 100,000 persons, and 9-45% of cancer patients developing brain metastases, secondary brain tumors far outnumber gliomas.¹¹⁻¹³ In the past decades, the incidence of brain metastases has increased, possibly due to prolonged survival as result of better control of the primary tumor and better neuro-imaging techniques to detect brain metastases.^{12,14,15} Treatment for brain metastases is in most cases palliative only and treatment choice depends on the age and condition of the patient, as well as the primary tumor type. Radiotherapy has an important role in treatment and encompasses both whole-brain radiotherapy (WBRT) and stereotactic radiotherapy (SRT). Currently, SRT is the

preferred treatment for patients with one to three brain metastases, while WBRT is often applied in case of more than three metastases.¹⁶ At the moment, several trials are under development to evaluate SRT in patients with more than four brain metastases,¹⁷ since WBRT is assumed to be more harmful in terms of risk of late neurotoxicity than focal treatment.^{18,19} Surgery can equally be applied in case of a solitary brain metastasis, depending on location and mass effect. Recent developments resulted in a variety of new treatment options for the primary tumor, including treatments based on the molecular genetics of a tumor and targeted therapies. These treatments may also have an effect on brain metastases. Indeed, immunotherapy and targeted tumor treatment have found to be effective for brain metastases, with metastases from melanoma being a prominent example.^{20,21}

The median overall survival of patients with brain metastases ranges considerably, from 2.6 to 15 months,^{22,23} with long term survivors becoming more frequent due to new systemic cancer treatments.

As most patients with glioma or brain metastases cannot be cured, treatment not only aims at prolonging survival, but also at maintaining or improving patients' functioning and well-being. Indeed, prolonged survival may not be meaningful if patients suffer from many problems or limitations in daily life functioning. A shorter survival duration without compromised functioning and well-being may in that case be preferred. In contrast to other cancer patients, brain tumor patients are characterized by impairments in neurocognitive functioning, which may be caused by both the tumor and its treatment. Impaired neurocognitive functioning may have a negative impact on the performance of activities in daily life as well as health-related quality of life (HRQoL) and should therefore be a key aspect in the treatment of brain tumor patients. This thesis focuses on the impact of having a brain tumor and receiving specific anti-tumor treatment on neurocognitive functioning and HRQoL.

The concepts of neurocognitive functioning and health-related quality of life

Neurocognitive functioning (NCF) comprises all aspects of human thinking, including reasoning and planning, attention, memory, speed of information processing, language, visuospatial abilities, and executive functions. These functions may be closely related to the integrity of specific brain areas (e.g. arcuate fasciculus involved in language) or merely to cortical and subcortical connections in the brain, resulting in networks subserving specific functions such as attention. Neurocognitive impairment is a deterioration of one or several cognitive functions, which is particularly seen after changes within the brain due to neurological illnesses or brain injury.

Quality of life is defined by the WHO as 'a person's perception of their physical, cognitive and affective state, as well as their perception of their interpersonal

relationships and social roles'.²⁴ Quality of life is thus a multi-dimensional concept that is self-reported. In brain tumor research both the terms 'quality of life' and 'health-related quality of life' (HRQoL) are used interchangeably. In the latter however, quality of life is related to the impact of illness or health specifically. In this thesis we will therefore use the term HRQoL.

The definition of the WHO on quality of life includes the persons' perception of their cognitive state. This is reflected in the inclusion of cognitive complaints in many HRQoL questionnaires. Although the concordance between cognitive complaints and objectively measured NCF is only moderate,^{25,26} previous research has shown that NCF is associated with various functioning scales of HRQoL questionnaires, including role limitations and mental health.^{27,28} Neurocognitive impairments also impact HRQoL in more indirect ways by negatively influencing return to work, interpersonal relationships and leisure activities.²⁹

Assessment of NCF and HRQoL

NCF can be objectively assessed with a variety of tests, ranging from short cognitive screening instruments to comprehensive standardized test batteries specifically designed to assess neurocognitive function in various domains. The patient's perception on how he or she is functioning can be assessed with subjective measures such as questionnaires.

In many randomized controlled trials (RCTs), NCF has been included as a secondary outcome, for which often screening instruments such as the Mini Mental State Examination (MMSE) were used, as they are short and simple in terms of administration and limited in costs. However, these instruments are not sensitive for detecting more subtle neurocognitive impairment in brain tumor patients, nor for detecting (subtle) changes over time.^{30,31} To obtain more reliable and informative results on NCF, a test battery should cover all relevant cognitive functions, should be repeatable and sensitive to change, should have standardized administration procedures, published normative data should be available, and the maximum administration time ideally should not exceed 40 minutes.^{32,33} To optimize NCF evaluation in clinical trials in brain tumor patients, suggestions have been made for implementing a standardized test protocol meeting most of the above criteria, for example by the response assessment in neuro oncology (RANO) group,^{34,35} and others.^{36,37} This test protocol assesses verbal memory, processing speed and aspects of executive functioning, and is included in recent RCTs of the EORTC and Radiation Therapy Oncology Group (RTOG), among others.³² However, this protocol does not include other relevant neurocognitive functions.^{38,39} As NCF is the primary outcome in the studies in this thesis, we made use of a comprehensive test battery comparable to earlier studies, covering all relevant neurocognitive functions (such as memory,

executive functioning, attention and information processing speed) for brain tumor patients.^{26,40,41}

Assessment of HRQoL in brain tumor research is typically done with validated self-report questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire C30 (EORTC QLQ-C30)^{42,43} or the Functional Assessment of Cancer Therapy (FACT),⁴⁴ often complemented by brain tumor specific questionnaires such as the EORTC Brain Module (QLQ-BN20)⁴³ or FACT-Brain. In the current studies we have used the EORTC QLQ-C30 and QLQ-BN20, which both have good psychometric properties.⁴⁵

NCF and HRQoL in brain tumor patients

Patients with brain tumors may experience both disease-specific and more general symptoms. Indeed, brain tumor patients often experience neurological symptoms and deficits, such as hemiparesis, sensory deficits or aphasia, epilepsy,^{46,47} changes in personality⁴⁸ and neurocognitive impairments.^{49,50} In addition, fatigue⁵¹ and depression⁵² are frequently reported.

Neurocognitive impairments can be the first presenting sign of a brain tumor,^{49,53} but may also develop later in the disease trajectory, i.e. at disease progression.⁵⁴ In rapidly growing high-grade gliomas, neurocognitive impairments might initially be overshadowed by more pronounced neurological deficits.²⁶ Mainly more widespread neurocognitive functions such as memory, attention, executive functioning and processing speed are hampered in brain tumor patients.^{40,55}

Although it has been shown that neurocognitive impairment is associated with the presence of a brain tumor,^{56,57} it is still not clear how brain tumors exactly affect discrete cognitive functions, and what aspects of the tumor (e.g. location or size, speed of growth) have a predominant impact on NCF. Similarly, it is still unclear what the precise impact is of anti-tumor treatment, such as resection, radiotherapy and chemotherapy, on NCF. Several studies have found that treatment with (various doses of) radiotherapy with or without chemotherapy resulted in impaired memory and attention in glioma patients.^{41,55,58,59} However, the impact of other treatments (such as SRT or chemotherapy) on short- and long-term discrete neurocognitive functions and HRQoL are less well known.^{60,61} Finally, also epilepsy and use of supportive treatment such as anti-epileptic drugs and corticosteroids can negatively influence NCF.⁶²

As NCF is essential for human functioning, neurocognitive dysfunction has a profound impact on daily functioning and HRQoL of both brain tumor patients and their proxies (i.e. relatives or close friends of the patient).^{55,63} Since the treatment of gliomas and brain metastases is in most cases not curative but aimed at prolonging life, maintaining patients' functioning and well-being during the survival time is essential for patients and their proxies. This holds true for patients with relatively

short survival times, such as glioblastoma and brain metastatic patients, but also for patients with longer survival, because patients with low-grade glioma are often relatively young and late effects of treatment may adversely impact their functioning over time. For clinical decision making, in which the potential benefit of treatment in terms of prolonged survival should be weighed against possible negative impact of treatment on NCF and HRQoL, insight in the specific roles of tumor- and treatment related factors is essential. Also, counselling patients regarding (neurocognitive) impairments or a negative impact on HRQoL, and offering patients adequate (cognitive) rehabilitation for their impairments, can be optimized when knowing the patient's NCF and HRQoL characteristics.

Aim and outline of this thesis

The primary aim of this thesis is to improve knowledge about the frequency, type and nature of (impaired) NCF in both primary and secondary brain tumor patients during the entire disease course. With this information, treatments can be optimized and personalized. A secondary aim is to shed more light on the impact of a brain tumor and its treatments on short- and long-term HRQoL of brain tumor patients. In addition, a tertiary aim is to evaluate the impact of neurocognitive outcomes on clinical decision making.

In part II, the short- and long-term effects of the tumor and anti-tumor treatment on NCF and HRQoL are explored, thereby providing information about the different and unique impact of the tumor and its treatment on these functions. NCF is measured with tests for verbal and working memory, attention, executive functioning, psychomotor function, information processing speed and visuoconstructive abilities, and HRQoL with the EORTC QLQ-C30 and BN20 questionnaires. Chapter 2 addresses the effects of the tumor itself and of resective surgery on NCF in patients with high-grade glioma, by evaluating NCF preceding and after surgery, but before subsequent anti-tumor treatment. In chapter 3, the impact of SRT, a focal form of radiation, on short-term NCF and HRQoL in patients with one to three brain metastases is investigated. These patients are tested prior to SRT, and three and six months after SRT. Also MRI scanning is included to correlate changes in metastatic disease to NCF and HRQoL. While NCF and HRQoL are assessed at *group* level in chapter 3, these are investigated on the *individual patient* level in chapter 4. In this study, changes in all neurocognitive domains and HRQoL scales for each individual patient are combined. Chapter 5 focusses on the long-term (> 8 years) effects of radiotherapy and chemotherapy on HRQoL and NCF in anaplastic glioma patients.

In part III, the association between NCF and tumor location (chapter 6) and

between NCF and resection cavity location (i.e. the space that is left after the surgical removal of a tumor; chapter 7) in low- and high-grade glioma patients are described. To study this association, we did use tumor localization maps, to obtain more detailed information about the relationship between discrete neurocognitive functions and tumor- or resection locations.

Part IV consists of a systematic review on the level of reporting of neurocognitive outcomes in randomized controlled trials on brain tumor patients. With adequate reporting of neurocognitive data, the outcomes of these studies can contribute in determining the net clinical benefit of a treatment, meaning that the benefits of a treatment in terms of improved survival are weighed against possible side-effects of the treatment on a patients' functioning. This information may be useful for clinical decision making.

Finally, in part V a summary and discussion of the main findings is provided, together with methodological challenges encountered and future directions for research.

References

1. Ho VK, Reijneveld JC, Enting RH, et al. Changing incidence and improved survival of gliomas. *Eur Cancer*. 2014;50(13):2309-2318.
2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97-109.
3. Turner CD, Chordas CA, Liptak CC, et al. Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only. *Pediatr Blood Cancer*. 2009;53(3):417-423.
4. van den Bent MJ, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. *Lancet*. 2017;390(10103):1645-1653.
5. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
6. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016;131(6):803-820.
7. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. *Lancet Oncol*. 2017;18(6):e315-e329.
8. Kumthekar P, Raizer J, Singh S. Low-grade glioma. *Cancer Treat Res*. 2015;163:75-87.
9. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol*. 2013;31(3):344-350.
10. Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol*. 2005;64(6):479-489.
11. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356-387.
12. Cagney DN, Martin AM, Catalano PJ, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. *Neuro Oncol*. 2017;19(11):1511-1521.
13. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698-2705.
14. Smedby KE, Brandt L, Bäcklund ML, Blomqvist P. Brain metastases admissions in Sweden between 1987 and 2006. *Br J Cancer*. 2009;101(11):1919-1924.
15. Rastogi K, Bhaskar S, Gupta S, Jain S, Singh D, Kumar P. Palliation of Brain Metastases: Analysis of Prognostic Factors Affecting Overall Survival. *Indian J Palliat Care*. 2018;24(3):308-312.
16. Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. *Cancer Treat Rev*. 2014;40(1):48-59.
17. Soike MH, Hughes RT, Farris M, et al. Does Stereotactic Radiosurgery Have a Role in the Management of Patients Presenting With 4 or More Brain Metastases? *Neurosurgery*. 2018.
18. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. *Radiat Oncol*. 2012;7:77.

19. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer*. 2012;118(9):2486-2493.
20. Gaudy-Marqueste C, Dussouil AS, Carron R, et al. Survival of melanoma patients treated with targeted therapy and immunotherapy after systematic upfront control of brain metastases by radiosurgery. *Eur J Cancer*. 2017;84:44-54.
21. Tawbi HA, Forsyth PA, Algazi A, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. *N Engl J Med*. 2018;379(8):722-730.
22. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419-425.
23. Jyothirmayi R, Saran FH, Jalali R, et al. Stereotactic radiotherapy for solitary brain metastases. *Clin Oncol (R Coll Radiol)*. 2001;13(3):228-234.
24. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1995;41(10):1403-1409.
25. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol*. 2009;27(22):3712-3722.
26. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery*. 2000;47(2):324-333.
27. Waagemans ML, van Nieuwenhuizen D, Dijkstra M, et al. Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. *Neurosurgery*. 2011;69(1):72-78; discussion 78-79.
28. Li J, Bentzen SM, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys*. 2008;71(1):64-70.
29. Mitchell AJ, Kemp S, Benito-Leon J, Reuber M. The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatr*. 2010;22(1):2-13.
30. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol*. 2014;32(6):535-541.
31. Meyers CA, Wefel JS. The use of the minimal state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol*. 2003;21(19):3557-3558.
32. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol*. 2012;108(2):309-318.
33. Caine C, Mehta MP, Laack NN, Gondi V. Cognitive function testing in adult brain tumor trials: lessons from a comprehensive review. *Expert Rev Anticancer Ther*. 2012;12(5):655-667.
34. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol*. 2013;14(10):e407-e416.
35. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol*. 2011;12(6):583-593.
36. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703-708.
37. Klein M, De Witt Hamer PC. Neurocognitive outcome and resective brain tumor surgery in adults. In: Duffau H, ed. *Brain mapping: from neural basis of cognition to surgical applications*. Vol 1. New York 2011.

38. Regine WF, Schmitt FA, Scott CB, et al. Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of Radiation Therapy Oncology Group trial BR-0018. *Int J Radiat Oncol Biol Phys*. 2004;58(5):1346-1352.
39. Witgert ME, Meyers CA. Neurocognitive and quality of life measures in patients with metastatic brain disease. *Neurosurg Clin N Am*. 2011;22(1):79-85, vii.
40. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol*. 2001;19(20):4037-4047.
41. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol*. 2009;8(9):810-818.
42. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
43. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 1996;5(1):139-150.
44. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570-579.
45. Fayes PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. *Eur J Cancer*. 2001;37(11):1331-1334.
46. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. *Lancet Neurol*. 2007;6(5):421-430.
47. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *Am J Phys Med Rehabil*. 2001;80(5):346-350.
48. Cavers D, Hacking B, Erridge SE, Kendall M, Morris PG, Murray SA. Social, psychological and existential well-being in patients with glioma and their caregivers: a qualitative study. *CMAJ*. 2012;184(7):E373-382.
49. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol*. 2017;134(1):9-18.
50. Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol*. 2010;97(1):89-94.
51. Powell C, Guerrero D, Sardell S, et al. Somnolence syndrome in patients receiving radical radiotherapy for primary brain tumours: a prospective study. *Radiother Oncol*. 2011;100(1):131-136.
52. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. *J Natl Cancer Inst*. 2011;103(1):61-76.
53. Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. *J Nurs Scholarsh*. 2004;36(3):197-206.
54. Klein M, Postma TJ, Taphoorn MJ, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. *Neurology*. 2003;61(12):1796-1798.
55. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3(3):159-168.
56. Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. *J Neurooncol*. 2007;81(3):305-313.

57. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.
58. Correa DD, DeAngelis LM, Shi W, Thaler HT, Lin M, Abrey LE. Cognitive functions in low-grade gliomas: disease and treatment effects. *J Neurooncol.* 2007;81(2):175-184.
59. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet.* 2002;360(9343):1361-1368.
60. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery.* 2007;60(2):277-283; discussion 283-274.
61. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys.* 2007;68(5):1388-1395.
62. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol.* 2003;54(4):514-520.
63. Boele FW, Zant M, Heine EC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neurooncol Pract.* 2014;1(2):40-46.

Part II

Short- and long-term effects of
the tumor and anti-tumor treatment
on neurocognitive functioning
and health-related quality of life

2

Tumor and surgery effects on cognitive functioning in high-grade glioma patients

Acta Neurochirurgica (Wien)

2014 Aug;156(8):1451-1459.

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Abstract

Background: Many high-grade glioma (HGG) patients have cognitive impairments, which impact daily functioning. Cognitive impairments can be caused by tumor-, treatment-, and patient-related factors. The effect of the tumor and of surgical resection on cognition is, however, not well known. We investigated tumor and surgical effects on cognitive functioning in patients with HGG.

Methods: At baseline, preceding surgery 62 patients with HGG underwent neuropsychological testing concerning 7 cognitive domains: verbal and working memory, attention, executive functioning, psychomotor function, information processing speed, and visuoconstructive abilities. Thirty-nine patients were included in follow-up testing after surgery, but before subsequent treatment. Tumor size and site, use of anti-epileptic drugs and corticosteroids, and extent of resection were recorded.

Results: Compared to healthy controls, cognitive functioning of patients was significantly impaired in all domains. Prior to surgery 79% (49 of 62) of patients had cognitive impairment in at least one domain. At median follow-up of 5 weeks after surgery, 59% (23 of 39) of patients were cognitively impaired in at least one domain. At follow-up, 49% showed improvement, while 23% declined. Left hemisphere tumor localization was associated with worse verbal memory ($p = 0.004$), and larger tumors in this hemisphere with poorer executive functioning ($p < 0.001$). Changes in cognitive performance at follow-up relative to baseline were not related to tumor characteristics or extent of resection.

Conclusions: Tumor-related cognitive deficits are present in a majority of HGG patients preceding surgery. Surgery does not result in cognitive deterioration in the short term in most patients.

Introduction

Patients with gliomas often experience subjective and objective limitations in cognitive functioning.^{1,2} Cognitive impairment can negatively influence daily functioning,³ and might compromise patients' and partners' health-related quality of life.⁴ Cognitive deficits in high-grade glioma (HGG) may be initially overshadowed by pronounced neurological deficits,⁵ while rapid tumor growth might cause more cognitive deficits than slowly growing tumors.⁶ As patients with glioma still cannot be cured, and median survival for patients with HGG (glioblastoma multiforme (GBM) and anaplastic glioma) ranges from 15-37 months,^{7,8} an important outcome measure of treatment is preservation of cognitive functions.

Cognitive functioning in HGG patients is influenced by factors related to the patient, the tumor and its treatment.^{1,2,9} A tumor may cause cognitive deficits by invasion of healthy brain tissue, or by compression due to edema surrounding the tumor, cyst formation, or hydrocephalus. However, data on the sole impact of an HGG on cognition are scarce,^{5,10-12} mainly because cognitive functioning in these patients has primarily been studied following surgery. But, in the postoperative stage, tumor, surgery, and medication effects on cognition cannot clearly be distinguished. Following surgery, the vast majority of HGG patients have cognitive deficits.¹³ Tumor location and volume have been related to cognitive deficits.^{4-6,14,15} Disease progression has been associated with cognitive worsening over time.¹⁶

Resection of the tumor will most likely result in functional improvement if serious cognitive deficits exist due to a large and rapidly developing tumor mass.¹⁰ On the other hand, cognitive functioning may deteriorate due to damage to healthy brain tissue caused by the surgery. Despite the abundance of data on language (dys)function during and following resection of low-grade glioma (LGG) in the dominant hemisphere,^{17,18} and of data on resection in non-tumor related epilepsy,¹⁹ studies specifically addressing the effects of surgery on cognitive functioning in HGG patients are virtually lacking. In the few studies, with mixed outcomes, heterogeneous patient groups with only a small number of HGG were included or cognitive measures inadequate for glioma patients were used.^{10-12,20,21} Results regarding the effects of anti-epileptic drugs (AEDs) and corticosteroids on cognition in brain tumor patients other than LGG are ambiguous.^{5,14,16,22,23}

Given the impact of cognitive impairments on daily functioning and the absence of proper information on how tumor and surgery will affect cognitive functioning in HGG patients, we examined tumor and resection effects on cognition in a group of only HGG patients. With the results, neurosurgeons and neuro-oncologists can better inform patients about the consequences of tumor and surgery on cognitive functioning, while postoperative findings may guide adequate (cognitive) treatment.

Methods

Patients and procedure

Consecutive de novo adult patients planned to undergo total or subtotal tumor resection for a radiologically suspected HGG (i.e. GBM or anaplastic glioma) were recruited from the Medical Centre Haaglanden between July 2007 and December 2010. Patients were informed about the study by the neurosurgeon and the neuropsychologist, and gave informed consent to undergo repeated cognitive testing if there was a histology confirmed HGG. Exclusion criteria were (1) history of neurological or severe psychiatric disorder potentially interfering with cognitive functioning, (2) insufficient command of the Dutch language. Baseline neurocognitive assessment was carried out in the week preceding surgery and follow-up assessment at least 3 weeks following surgery, but before subsequent therapy was initiated. All participants gave informed consent.

Outcome measures

Cognitive functioning was assessed by a battery of various standardized neuropsychological tests covering the wide range of cognitive functions which can be affected in glioma patients and are sensitive for detecting changes in cognitive functioning over time.^{5,14,20} Based on previous studies and consensus in neuropsychological practice, we combined test scores into 7 cognitive domain scores (Table 1).^{20,24,25}

Performance of the patients on the tests was compared to performance data of healthy controls.²⁶ These controls were individually matched with respect to age, sex, and educational level.²⁷ For working memory and visuoconstruction, published normative data were used, corrected for age and educational level.^{28,29} Individual patients test scores were converted into standardized z-scores with use of mean and standard deviation (SD) of the matched healthy controls on that test. Domain summary measures were calculated for the patients at baseline and at follow-up.

We categorized the extent of resection into either total resection (more than 95% of tumor tissue removed) or subtotal resection (less than 95% removed), based on post-surgical MRI scan compared to pre-surgical MRI scan, or otherwise on the neurosurgeon's opinion.

Statistical analysis

According to neuropsychological practice, an individual z-score of ≥ 1.5 SD below the mean of controls was defined as a clinically significant cognitive impairment.²⁵ We defined impairment as mild if one domain was affected, moderate if two to three domains were affected, and severe if four or more domains were affected. If a z-score progressed ≥ 1.5 SD between baseline and follow-up, and the post-operative score

Table 1. Cognitive domains and tests

Domain	Test(s)
Verbal memory	Verbal learning test (first trial, total of five trials, delta score trial 5-trial 1, active delayed recall and delayed recognition) ³⁰
Working memory	Digit span forward and backward ²⁹
Executive functioning	Concept Shifting Test (condition A [numbers], B [letters], C [number-letter]); categoric word fluency test ²⁵
Psychomotor function	Concept Shifting Test (condition O) ³¹
Information processing speed	Letter digit modalities test (written) ²⁵
Attention	Stroop color word test (word condition, color condition, color-word condition and interference score) ²⁵
Visuoconstruction	Rey Complex figure test- copy ³²

felt into the normal performance range of controls, it was called clinically significant improvement. A z-score worsening of ≥ 1.5 SD, or if the post-operative score dropped to ≥ 1.5 SD below the mean of controls, was called clinically significant deterioration. In all other situations a score was defined as stable. If one domain score improved or declined between baseline and follow-up, it was called mild improvement or mild deterioration, respectively. If a score on more than one domain significantly improved or declined, it was called evident improvement or decline, respectively.

Statistical analyses were performed with SPSS. Pearson χ^2 test or Students' *t*-test for independent samples were used to compare differences in sociodemographic and clinical characteristics between patients who completed follow-up and patients who dropped out of the study. Students' *t*-test was used to analyze differences between patients and healthy controls. Wilcoxon signed-rank test for paired samples were used to analyze changes in performance between baseline and follow-up within the patient group. Possible predictors of cognitive functioning (pre-operative symptoms as epilepsy, neurological deficits and headache, tumor size, tumor location, use of corticosteroids, use of AED's, age, and amount of resection) were analyzed with Pearson χ^2 tests or logistic regression analysis. The level of significance was set at $p < 0.05$, but for the 7 cognitive domain scores, a Bonferroni correction was applied to adjust for multiple comparisons, requiring $p < 0.007$ for statistical significance.

Results

Patients' characteristics

Sixty-two of the 93 patients who underwent resection for a suspected HGG during the study period, participated at baseline preceding surgery. Of the 31 patients not included, informed consent could not be obtained in time in 22 patients (in 6 cases due to emergency operation, in 16 cases due to time constraints caused by other reasons). The remaining 9 patients declined participation because they considered testing to be too burdensome. Non-participating patients did not differ from participating patients according to age or tumor histology. Table 2 shows the sociodemographic and clinical characteristics of the patient group.

Analyses of cognitive performance were done with all patients who participated at baseline ($n = 62$). Eighteen patients (29%) could not complete more than half of the test battery. This was due to fatigue, visual or dysphasic disorder, emotional disturbances, and/or time constraints. The few patients with anaplastic glioma were significantly younger than patients with GBM ($z = -2.72$, $p = 0.004$).

At follow-up after surgery, 36 patients (58%) could be tested again with a median interval of 5 weeks. Reasons for drop-out were refusal because testing was considered too burdensome (13 patients); no further tumor treatment started due to progressive disease immediately following surgery (6 patients); tumor treatment elsewhere (4 patients); post-surgical complications including brain infarction or hemorrhage (3 patients). Because we considered post-surgical complications as an effect of the surgery, these last 3 patients were included in the follow-up analyses and were considered severely cognitively impaired. Extent of resection was based on post-operative MRI scan in 44 cases (71%). Twenty-four patients (39%) underwent a total resection (Table 2).

Patients who could not be tested post-operatively were significantly older than patients who stayed in the study ($t = 2.8$, $p = 0.007$), were more often females (χ^2 ; $p = 0.009$), and had completed fewer tests at baseline compared to patients who were also tested at follow-up ($t = -3.09$, $p = 0.003$).

Cognitive functioning in mean domain scores at baseline and follow-up

At baseline preceding surgery, mean domain z-scores of all 7 domains were significantly lower compared to healthy controls (verbal memory: $t = -4.74$, $p < 0.001$; working memory: $t = -3.11$, $p = 0.003$; attention: $t = -4.38$, $p < 0.001$; executive functioning: $t = -6.33$, $p < 0.001$; psychomotor function: $t = -3.57$, $p = 0.001$; information processing speed: $t = -5.46$, $p < 0.001$; visuoconstruction: $t = -4.66$, $p < 0.001$; Figure 1). Cognitive domain scores did not differ between patients lost to follow-up and patients who had follow-up.

Table 2. Sociodemographic and clinical characteristics of the study patients

	baseline, pre-surgery (n = 62)	with follow-up post- surgery (n = 39)	without follow- up post-surgery (n = 23)
Age ¹ ; mean ± SD	60.6 ± 12.5	57.8 ± 12.7*	66.6 ± 10.5*
Sex; Male / Female	38 (61%) / 24 (39%)	29 (74%) / 10 (26%)*	9 (39%) / 14 (61%)*
Educational level ² ; mean ± SD	3.7 ± 2.2	4.2 ± 2.3*	2.7 ± 1.6*
Tumor histology			
GBM	57 (92%)	34	23
Anaplastic glioma (AO, O)	5 (8%)	5	0
Tumor localization			
Left / Right	28 (45%) / 34 (55%)	19 (49%) / 20 (51%)	9 (39%) / 14 (61%)
Left frontal	12	10	2
Left frontoparietal	2	1	1
Left temporo(occipital)	5	3	2
Left parietal	1	0	1
Left parietooccipital	5	3	2
Left parietotemporal	3	2	1
Right frontal	6	4	2
Right frontoparietal	1	1	0
Right temporal	12	7	5
Right temporoinsular	1	1	0
Right parietal	5	2	3
Right parietooccipital	7	3	4
Right parietotemporal	2	2	0
Tumor size ³			
Overall mean ±SD/ median	51.5 ± 18.1/52	52.0 ± 20.2/52	50.6 ± 14/53
Left mean ± SD / median	45.6 ± 18.2*/44	46.2 ± 20.5/42	44.4 ± 13.2/45
Right mean ± SD / median	56.3 ± 16.7*/56	57.6 ± 18.8/56	54.6 ± 13.5/56
Symptoms prior to surgery			
Epilepsy	31 (50%)		
Neurological deficits	30 (48%)		
Headache	19 (31%)		
Use of AEDs			
At baseline	34 (55%)	18	16
At follow-up		30 (77%)	
Use of corticosteroids			
At baseline	40 (65%)	20	20
At follow-up		12 (31%)	
Interval baseline and surgery ⁴ ;			
Mean ± SD/median / Range	4 ± 7.9/1 / 1-49		
Test interval (baseline vs. follow-up) ⁴ ;			
Mean ± SD / median		38.4 ± 13.4 / 36	
Range		20-91	
Extent of resection			
Subtotal (<95%)		22 (56%)	14 (61%)
Total (>95%)		15 (39%)	9 (39%)
Unknown		2 (5%)	
Number of tests completed; mean ± SD			
At baseline/ at follow-up	4.6 ± 2/-	5.18 ± 2*/5.6 ± 1.8	3.7 ± 1.5*/-

¹ Years; ² Code 1-8²⁷; ³ Largest diameter in mm on MRI T1 with contrast; ⁴ Days; * significant difference ($p < 0.05$)

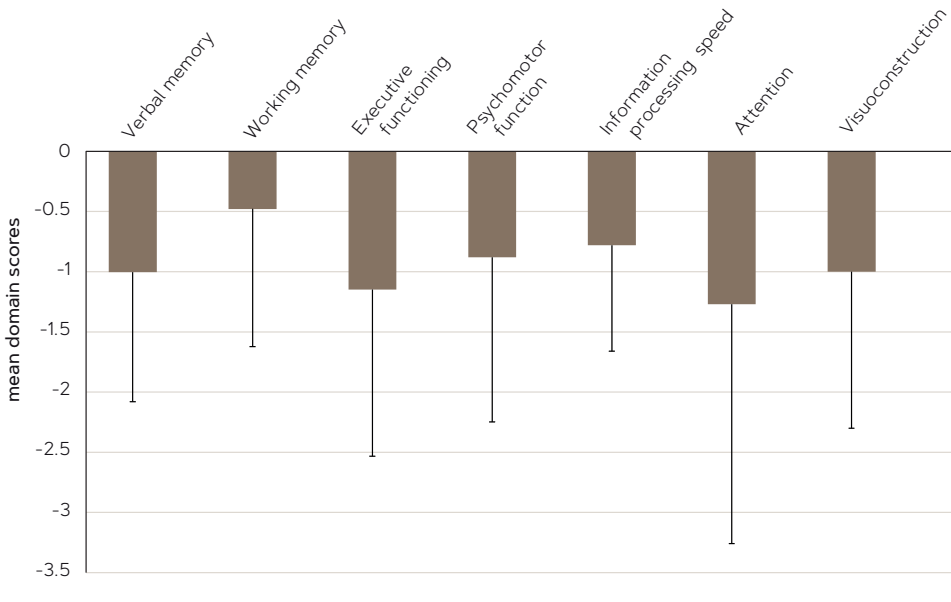


Figure 1. Mean z-scores (SD) of the patients for each cognitive domain at baseline. The patients’ performance is compared to age-, sex-, and education-matched healthy controls (represented by the 0 line). A score closer to 0 means a better performance. All mean domain scores of patients are significantly lower compared to healthy controls ($p < 0.005$)

To evaluate changes in cognitive functioning after surgery, only patients with cognitive domain scores both at baseline and follow-up were included in this analysis ($n = 39$). Individual trajectories and mean group scores on each of the 7 domains at baseline and follow-up are depicted in Figure 2. At the group level, significant improvement was observed in information processing speed ($z = 2.98$, $p = 0.003$) and visuoconstruction ($z = 3.19$, $p = 0.001$).

Cognitive functioning in percentages at baseline and follow-up

At baseline, 79% (49 of 62 patients) showed impairment in at least one cognitive domain, while 21% were not impaired. Thirty-five percent of patients had mild, 34% moderate, and 10% severe impairment (22, 21 and 6 patients, respectively). Of the 39 patients who were included in follow-up after surgery, preceding surgery 20% (8 patients) were not cognitively impaired, 36% (14 patients) were mildly, 31% (12 patients) were moderately and 13% (5 patients) were severely impaired. Verbal memory and attention were the domains most frequently impaired (Figure 3). At follow-up, 59% (23 of 39 patients) had impairment in at least one cognitive domain, while no impairment was observed in 41%. Impairment was mild in 33%, and moderate or severe in 13% of patients (13, 5 and 5 patients, respectively). Psychomotor function was the most frequently impaired domain (Figure 3).

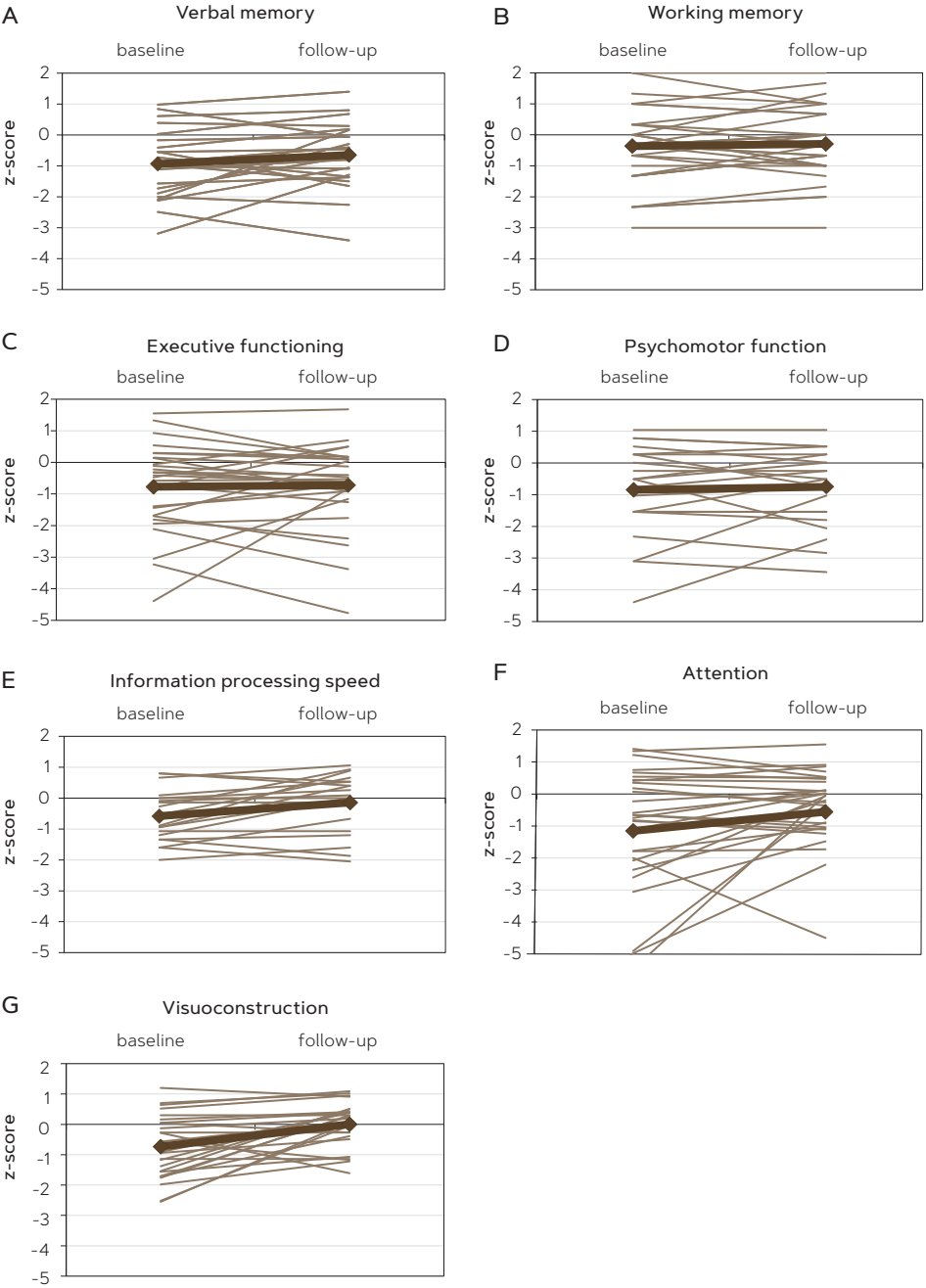


Figure 2. Mean group z-scores (represented by the dark brown line) and individual patient z-scores (represented by the light brown lines) at baseline and follow-up for each of the 7 cognitive domains. Patients' scores are compared to age-, sex- and education-matched healthy controls, represented by the 0 line. A higher score means better performance

Cognition at individual level: changes between baseline and follow-up

Individual patient scores on the cognitive domains at baseline and follow-up are depicted in Figure 2. In the 39 patients included, we observed clinically significant improvement between baseline and follow-up primarily in the domains of visuoconstruction (24%; 7 of 29 patients), verbal memory (21%; 6 of 29 patients) and attention (18%; 6 of 33 patients). In the other domains, only few patients improved significantly. Clinically significant decline was observed mainly in verbal memory in 17% (5 of 29 patients), in attention in 15% (5 of 33 patients), and in psychomotor function in 15% (4 of 27 patients). In the other domains, few patients deteriorated significantly. Taken all 7 domains together, 49% of patients showed improvement, with 36% (14 of 39 patients) showing mild improvement and 13% (5 of 39 patients) showing evident improvement. Ten percent had mild, and 13% had evident deterioration (4 and 5 patients, respectively).

Predictors of cognitive functioning at baseline and follow-up

Tumors in the dominant hemisphere were smaller than those in the non-dominant hemisphere ($t = -2.41$, $p = 0.019$). Also after taking tumor size as a covariate in the comparison for hemispheric tumor location, patients with tumors in the left hemisphere had significantly poorer baseline verbal memory ($F = 10.08$, $p = 0.004$) and tended to have worse working memory ($F = 7.28$, $p = 0.009$) and attention ($F = 5.15$, $p = 0.028$) than patients with tumors in the right hemisphere. For patients with left hemispheric tumors, a larger tumor was a predictor of significantly poorer baseline executive ($t = -4.09$, $p < 0.001$) and a trend towards slower psychomotor functioning ($t = -3.1$, $p = 0.008$). For patients with right hemispheric tumors, tumor size was not related to cognitive functioning.

Because of small subgroups, no statistical analyses on the association between precise tumor location and cognitive domain scores could be performed. Exploratory analyses only showed that for both hemispheres, non-frontal tumors tended to be associated with worse visuoconstructive abilities compared to frontally located tumors.

Patients on corticosteroids had worse baseline attention ($t = 3.23$, $p = 0.002$) and executive functioning ($t = 2.83$, $p = 0.006$) and lower information processing speed ($t = 3.02$, $p = 0.003$) than patients not using corticosteroids. Use of AEDs and pre-operative symptoms were not predictors of cognitive functioning.

At follow-up after surgery, patients who showed improvement were compared to patients who did not improve (stable or decline). No factors (including age, pre-operative epilepsy, headache and neurological deficits, tumor site, tumor size, and amount of tumor resected) could be identified as predictors of improvement of cognitive performance. Because of the small number of patients deteriorating ($n = 9$), no statistical analysis could be performed to detect possible predictors of deterioration (versus stable or improved cognition). Descriptive analyses showed that

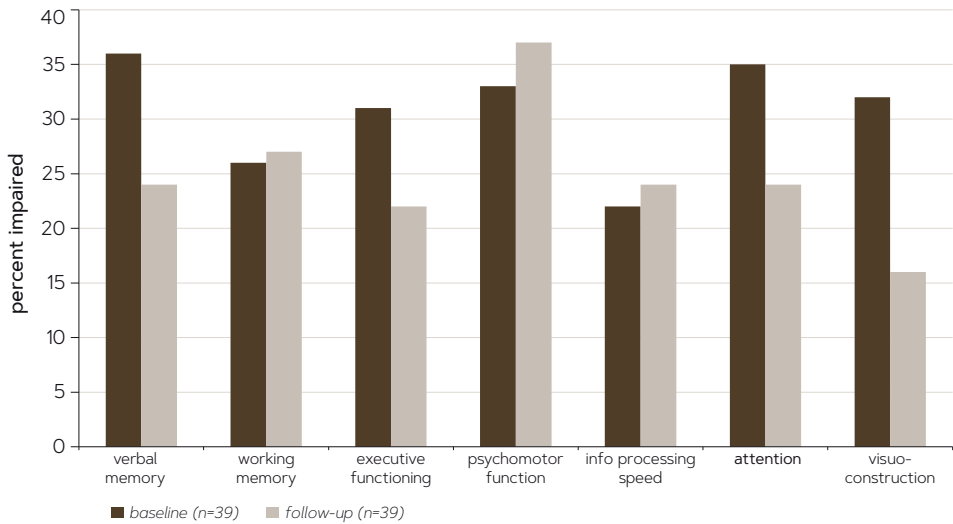


Figure 3. Percentage of patients with impairment at baseline and follow-up for each cognitive domain

pre-operative epilepsy was correlated with deterioration (χ^2 ; $p = 0.032$), while older age showed a non-significant correlation with deterioration. With exploratory analysis, we did not find an association between precise tumor location and improvement or decline.

Despite improvement following surgery, patients with left hemispheric tumors tended to remain performing worse than patients with right hemispheric tumors in executive functioning ($F = 5.98$, $p = 0.021$) and attention ($F = 5.51$, $p = 0.026$) after surgery, but differences were not significant.

Discussion

We prospectively investigated the influence of tumor and tumor resection on cognitive functioning in HGG patients. Not unexpectedly, the majority of the HGG patients had cognitive impairments preceding surgical treatment, particularly caused by the tumor itself.

To our knowledge, this is the first study to evaluate pre- and post-operative cognitive functioning in a patient sample of only HGG. In previous research including various types of brain tumor patients, the percentage of patients with cognitive impairments preceding surgery varied from 30% to 91%, with memory and executive functioning as the most frequently affected domains.^{5,10,11,21} This large variation can partly be explained by differences in patient sample and methodology.

Even after correcting for the smaller tumor size in the dominant hemisphere, we found a correlation between cognitive functioning and tumor site, in line with earlier research.^{4,12,14,15} Tumor size was related to baseline cognition only for left hemisphere location, probably reflecting that cognitive testing is mainly influenced by dominant hemisphere functioning. As to medication, the use of corticosteroids was related to worse baseline cognitive functioning, which may be due to more mass effect in these patients, also beyond tumor size. In earlier studies, use of AEDs has been related to a negative effect on working memory, psychomotor speed and executive functioning in HGG patients,^{14,16} although a positive effect was found for verbal memory.²³ We, and others,⁵ did not find an effect of AEDs on baseline cognition, perhaps because our patients had only recently started AEDs.

Following surgery, nearly half of our patients showed cognitive improvement, while 23% of patients declined, partly due to post-surgical complications. Most changes were seen in verbal memory and attention, while domains related to speed tended to be vulnerable for decline. Fifty-nine percent of our studied patients had some cognitive impairment post-operatively. In previous research, 38% of LGG and HGG patients were found to be impaired shortly after surgery,¹⁰ while in a small sample of post-operative GBM patients as much as 89% had cognitive deficits, also including patients with biopsies.¹³ The effect of tumor resection on cognition in HGG patients has only sporadically been studied before, with results varying from generally no change,¹² to a subtle decline,^{11,21} to improvement of some cognitive functions.^{10,33} In some of these studies, a subgroup of patients received chemotherapy or radiotherapy before follow-up assessment,^{11,21} which may have affected cognition as well.²

Unfortunately, we could not identify possible predictors of cognitive improvement after surgery. Perhaps this is due to the relatively small patient sample included in the post-surgery analysis. Earlier results regarding the influences of extent of resection, tumor location and tumor size on changes in cognitive functioning after surgery compared to pre-operative performance were mixed.^{10,21} We found pre-operative epilepsy to be correlated with post-operative cognitive deterioration. Although negative effects of epilepsy and use of AEDs have been observed in glioma patients,^{16,34} it remains speculative if the cognitive decline post-operatively is due to anti-epileptic medication. The finding that patients with left hemispheric tumors in our sample, despite improvement after resection, did not reach the level of right hemispheric tumor patients for attention and executive functioning, might be an advocate for developing intraoperative monitoring of these cognitive functions during awake surgery.³⁵

Regarding our study, we tested many patients the day before surgery. This design could have resulted in an overestimation of cognitive deficits, because some patients might have been so preoccupied with the upcoming surgery, that concentrating on the tests was difficult. On the other hand, patients in whom complete assessment was too burdensome would likely have shown deficits in the non-evaluated cognitive

domains. The exclusion of patients who only had biopsies may have added to an underestimation of cognitive deficits on presentation, since biopsy is the preferred method for large, deeply and/or eloquently located tumors.

Clearly, there may be a bias towards improved cognition in our postoperative results. Only 58% of patients could be tested following surgery. In other surgery studies on gliomas, drop-out was reported less frequently, perhaps related to the malignancy of the tumor.^{10,11} A selection bias might exist towards a larger percentage of follow-up data in better functioning patients. Also, in patients who refused to be tested again and in patients who deteriorated rapidly following surgery due to progressive tumor growth, cognitive functioning must have declined compared to baseline level. Nonetheless, patients without baseline data due to severe cognitive dysfunction and improving postoperatively, were also not included in our study. It is difficult, however, to overcome these limitations in patients diagnosed with malignant brain tumors. Although parallel versions of the cognitive tests were applied, practice effects due to the relatively short test interval cannot be ruled out completely. On the other hand, transient post-surgical neurological deficits and fatigue may have negatively affected cognition apart from surgery. Furthermore, anxiety and depression, which were observed in some glioma patients,^{10,36} were not systematically investigated.

In conclusion, the results of our study emphasize the need to be aware of frequently occurring cognitive deficits already present early in the disease course of HGG. Although resective surgery appears to be a safe treatment in terms of cognitive functioning, still many patients have cognitive impairments following surgery. Adequate information, counseling and (cognitive) rehabilitation programs should, therefore, be integrated early in the disease course. More research with larger sample sizes is needed to detect which patients benefit the most from resection. With baseline measurements, changes in cognitive functioning in the course of disease or further treatment can be more easily related to the cause, thereby optimizing future treatment decisions.

References

1. Kayl AE, Meyers CA. Does brain tumor histology influence cognitive function? *Neuro Oncol.* 2003;5(4):255-260.
2. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3(3):159-168.
3. Weitzner MA, Meyers CA, Byrne K. Psychosocial functioning and quality of life in patients with primary brain tumors. *J Neurosurg.* 1996;84(1):29-34.
4. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC. Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *Int J Radiat Oncol Biol Phys.* 2003;55(4):992-999.
5. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery.* 2000;47(2):324-333.
6. Hom J, Reitan RM. Neuropsychological correlates of rapidly vs. slowly growing intrinsic cerebral neoplasms. *J Clin Neuropsychol.* 1984;6(3):309-324.
7. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10(5):459-466.
8. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013;31(3):344-350.
9. Kaleita TA, Wellisch DK, Cloughesy TF, et al. Prediction of neurocognitive outcome in adult brain tumor patients. *J Neurooncol.* 2004;67(1-2):245-253.
10. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.
11. Wu AS, Witgert ME, Lang FF, et al. Neurocognitive function before and after surgery for insular gliomas. *J Neurosurg.* 2011;115(6):1115-1125.
12. Yoshii Y, Tominaga D, Sugimoto K, et al. Cognitive function of patients with brain tumor in pre- and postoperative stage. *Surg Neurol.* 2008;69(1):51-61.
13. Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol.* 2010;97(1):89-94.
14. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol.* 2001;19(20):4037-4047.
15. Scheibel RS, Meyers CA, Levin VA. Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment. *J Neurooncol.* 1996;30(1):61-69.
16. Bosma I, Vos MJ, Heimans JJ, et al. The course of neurocognitive functioning in high-grade glioma patients. *Neuro Oncol.* 2007;9(1):53-62.
17. Duffau H, Capelle L, Denvil D, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry.* 2003; 74(7):901-907.
18. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med.* 2008;358(1):18-27.
19. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol.* 2012;108(2):309-318.
20. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP,

- Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning*. New York: Psychology Press, Inc.; 2003:159-173.
21. Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A. Cognitive functioning early after surgery of gliomas in eloquent areas. *J Neurosurg*. 2012;117(5):831-838.
 22. Brown ES, Chandler PA. Mood and Cognitive Changes During Systemic Corticosteroid Therapy. *Prim Care Companion J Clin Psychiatry*. 2001;3(1):17-21.
 23. De Groot M, Douw L, Sizoo EM, et al. Levetiracetam improves verbal memory in high-grade glioma patients. *Neuro Oncol*. 2013;15(2):216-223.
 24. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol*. 2009;8(9):810-818.
 25. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4. New York: Oxford University Press; 2004.
 26. Jolles J, Van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr*. 1998;29(3):120-129.
 27. De Bie SE. [Proposal for uniformisation of questions regarding background variables and interviews]. Leiden: Leiden University Press; 1987.
 28. Fastenau PS, Denburg NL, Hufford BJ. Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol*. 1999;13(1):30-47.
 29. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual]*. Lisse 2000.
 30. Schmand B, Lindeboom J, Van Harskamp F. [The 15 words test A and B (a preliminary manual)]. Groningen: Afdeling Neuropsychologie, AZG; 1992.
 31. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess*. 2006;18(4):424-432.
 32. Osterreith PA. Le test de copie d'une figure complexe [A test regarding a complex figure]. *Archives de Psychologie/ The Clinical Neuropsychologist*. 1944;30/ 7:206/ 209-356/ 215.
 33. Santini B, Talacchi A, Squintani G, Casagrande F, Capasso R, Miceli G. Cognitive outcome after awake surgery for tumors in language areas. *J Neurooncol*. 2012;108:319-326.
 34. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol*. 2003;54(4):514-520.
 35. Klein M, De Witt Hamer PC. Neurocognitive outcome and resective brain tumor surgery in adults. In: Duffau H, ed. *Brain mapping: from neural basis of cognition to surgical applications*. Vol 1. New York; 2011.
 36. Pringle AM, Taylor R, Whittle IR. Anxiety and depression in patients with an intracranial neoplasm before and after tumour surgery. *Br J Neurosurg*. 1999;13(1):46-51.

3

Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: *a prospective study*

Neuro Oncology

2016 Mar;18(3):435-444.

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Abstract

Background: Stereotactic radiotherapy (SRT) is expected to have a less detrimental effect on neurocognitive functioning and health-related quality of life (HRQoL) than whole-brain radiotherapy. To evaluate the impact of brain metastases and SRT on neurocognitive functioning and HRQoL, we performed a prospective study.

Methods: Neurocognitive functioning and HRQoL of 97 patients with brain metastases were measured before SRT and 1, 3 and 6 months after SRT. Seven cognitive domains were assessed. HRQoL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and BN20 questionnaires. Neurocognitive functioning and HRQoL over time were analyzed with linear mixed models and stratified for baseline Karnofsky Performance Status (KPS), total metastatic volume, and systemic disease.

Results: Median overall survival of patients was 7.7 months. Before SRT, neurocognitive domain and HRQoL scores were lower in patients than in healthy controls. At group level, patients worsened in physical functioning and fatigue at 6 months, while other outcome parameters of HRQoL and cognition remained stable. KPS <90 and tumor volume >12.6 cm³ were both associated with worse information processing speed and lower HRQoL scores over 6 months time. Intracranial tumor progression was associated with worsening of executive functioning and motor function.

Conclusions: Prior to SRT, neurocognitive functioning and HRQoL are moderately impaired in patients with brain metastases. Lower baseline KPS and larger tumor volume are associated with worse functioning. Over time, SRT does not have an additional detrimental effect on neurocognitive functioning and HRQoL, suggesting that SRT may be preferred over whole-brain radiotherapy.

Introduction

Brain metastases are the most common type of brain cancer and develop in 9%–45% of patients with systemic cancer.^{1,2} Neurocognitive deficits, impaired health-related quality of life (HRQoL) and fatigue are often present in patients with brain metastases and can be caused by the metastasis itself, anti-tumor treatment, or supportive medication.^{3–6} Median survival of brain metastatic patients ranges considerably, from 2.6 to 15 months, depending on age and condition of the patient, primary tumor, and treatment.^{7,8} Also, due to improved treatments for primary tumors, specific patient groups survive longer.^{8,9} However, most patients with brain metastases cannot be cured. Therefore, preservation of neurocognitive functioning and HRQoL for maintaining daily functioning is important.

In recent years, treatment with stereotactic radiosurgery and stereotactic radiotherapy (SRT) as an alternative or addition to whole-brain radiotherapy (WBRT) has gained interest, especially in patients with 1–3 small brain metastases and relatively good prognosis.¹⁰ Because in SRT a high dose of focal irradiation is delivered to the tumor, while irradiation to healthy brain tissue is minimized, it is expected to have fewer (long-term) side effects on cognition and functional outcome than WBRT,^{11,12} while overall survival (OS) is comparable.^{13,14} Conversely, tumor control outside the initial site has been found to be worse in patients treated with SRT alone compared to SRT combined with WBRT,¹⁴ with brain tumor recurrence probably resulting in cognitive deterioration.^{15,16}

Up to now, data on the impact of SRT on neurocognitive functioning and HRQoL have been scarce. Previous studies suggest some (transitory) decline in neurocognitive functioning and an increase in self-reported cognitive dysfunction in the months after SRT.^{5,16,17} HRQoL scores after radiotherapy, including SRT, may further deteriorate, stabilize or improve.^{6,18–20} However, small patient samples, the use of inappropriate measurement tools, the absence of preradiation treatment assessment, and short follow-up periods hamper the interpretation of results and subsequently limit their ability to inform clinical decision making.

As preservation of neurocognitive functioning and HRQoL in patients treated with SRT is essential, we set out to investigate the impact of SRT on these outcomes prospectively in a cohort of patients with 1–3 brain metastases. In addition, we investigated the impact of several other factors that could potentially influence neurocognitive functioning and HRQoL in these patients.

Materials and methods

Patients and procedure

Consecutive adult patients scheduled to undergo SRT for 1-3 brain metastases, with a maximum diameter of 4 cm per metastasis, were recruited in the Medical Center Haaglanden, a tertiary hospital in The Hague, the Netherlands, between January 2009 and February 2012. Exclusion criteria were: prior treatment of brain metastases, including resection, Karnofsky Performance Status (KPS) <70, and insufficient command of the Dutch language. Baseline assessment was carried out in the week preceding SRT, and follow-up assessments took place 1 month (only HRQoL) and 3 and 6 months after SRT. The study protocol was approved by the medical ethics committee of the institution. All patients gave written informed consent.

Treatment and follow-up schedule

In all patients, the gross tumor volume was contoured on a T1-weighted contrast-enhanced MRI, the clinical target volume was equal to the gross tumor volume, and the planning target volume (PTV) was created by 3D expansion of the clinical target volume with 2 mm. Metastases with PTV <8 cm³ received 21 Gy and metastases with PTV of 8-13 cm³ received 18 Gy, both in a single fraction, whereas metastases with PTV > 13 cm³ and metastases near the brainstem were given 24 Gy in 3 fractions of 8 Gy. From 1 day prior to SRT to 7 days after SRT, patients received corticosteroids (dexamethasone 16 mg/d), which were gradually discontinued afterward.

Follow-up MRI scans were made 1, 3 and 6 months after treatment. As for brain metastases no standard criteria are available for defining response to treatment,²¹ we used the criteria of Lin et al.²² Partial response was defined as ≥50% reduction in the total volumetric sum of contrast-enhancing lesions, and intracranial progression as ≥40% increase in the total sum of enhancement of tumor volume, or the presence of any new contrast-enhancing lesions visible on MRI.²² In case of progressive disease during the study period, patients stayed in the study provided they underwent renewed SRT. Patients treated with WBRT because of progression, or with no further tumor treatment, were no longer assessed.

Neurocognitive functioning

Neurocognitive functioning was assessed with a comprehensive test battery consisting of validated neuropsychological tests covering a wide range of neurocognitive functions found to be affected in brain tumor patients and sensitive to subtle changes over time^{23-25, 47-51} (Supplementary Table 1). Test scores were combined into 7 compound neurocognitive domain scores: verbal memory, visual memory, working memory, attention, information processing speed, executive functioning, and visuoconstructive abilities. Patients' performances on verbal memory, attention,

information processing speed, and executive functioning were compared with healthy controls,^{26,27} who were individually matched to the patients with respect to age, sex and educational level.²⁸ For working memory, visuoconstruction, and visual memory, published norms were used,^{29,30} correcting for age and education. Individual test scores of patients were converted into standardized z-scores with use of means and standard deviations of controls on that test. We calculated domain summary scores at each assessment.

Health-related quality of life

We assessed HRQoL with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the EORTC QLQ-Brain Cancer Module (QLQ-BN20).^{31,32} The EORTC QLQ-C30 is a generic questionnaire, while the QLQ-BN20 assesses issues relevant for brain cancer patients. Both questionnaires showed good psychometric properties. Scores were transformed into standardized scores ranging from 0 to 100. For global health status/QoL and functional scales, a higher score means better HRQoL. For symptom scales and BN20 scales, a higher score indicates more symptoms. Based on functions previously found to be relevant for brain metastatic patients,¹⁸ we selected 7 HRQoL scales for the primary analysis, including global health status/QoL; physical functioning; role functioning; emotional functioning; self-perceived cognitive functioning; motor dysfunction; and communication deficits. The remaining HRQoL scales were analyzed on an exploratory basis. Scores on the QLQ-C30 were compared with reference data.³³ Fatigue was assessed with the Fatigue Severity Scale,³⁴ including questions on the occurrence and severity of fatigue, and its impact on daily life. The total score ranges between 1 and 7, with a score of ≥ 4 indicating moderate to severe fatigue.³⁵

Statistical analysis

For each cognitive domain, we considered an individual z-score of ≥ 1.5 SD below the mean of healthy controls as clinical significant impairment.²³ Differences in sociodemographic and clinical characteristics between patients who completed follow-up and patients who dropped out were tested using the χ^2 test for categorical data and Students' t-tests or Mann-Whitney U-test for continuous data, depending on the distribution of the tested variable. Overall survival was analyzed with Kaplan-Meier curves, and log-rank tests were used to assess differences in survival between patients with different numbers of metastases (1 vs >1), tumor volume (based on the total volume of the contrast enhancement of all metastases on MRI scan and categorized into large [>12.6 cm³], medium [4.8 - 12.6 cm³] and small [<4.8 cm³]), and baseline KPS. In line with previous studies on brain metastases,^{4,36} we compared patients with KPS <90 with those with KPS ≥ 90 . Linear mixed models were used to analyze neurocognitive functioning and HRQoL

over time (unadjusted for possible confounders), as well as separately for patients categorized into high (≥ 90) and low (< 90) baseline KPS, tumor volume (large/medium/small), and presence of active systemic disease. In linear mixed models, contrary to a complete-case analysis, data of all patients at each time point are included in the analysis by imputation of missing data. This sophisticated method of multiple imputation depends on fitting a specific covariance structure, which assesses the correlations among the different measurements at different time points.

The influence of treatment response was analyzed by comparing (i) the difference between the neurocognitive and HRQoL scores at time of progression and the patient's own baseline score with (ii) the difference scores of patients without progressive disease, using an independent samples *t*-test. Statistical analyses were performed with SPSS version 20.0 software. The level of significance was set at $p < 0.05$.

Results

Patient characteristics and survival

Baseline sociodemographic and clinical characteristics of the study population are presented in Table 1. Ninety-seven patients (mean age, 63 ± 11 y) were included prior to SRT treatment. The most frequent primary tumor site was lung (50%). In 19 patients (20%) brain metastases were the first presentation of cancer. In 5 patients, the planning MRI scan showed a fourth metastasis, which was in all cases small (< 0.5 cm³). Despite this fourth metastasis, we included these patients in our study.

Median OS was 7.7 months (inter quartile range: 8.1). One-year survival rate was 30%. Median OS was significantly shorter for patients with baseline KPS < 90 compared with KPS ≥ 90 (5.3 vs 11.1 mo, $p = 0.003$) (Supplementary Figure 1) and for patients with large compared with medium or small tumor volume (4.5 vs 10.4 vs 7.7 mo, $p = 0.042$). Number of brain metastases and active systemic disease at baseline were not associated with survival (5.5 mo for 1 metastasis vs 8.2 mo for > 1 metastases, $p = 0.437$; 8 mo for no active systemic disease vs 7.2 mo for systemic disease, $p = 0.737$).

During follow-up, intracranial progression was observed in 47/90 evaluable patients (52%), in 27 patients solely due to new enhancing lesions without increment in initial tumor volume. Seventeen of 47 patients (36%) had progression at more than one follow-up moment. For progression, 13 patients were treated with WBRT and 7 with renewed SRT. Reasons for no salvage therapy being initiated were poor physical condition, progressive systemic disease, and the consideration of intracranial progression to be the result of radiation (i.e. pseudoprogression).

Table 1. Sociodemographic and baseline clinical characteristics of the study patients

	No. of patients	% of patients
No. of patients included	97	
Age; mean $\pm$ SD / range	63 $\pm$ 11 / 33-82	
Sex; male	46	47
Educational level ^a ; mean $\pm$ SD	3.1 $\pm$ 1.7	
Number of brain metastases		
1	43	44
2	31	32
3	18	19
4	5	5
Total tumor volume by patient, cm ³		
Median (range)	7.8 (0.12-63.9)	
Tertiles	< 4.8 / 4.8-12.6 / >12.6	
Primary cancer		
Non-small cell lung	48	50
Renal cell carcinoma	12	13
Melanoma	9	9
Colorectal	9	9
Breast cancer	8	8
Other	11	11
Active systemic disease	52	54
Chemotherapy treatment (<3 months of baseline)	13	13
Extra cranial metastases	54	56
Use of corticosteroids	85	88
Use of AEDs	21	22
KPS		
Median (range)	80 (60-100)	
KPS $\geq$ 90	35	36

^aLevel 1-8²⁸

Twenty-five out of 90 patients (28%) had at least a radiologically partial response ($\geq 50\%$ decrease in total tumor volume). Active systemic disease was present in 52/97 (54%) at baseline, in 52/84 (62%) at 1 month, in 42/70 (60%) at 3 months, and in 27/45 patients (60%) at 6 months. Of the patients with systemic disease, between 25% (13/52, at baseline) and 52% (27/52, at 1 mo; 22/42, at 3 mo; and 14/27, at 6 mo) received chemotherapy. Patients with systemic disease at baseline did not significantly differ from patients without systemic disease according to age, KPS or tumor volume. Use of corticosteroids declined during the study period: from 91% at baseline to 56% at 1 month, 44% at 3 months, and 36% at 6 months. Because of the occurrence of one or more epileptic seizures, about 25% of patients received prophylactic anti-epileptic drugs (AEDs) on daily dosage during follow-up.

Compliance

Compliance during follow-up was at least 70% for HRQoL and 53% for neurocognitive assessments (Table 2). Reasons for noncompliance were poor neurological or physical condition, refusal because testing was considered too burdensome, and time constraints. At all measurements, no statistically significant differences between patients alive who did and who did not complete assessments were found for median KPS or age.

Neurocognitive functioning

Baseline

Preceding SRT, 53% of patients had an impairment in at least one neurocognitive domain. The most frequently affected domains were verbal memory (33%) and visuoconstruction (22%). Neurocognitive domain scores of patients were significantly worse compared with healthy controls for verbal memory, attention, working memory, executive functioning, and visuoconstruction (Table 3). KPS < 90 compared with KPS ≥ 90 was associated with worse executive functioning (mean z-score -0.81 vs -0.13 , $p = 0.002$), information processing speed (mean z-score -0.57 vs 0.38 , $p = 0.015$), and working memory (mean z-score -0.7 vs -0.27 ; $p = 0.054$). Patients with large volumes, compared with small or medium volumes, showed a trend towards worse verbal memory (mean z-score -0.79 vs -0.62 vs -1.5 respectively, $p = 0.077$) and information processing speed (mean z-score 0.02 vs 0.24 vs -0.82 , $p = 0.069$). The number of brain metastases, presence of active systemic disease, or use of AEDs was not associated with baseline neurocognitive functioning (data not shown).

Over time

Over 6 months time, neurocognitive domain scores did not significantly change (Figure 1). Verbal memory showed a nonsignificant trend toward improvement (mean change 0.42 , $p = 0.084$). Compared with patients with baseline KPS ≥ 90 , patients with

Table 2. Compliance with neurocognitive and HRQoL assessments

	No. of forms / assessments expected ^a	No. of forms received / assessments performed	
		Neurocognition	HRQoL
Baseline	97	77 (79%)	95 (98%)
1 month	90	-	75 (83%)
3 months	73	39 (53%)	51 (70%)
6 months	49	29 (59%)	41 (84%)

^a Based on alive participating patients

KPS <90 had worse information processing speed (mean -0.6 vs 0.5, $p = 0.002$) and executive functioning (mean -0.76 vs -0.08, $p = 0.003$) over time. Large tumor volume compared with small or medium volumes was associated with worse information processing speed (mean -1.1 vs 0.2 vs 0.3, $p = 0.02$). Surprisingly, patients without systemic disease had worse information processing speed (mean -0.4 vs 0.06, $p = 0.03$) and visuoconstructive abilities (mean -0.78 vs -0.23, $p = 0.037$) over time than patients with active systemic disease, while on other domains no differences were found. Use of corticosteroids did not influence neurocognitive functioning.

Progression

An association between neurocognitive functioning and intracranial changes was found only for executive functioning; patients who had radiological partial response improved, while patients with stable or progressive disease deteriorated (mean 0.43 vs -0.29, $p = .032$). Other neurocognitive domain scores did not differ between patients with or without progressive disease.

Health-related quality of life

Baseline

Compared with the general population,³³ scores on all preselected HRQoL scales were significantly lower in patients at baseline, with lowest scores in role functioning. All differences were clinically relevant. Baseline HRQoL scores were significantly lower in patients with KPS <90 compared with KPS ≥90 (Table 4). Similar results were found for exploratory HRQoL items (Supplementary Table 2). Presence of active systemic disease did not result in lower HRQoL scores, indeed physical functioning and global health status/QoL were even higher than in patients without systemic disease (mean 76 vs 61, $p = 0.008$ and 72 vs 62, $p = 0.038$, respectively). Tumor volume and number of metastases did not affect baseline HRQoL (data not shown).

Over time

At group level, patients worsened significantly and clinically in physical functioning (mean change -14, $p = 0.027$) and fatigue (mean change 0.93, $p = 0.009$) over 6 months time, while other HRQoL scales did not change significantly (Figure 2). Mean HRQoL scores over time were significantly lower for patients with baseline KPS <90 compared with patients with KPS ≥ 90 for physical (54 vs 74, $P < 0.001$), self-perceived cognitive (75 vs 85, $p = 0.029$) and role functioning (46 vs 70, $p < 0.001$), motor dysfunction (21 vs 9, $p = 0.006$) and fatigue (37 vs 29, $p = 0.015$). Large tumor volume resulted in lower mean scores of physical (48 vs 66 vs 70 for large, medium and small volumes respectively; both $p < 0.05$) and self-perceived cognitive functioning (70 vs 84 for large and medium volumes, $p = 0.045$, 78 for small volumes) over time. Number of metastases and baseline systemic disease did not influence HRQoL scores of the preselected scales over time.

Exploratory analyses (Supplementary Table 3) showed that at group level, patients experienced significantly more nausea and appetite loss and were more bothered by hair loss over time. Patients with KPS <90 had more fatigue, pain, visual disorders, and drowsiness than patients with KPS ≥ 90 . The presence of systemic disease was associated with more nausea and appetite loss (mean scores, nausea: 10 vs 5.9, $p = 0.043$; appetite loss: 18 vs 6.8, $p = 0.015$) compared with no systemic disease. Tumor volume and number of metastases did not influence exploratory HRQoL items/scales (data not shown).

Progression

Overall, patients with intracranial progression deteriorated in preselected HRQoL scales, while patients without progressive disease showed less profound deterioration or even improvement at follow-up (Supplementary Table 4). However, a significant difference between patients with progressive disease and those with stable disease/partial response was only found for motor dysfunction (mean change 7.7 vs -10, $p = 0.006$), while role functioning showed a trend (mean change -15 vs 0.2, $p = 0.084$). For exploratory scores, no differences between patients with and without intracranial progression were found. Although the use of corticosteroids resulted in lower HRQoL at different time points, there was no significant deterioration over time.

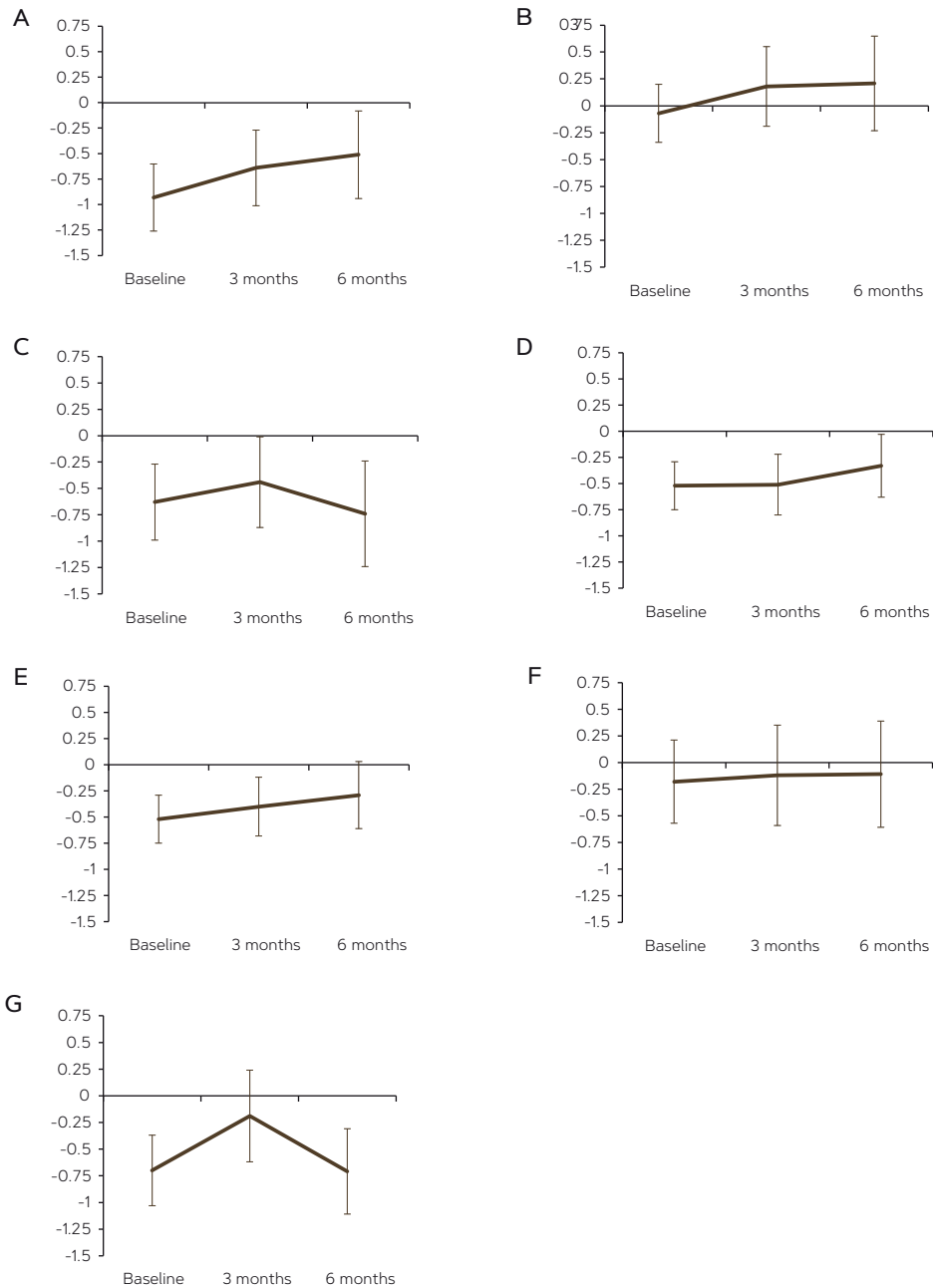


Figure 1. Neurocognitive domain scores over time. Mean z-scores are predicted from linear mixed model analysis with their 95% CIs for (A) verbal memory, (B) visual memory, (C) attention, (D) executive functioning, (E) working memory, (F) information processing speed, and (G) visuoconstruction. Verbal memory showed a nonsignificant improvement over time ($p = 0.084$)

Table 3. Neurocognitive domain scores at baseline

	Total patient group (n = 77)		Patients vs controls ^a
	Mean score	95% CI	
Verbal memory	-0.93	-1.26 to -0.6	$p < .001$
Visual memory	-0.07	-0.34 to 0.2	$p = .336$
Attention	-0.63	-0.99 to -0.26	$p = .002$
Executive functioning	-0.52	-0.75 to -0.29	$p < .001$
Working memory	-0.52	-0.74 to -0.29	$p < .001$
Information processing speed	-0.18	-0.57 to -0.2	$p = .361$
Visuoconstruction	-0.7	-1.03 to -0.37	$p < .001$

^aMean z-scores (SD) of controls: 0 (1)

Table 4. Preselected HRQoL scores at baseline

	Total patient group (n = 95)		Reference data from general population ³³
	Mean score	95% CI	Mean score
QLQ-C30			
Global health status/QoL	67	62-72	78
Physical functioning	69	64-75	90
Emotional functioning	73	69-78	89
Role functioning	58	51-65	89
Cognitive functioning	75	70-80	92
BN 20			
Motor dysfunction	21	16-26	-
Communication deficits	10	6.4-13	-
Fatigue Severity scale	3.2	2.8-3.6	-

Scores >10 are rounded. Differences between total patient group and reference data are all significant ($p < .05$).

Patients with KPS <90 (n = 47)		Patients with KPS ≥90 (n = 30)		KPS <90 vs KPS ≥90
Mean score	95% CI	Mean score	95% CI	
-1.16	-1.56 to -0.76	-0.74	-1.29 to -0.18	$p = 0.202$
-0.09	-0.57 to 0.38	-0.15	-0.46 to 0.17	$p = 0.842$
-0.86	-1.3 to -0.41	-0.23	-0.89 to 0.42	$p = 0.105$
-0.81	-1.09 to -0.53	-0.13	-0.43 to 0.17	$p = 0.002$
-0.7	-0.97 to -0.44	-0.27	-0.65 to 0.12	$p = 0.054$
-0.57	-1.15 to 0	0.38	-0.04 to 0.8	$p = 0.015$
-0.81	-1.31 to -0.31	-0.58	-1.05 to -0.11	$p = 0.493$

Patients with KPS <90 (n = 61)		Patients with KPS ≥90 (n = 34)		KPS <90 vs KPS ≥90 p-value
Mean score	95% CI	Mean score	95% CI	
60	54-66	80	74-87	< 0.001
58	52-65	90	85-95	< 0.001
73	67-79	74	66-82	0.785
46	37-54	80	73-88	< 0.001
68	61-75	87	81-93	< 0.001
28	21-35	8.8	5-13	< 0.001
12	7.2-17	6.4	1.5-11	0.136
3.8	3.3-4.3	2.2	1.6-2.7	< 0.001

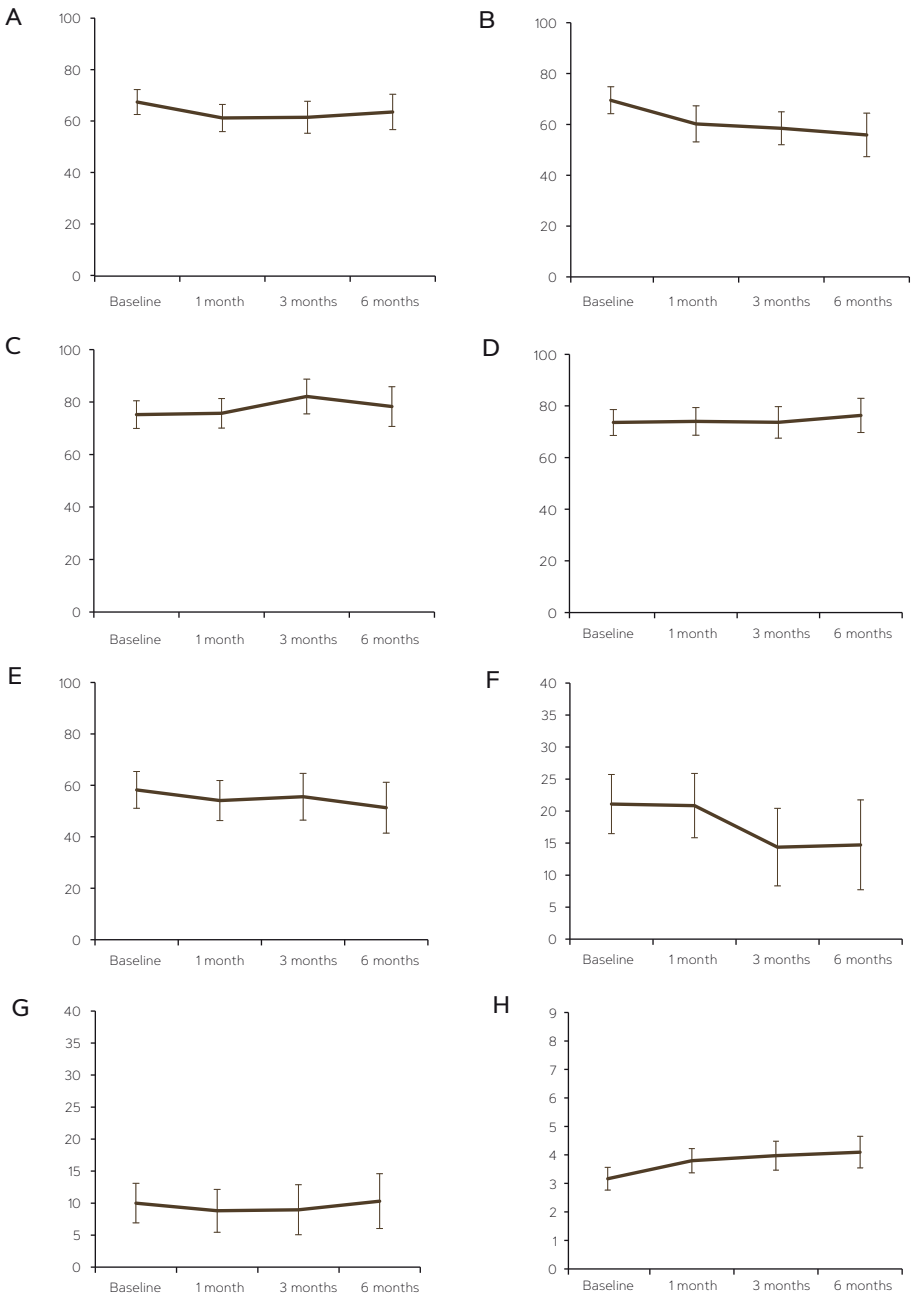


Figure 2. HRQoL scores over time. Data are predicted means based on linear mixed model analysis with their 95% CIs for (A) global health status/ QoL, (B) physical functioning, (C) cognitive functioning, (D) emotional functioning, (E) role functioning, (F) motor dysfunction, (G) communication deficits, and (H) fatigue. Physical functioning ($p = 0.027$) and fatigue ($p = 0.009$) worsened significantly over time

Discussion

We found that newly diagnosed brain metastases patients suffer from moderate impairments in HRQoL and neurocognitive functioning prior to SRT. Of note, up to 6 months after SRT, overall neurocognitive and HRQoL scores remained relatively stable on group level and did not further deteriorate. To our knowledge, this is the first study in which neurocognitive functioning and HRQoL have been comprehensively and prospectively examined in a relatively large group of patients treated with SRT only. Overall survival in our study was comparable to survival after WBRT, as well as to other studies on SRT.^{36,37}

Regarding neurocognitive functioning, we found 53% of patients to have at least some neurocognitive impairment at baseline. In earlier studies, 67%-80% of brain metastatic patients had neurocognitive impairments before any radiotherapy.^{5,38} These differences might be explained by the fact that other studies included patients who were scheduled to undergo WBRT³⁸ and used different neurocognitive tests.^{5,38} Also, we combined test scores into domain scores, resulting in loss of information. Nevertheless, mean neurocognitive domain scores in our study were similar to scores observed in earlier studies, with memory as the most frequently impaired domain.^{5,39} We also observed a relatively frequent impairment in visuoconstructive abilities, which may impact spatial orientation in daily life. It may therefore be relevant to include these measures in future neurocognitive assessments.

The observation that neurocognitive functioning remained relatively stable up to 6 months after SRT, is in line with few earlier (pilot) studies in brain metastatic patients^{5,40-42} and with more comprehensive studies on long-term neurocognitive functioning after stereotactic irradiation for other intracranial lesions - for example cerebral arteriovenous malformations.⁴³ Also, patients treated with SRT were found to have lower risk of deteriorating in learning and memory 4 months after treatment (24%) than SRT plus WBRT patients (52%).³⁹ Comparable results were observed in a recent trial by Brown et al.,⁴⁴ in which cognitive decline 3 months after treatment was more frequent in patients receiving SRT plus WBRT compared with SRT alone, despite better intracranial tumor control with the addition of WBRT. A decline in Mini-Mental State Examination (MMSE) is mainly found at recurrence.¹⁶ Even though we used instruments more sensitive to change than the MMSE,⁴⁵ we did not find an association between brain tumor progression and neurocognitive decline, except for executive functioning, which deteriorated in patients with stable or progressive disease and improved in those with partial response. Perhaps our patients did not deteriorate because they often developed only small new lesions. Surprisingly, we found that information processing speed and visuoconstruction were more severely impaired over time in patients without compared to patients with active systemic

disease at baseline, while clinical characteristics and overall condition of patients with systemic activity did not differ from those without active systemic disease.

Baseline HRQoL outcomes in our study are comparable to the results of earlier studies evaluating radiotherapy in brain metastatic patients.¹⁸⁻²⁰ This implies that patients with brain metastases are impaired already at onset in all facets of daily life, including physical and mental functioning. Some aspects of physical functioning, including nausea and fatigue, were augmented during follow-up, probably related to systemic disease or chemotherapy. Despite treatment and disease-related symptoms, most functioning scales and global health status/QoL remained stable over time, which is in line with previous results.^{18,42} This might be explained by the occurrence of a “response shift”, or adaptation of the patient to increased symptoms and a recalibration of priorities.⁹ Two other studies on HRQoL in patients with brain metastases showed either improvement or deterioration of HRQoL within 3 months after radiation compared to baseline.^{19,20} However, in both studies, only a minority of patients received SRT alone. The robust association between intracranial progression and HRQoL decline found in glioma patients (e.g.⁴⁶) might be less clear in brain metastatic patients, as we only found a significant and clinically relevant deterioration for motor dysfunction in progressive patients, while patients with stable disease or a partial response improved. Similarly, in a previous study on brain metastases, no association between intracranial recurrence and worsening of HRQoL was observed.¹⁸ Perhaps this lack of association might be related to the occurrence of pseudoprogression, or because close monitoring with MRI resulted in early detection of new small, and therefore asymptomatic, lesions.

We found that KPS and brain metastatic volume, but not number of metastases, were associated with survival, neurocognitive functioning, and HRQoL, which is in accordance with earlier findings.^{4,5,16,20,36} Although patients with large tumor volumes were impaired in some aspects of HRQoL and neurocognitive functioning, most scores did not differ significantly from those of patients with smaller tumors. Moreover, the median total volume of brain metastases in our study was larger than described in other studies using SRT,^{16,39} suggesting that also in patients with relatively large metastatic volume, SRT is adequate to achieve maintenance of HRQoL and cognition. Although HRQoL and neurocognitive functioning may be preserved in patients with low baseline performance status, their mean scores remained lower over 6 months time when compared to patients with good performance status.

Our study clearly had several limitations. First, the study population was heterogeneous in that several types of primary tumors were included. As prognosis is partly based on primary tumor histology, this may have influenced survival and functional outcomes. Due to small numbers of the different tumor types, it was not feasible to assess the effect of each tumor separately. This sample is, however, representative

of brain metastatic patients undergoing SRT in a tertiary hospital. Another challenge is the level of compliance during the study period, especially with the neurocognitive assessments. Noncompliance was partly due to logistic reasons, but also to poor physical or neurological condition of the patient. Therefore, our findings might have been an underestimation of truly neurocognitive impairments. We have tried to overcome this problem by fitting linear mixed models, confirming that neurocognitive functioning and HRQoL were stable over time. Moreover, the level of compliance in our sample was comparable with other studies on HRQoL¹⁸⁻²⁰ and neurocognitive functioning¹⁶ in radiotherapy patients. Finally, we examined effects of SRT on neurocognitive functioning and HRQoL up to 6 months, but longer follow-up periods would be informative to examine possible late effects of SRT.

To conclude, this prospective study showed that SRT is safe in terms of preservation of neurocognitive functioning and HRQoL in patients with up to 3 brain metastases. With similar OS rates as WBRT, these results suggest that SRT should be the preferred treatment. Moreover, evaluation of neurocognitive functioning and HRQoL during the disease course is essential for providing adequate information and counseling for patients with brain metastases.

References

- Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698-2705.
- Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol*. 2012;14(7):910-918.
- Kaal EC, Niel CG, Vecht CJ. Therapeutic management of brain metastasis. *Lancet Neurol*. 2005;4(5):289-298.
- Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol*. 2004;22(1):157-165.
- Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery*. 2007;60(2):277-283.
- Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Radiosurgery with or without whole-brain radiotherapy for brain metastases: the patients' perspective regarding complications. *Am J Clin Oncol*. 2005;28(2):173-179.
- Jyothirmayi R, Saran FH, Jalali R, et al. Stereotactic radiotherapy for solitary brain metastases. *Clin Oncol (R Coll Radiol)*. 2001;13(3):228-234.
- Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4):419-425.
- Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol*. 2013;14(10):e407-e416.
- Lippitz B, Lindquist C, Paddick I, Peterson D, O'Neill K, Beaney R. Stereotactic radiosurgery in the treatment of brain metastases: the current evidence. *Cancer Treat Rev*. 2014;40(1):48-59.
- Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer*. 2012;118(9):2486-2493.
- Platta CS, Khuntia D, Mehta MP, Suh JH. Current treatment strategies for brain metastasis and complications from therapeutic techniques: a review of current literature. *Am J Clin Oncol*. 2010;33(4):398-407.
- Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys*. 2005;63(1):37-46.
- Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2):134-141.
- Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys*. 2001;51(3):711-717.
- Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2007;68(5):1388-1395.
- Cole AM, Scherwath A, Ernst G, Lanfermann

- H, Bremer M, Steinmann D. Self-reported cognitive outcomes in patients with brain metastases before and after radiation therapy. *Int J Radiat Oncol Biol Phys.* 2013;87(4):705-712.
18. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol.* 2013;31(1):65-72.
 19. Steinmann D, Paelecke-Habermann Y, Geinitz H, et al. Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. *BMC Cancer.* 2012;12:283.
 20. Caissie A, Nguyen J, Chen E, et al. Quality of life in patients with brain metastases using the EORTC QLQ-BN20+2 and QLQ-C15-PAL. *Int J Radiat Oncol Biol Phys.* 2012;83(4):1238-1245.
 21. Lin NU, Lee EQ, Aoyama H, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. *Lancet Oncol.* 2013;14(10):e396-e406.
 22. Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res.* 2009;15(4):1452-1459.
 23. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment.* New York: Oxford University Press; 2004.
 24. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning.* New York: Psychology Press, Inc.; 2003: 159-173.
 25. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery.* 2000;47(2):324-333.
 26. Jolles J, Van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr.* 1998;29(3):120-129.
 27. van der Elst W. *The neuropsychometrics of aging; normative studies in the Maastricht Aging Study.* Universiteit Maastricht; 2006.
 28. De Bie SE. [Proposal for uniformisation of questions regarding background variables and interviews]. Leiden: Leiden University Press; 1987.
 29. Fastenau PS, Denburg NL, Hufford BJ. Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol.* 1999;13(1):30-47.
 30. Kessels RP, van den Berg E, Ruis C, Brands AM. The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment.* 2008;15(4):426-434.
 31. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-376.
 32. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res.* 1996;5(1):139-150.
 33. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer.* 2011;47(5):667-675.
 34. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.

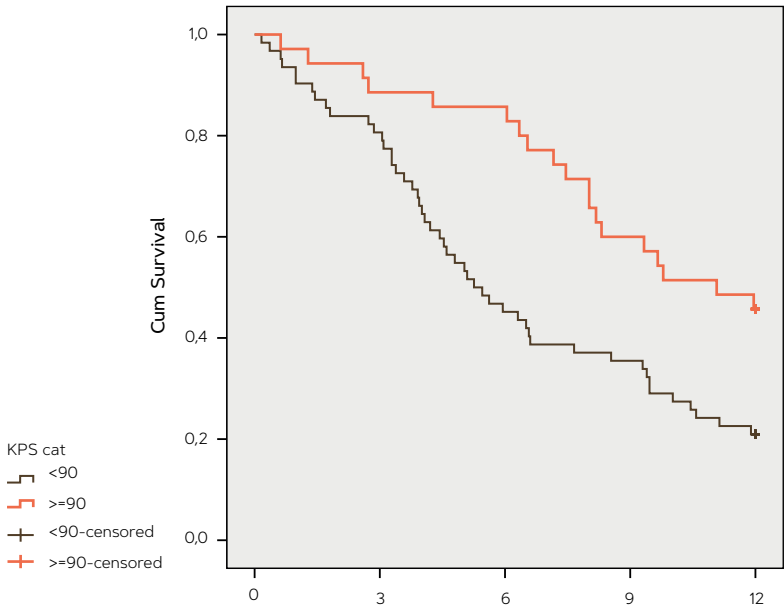
- Arch Neurol.* 1989;46(10):1121-1123.
35. Mathiowetz V, Matuska KM, Murphy ME. Efficacy of an energy conservation course for persons with multiple sclerosis. *Arch Phys Med Rehabil.* 2001;82(4):449-456.
 36. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006;295(21):2483-2491.
 37. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys.* 2002;53(3):519-526.
 38. Gerstenecker A, Nabors LB, Meneses K, et al. Cognition in patients with newly diagnosed brain metastasis: profiles and implications. *J Neurooncol.* 2014;120(1):179-185.
 39. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037-1044.
 40. Onodera S, Aoyama H, Tha KK, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. *J Neurooncol.* 2014;120(2):311-319.
 41. Minniti G, Esposito V, Clarke E, et al. Stereotactic radiosurgery in elderly patients with brain metastases. *J Neurooncol.* 2013;111(3):319-325.
 42. Kirkpatrick JP, Wang Z, Sampson JH, et al. Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2015;91(1):100-108.
 43. Steinvorth S, Wenz F, Wildermuth S, et al. Cognitive function in patients with cerebral arteriovenous malformations after radiosurgery: prospective long-term follow-up. *Int J Radiat Oncol Biol Phys.* 2002;54(5):1430-1437.
 44. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiotherapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases [abstract]. *J Clin Oncol.* 2015;33(suppl; LBA4).
 45. Meyers CA, Wefel JS. The use of the minimal state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol.* 2003;21(19):3557-3558.
 46. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol.* 2009;11(1):51-58.
 47. Schmand B, Lindeboom J, Van Harskamp F. [The 15 words test A and B (a preliminary manual)]. Groningen: Afdeling Neuropsychologie, AZG; 1992.
 48. Osterreith PA. Le test de copie d'une figure complexe [A test regarding a complex figure]. *Archives de Psychologie/ The Clinical Neuropsychologist.* 1944;30(7):206-9-356/ 15.
 49. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual]*. Lisse: 2000.
 50. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess.* 2006;18(4):424-432.
 51. Krabbendam L, Kalff AC. *The Behavioural Assessment of the Dysexecutive Syndrome: Dutch Version.* Lisse: Swets and Zeitlinger; 1998.

Supplementary data

Table S1. Cognitive tests and domains

Cognitive tests	Objective measures	Cognitive domain(s)
Auditory verbal learning test ⁴⁷	Total of five trials (no. correct: 0-75) * delta score (no. correct: 0-15) delayed recall (no. correct: 0-15) * delayed recognition (no. correct: 0-30) *	Verbal memory
Rey Complex figure test ⁴⁸	Copying and delayed recall (both no. correct: 0-36)*	Visual construction and visual memory
Stroop color word test ²³	Subtests: card I: word condition (time in seconds), card II: color condition, card III: color-word condition (time in seconds) * and interference #	Information processing speed, attention
Letter digit modalities test ²³	90 seconds writing (no. correct: 0-125) *	Information processing speed
Digit span ⁴⁹	Forward (no. correct * span: 0-144) and backward (no. correct*span: 0-112) *	Attention, working memory
Concept Shifting Test ⁵⁰	Condition A (numbers 1-16), B (letters A-P), C (shifting between numbers and letters) Score: time to complete in seconds. Shifting score: C/ (A+B)	Executive functions (shifting, searching in semantic memory, strategy formation)
Word fluency ²³	Animals and letters (both no. correct: 0- ∞)*	
Behavioral Assessment of the Dysexecutive Syndrome ⁵¹	Subtest: key-search test (profile score: 0-4) *	

Number of patients at risk



KPS <90	62	50	28	22	13
KPS ≥90	35	31	30	21	16

Figure S1. Overall survival, separately for patients with baseline KPS <90 and KPS ≥ 90

Table S2. Exploratory HRQoL scores at baseline

	Total patient group (n = 95)		Reference data from general population ³³	Patients with KPS <90 (n = 61)		Patients with KPS ≥90 (n = 34)		KPS <90 vs KPS ≥90 p-value
	Mean score	95% CI	Mean score	Mean score	95% CI	Mean score	95% CI	
QLQ-C30								
Social functioning	81	76-86	94	77	70-84	88	81-95	0.037
Insomnia	41	33-48	14	43	34-52	36	23-50	0.403
Dyspnoea	21	15-27	7.1	25	17-34	13	3.8-22	0.05
Pain	14	8.7-18	15	18	11-25	6.1	1.9-10	0.005
Fatigue	31	26-37	17	39	32-46	17	11-23	<0.001
Constipation	6.6	2.7-10	4.8	8	2.6-14	42	-0.9-8.9	0.330
Financial difficulties	6.3	1.5-11	3.1	8.2	1.5-15	3	-3.1-9.2	0.258
Nausea	3.3	1.5-5.1	2.7	4.5	1.9-7.2	1	-0.4-2.4	0.022
Diarrhoea	2.9	0.7-5.2	3.9	4	0.7-7.6	1	-1-3.1	0.124
Appetite loss	3.7	0.7-6.7	3.3	5.8	1.1-11	0		0.017
BN 20								
Future uncertainty	28	23-33	-	30	23-37	26	19-33	0.489
Visual disorder	14	9.6-19	-	18	12-25	6.7	1.8-12	0.004
Headache	16	12-21	-	19	13-25	12	4-19	0.136
Seizures	8.9	4.4-13	-	12	5-18	4	0.1-8	0.05
Drowsiness	14	9.8-19	-	19	13-25	6.1	1.4-11	0.001
Bothered by hair loss	4	0.8-7.3	-	4	0.3-7.7	4	-2.4-10	0.996
Bothered by itching skin	6.2	2.8-9.6	-	8	3.3-13	3	-1.5-7.6	0.126
Weakness of legs	13	7.3-18	-	18	10-26	3	-0.2-7.6	0.001
Difficulty controlling bladder	8.7	4.6-13	-	10	4.8-16	6.1	-1.5-12	0.34

Table S3. Exploratory HRQoL scales over time: total group and KPS <90 vs KPS ≥90

	Baseline		1 month		3 months		6 months	
	Mean score	95% CI	Mean score	95% CI	Mean score	95% CI	Mean score	95% CI
QLQ-C30								
Social functioning	81	76-86	76	69-83	73	64-81	78	70-86
Fatigue	31	26-37	45	38-51	45	37-52	38	30-47
Nausea	3.2	1.5-5	3.9	1.6-6.2	12	7-17	15	7.3-23
Pain	14	9.3-19	20	14-26	25	16-34	21	13-29
Dyspnoea	21	15-28	32	25-39	31	24-40	31	23-40
Sleeplessness	40	33-48	34	26-42	23	14-32	30	21-40
Appetite loss	3.7	0.6-6.7	9.7	3.5-16	23	13-33	19	8.8-28
Diarrhoea	2.9	0.7-5.1	4.1	1.3-6.9	12	3.2-18	15	6.3-25
Constipation	6.6	2.7-10	5.2	1.1-9.3	10	2.5-17	8.2	1.6-15
Financial difficulties	6.4	1.7-11.1	7.8	3.4-12	9	3.6-14	7.5	2.8-12
BN 20								
Future uncertainty	28	23-33	30	24-36	29	23-36	31	24-38
Visual disorder	14	9.9-19	14	9.6-18	10	6.7-14	19	11-26
Headache	16	11-21	19	14-25	16	9-22	15	7-23
Seizures	8.8	4.4-13	6.8	2.5-11	2.3	-0.6-5.3	4.8	-0.4-10
Drowsiness	14	9.8-19	19	12-26	12	6.1-17	3.2	-2.8-9.1
Bothered by hair loss	4	0.7-7.3	25	18-32	26	18-34	25	15-35
Bothered itching skin	6.2	2.8-9.6	9	4.7-13	11	5.4-17	13	5.9-20
Weakness of legs	13	7.3-18	28	20-37	24	16-33	18	11-26
Difficulty controlling bladder	8.6	4.6-13	7.9	3.8-12	8.9	3.9-14	15	7.4-24

Data are adjusted means from linear mixed model with their 95% CIs.

6 months vs baseline	Patients with KPS <90		Patients with KPS ≥90		KPS <90 vs KPS ≥90
	mean	95% CI	mean	95% CI	
-3, $p = 1$	74	67-80	83	76-91	-9, $p = 0.054$
7, $p = 0.802$	44	38-51	34	26-42	10, $p = \mathbf{0.048}$
11.8, $p = \mathbf{0.037}$	11	6.6-15	5	-0.1-10	6, $p = 0.076$
7, $p = 0.604$	24	18-30	13	6-21	11, $p = \mathbf{0.029}$
10, $p = 0.237$	28	20-36	29	19-39	-1, $p = 0.883$
-10, $p = 0.31$	34	26-42	30	20-40	4, $p = 0.535$
15.3, $p = \mathbf{0.029}$	18	12-24	9	2.1-16	9, $p = 0.063$
12.1, $p = 0.052$	9.3	4.1-15	8.8	2.9-15	0.5, $p = 0.895$
1.6, $p = 1$	7.6	3.3-12	7.5	2.6-12	0.1, $p = 0.965$
1.1, $p = 1$	9.2	3.9-15	5	-2-12	4.2, $p = 0.334$
3, $p = 0.744$	31	24-37	28	20-36	3, $p = 0.574$
5, $p = .0415$	17	12-22	8.6	2.6-15	8.4, $p = \mathbf{0.030}$
-1, $p = 1$	19	14-24	13	7.4-19	6, $p = 0.167$
-4, $p = 0.371$	6	2.8-9.3	3.8	0.1-7.4	2.2, $p = 0.355$
-10.8, $p = 0.056$	14	10-18	7.4	2.6-12	6.6, $p = \mathbf{0.027}$
21, $p = \mathbf{0.001}$	21	14-27	19	12-26	2, $p = 0.736$
6.8, $p = 0.589$	12	7.7-16	6	1.2-11	6, $p = 0.074$
5, $p = 1$	25	18-31	15	6.9-23	10, $p = 0.056$
6.4, $p = 0.69$	10	4.6-16	11	4-17	-1, $p = 0.915$

Table S4. HRQoL scores at time of progression

	Progressive disease (n = 36)		No progressive disease (n = 37)		p-value of difference
	Mean change*	95% CI	Mean change	95% CI	
QLQ-C30					
Global health status/QoL	-14	-23 to -5.9	-6.4	-16 to 2.8	0.199
Physical functioning	-18	-27 to -8.5	-9.2	-21 to 2.2	0.248
Emotional functioning	-5.5	-14 to 2.8	1.6	-4.9 to 8.1	0.173
Role functioning	-15	-26 to -3.4	0.2	-13 to 13	0.084
Cognitive functioning	-1.5	-11 to 7.8	7	-1.5 to 16	0.178
Social functioning	-16	-27 to -5.2	-6	-18 to 6.2	0.22
Insomnia	-5.6	-22 to 11	-7.4	-19 to 4.7	0.854
Dyspnoea	11	-0.3 to 23	14	6.8 to 22	0.626
Pain	12	4.5 to 21	5	-2.7 to 13	0.17
Fatigue	20	9.1 to 30	9.6	-2.2 to 21	0.204
Constipation	1.9	-8.8 to 13	-0.9	-4.2 to 2.4	0.606
Financial difficulties	2.9	-2.3 to 8.2	1.8	-0.8 to 4.3	0.685
Nausea	4.6	-1.3 to 11	4.2	-0.6 to 8.9	0.902
Diarrhoea	5.7	-3.3 to 15	4.6	-0.9 to 10	0.834
Appetite loss	20	6.8 to 32	13	2.8 to 23	0.399
BN 20					
Motor dysfunction	7.7	-1.2 to 17	-10	-19 to -1	0.006
Communication deficit	-1.3	-8.2 to 5.6	-1.8	-5.8 to 2.2	0.891
Future uncertainty	3.3	-4.6 to 11	3.8	-4.3 to 12	0.922
Visual disorder	2.5	-4.4 to 9.4	-4.7	-11 to 1.9	0.129
Headache	-1.9	-10 to 6.7	4.1	-4.2 to 12	0.314
Seizures	-0.5	-12 to 11	-3.6	-10 to 3.2	0.639
Drowsiness	7.4	-2 to 17	7.2	-3.9 to 18	0.978
Bothered by hair loss	18	8.4 to 28	25	14 to 36	0.337
Bothered by itching skin	0.9	-7.8 to 9.7	5.6	-2.3 to 13	0.426
Weakness of legs	18	5.7 to 29	15	3.9 to 27	0.78
Difficulty controlling bladder	2.3	-5.3 to 10	0.9	-5.9 to 7.8	0.785
Fatigue Severity scale	0.8	0.2 to 1.5	1.1	0.4 to 1.8	0.572

* Mean change is based on score at time of progressive disease or, in case of no progression, on score at last follow-up, minus score at baseline.

4

Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy

Journal of Neuro-Oncology

2018 Sep;139(2):359-368.

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Abstract

Background: Recently, it has been shown that at group level, patients with limited brain metastases treated with stereotactic radiotherapy (SRT) maintain their pre-treatment levels of neurocognitive functioning (NCF) and health-related quality of life (HRQoL). The aim of this study was to evaluate NCF and HRQoL changes over time at the individual patient level.

Methods: NCF (seven domains assessed with a standardized test battery) and HRQoL (eight predetermined scales assessed with the EORTC QLQ-C30 and BN20 questionnaires) were measured prior to SRT and at 3 and/or 6 months follow-up. Changes in NCF and HRQoL were evaluated at (1) a domain/scale level and (2) patient level.

Results: A total of 55 patients were examined, of which the majority showed stable NCF 3 months after SRT, on both the domain level (78–100% of patients) and patient level (67% of patients). This was different for HRQoL, where deterioration in the different scales was observed in 12–61% of patients, stable scores in 20–71%, and improvement in 16–40%, 3 months after SRT. At patient level, most patients (64%) showed both improvement and deterioration in different HRQoL scales. Results were similar between 3 and 6 months after SRT.

Conclusion: In line with results at group level, most brain oligometastases patients with ≥ 6 months follow-up and treated with SRT maintained their pre-treatment level of NCF during this period. By contrast, changes in HRQoL scores differed considerably at domain and patient level, despite stable HRQoL scores at group level.

Introduction

Brain metastases are a common manifestation of systemic cancer, with an estimated 9–45% of cancer patients developing brain metastases.^{1,2} The increasing incidence of brain metastases is most likely attributable to an aging population, the availability of improved imaging to detect smaller lesions, and better treatment modalities for systemic cancer which prolong life, thereby increasing the risk of dissemination of the systemic cancer to the brain.^{3,4} Although a subgroup of patients experiences longer survival,⁵ brain metastases are still incurable for most patients and the focus of treatment is mainly palliative.⁶ Neurocognitive deficits and a reduced health-related quality of life (HRQoL) are often observed in patients with brain metastases and may be caused by the primary tumor, presence of (brain) metastases themselves, anti-tumor treatment, or supportive medication.^{4,7–10} Although survival is an important treatment endpoint for these patients, maintenance or improvement of neurocognitive functioning (NCF) and HRQoL during the course of the disease are at least as important.^{11,12}

Whole-brain radiotherapy (WBRT) has been the standard of care in the past decades, but use of stereotactic radiotherapy (SRT) as an addition to, or as an alternative for, WBRT have increased considerably in recent years.¹³ The main component of SRT is precise delivery of focal high dose radiation to a discrete target volume in 1–5 sessions, while minimizing irradiation of surrounding normal tissue.^{8,14} This treatment is particularly useful for patients presenting with limited brain metastases,¹⁵ which is the largest subgroup of patients, considering that 70% of the patients have three or fewer metastases.¹⁶ SRT alone is associated with better NCF and HRQoL, while overall survival (OS) is comparable with WBRT alone or a combination of WBRT and SRT.^{5,17,18} In contrast, SRT alone carries a risk of intracranial recurrences and patients treated with SRT undergo salvage treatment significantly more often compared with patients receiving both WBRT and SRT.¹⁹ These salvage treatments may increase the risk of neurologic deficits and radionecrosis.^{4,20}

Habets et al.²¹ evaluated NCF and HRQoL prospectively in patients treated with SRT alone for 1–3 brain metastases and found that at group level, NCF and HRQoL remained relatively stable during 6 months from initial treatment, with the exception of physical functioning and fatigue, which worsened over time.²¹ Although at group level patients maintained their pre-treatment levels of NCF and HRQoL to a large extent, this may not hold true for all individual patients. Since maintaining or improving NCF and HRQoL is important for all patients treated with SRT, we sought to evaluate changes over time in NCF and HRQoL at the individual patient level.

Materials and methods

Study population

Patients were eligible if they were ≥ 18 years; had ≤ 3 newly diagnosed brain metastases (maximum diameter of 4 cm); and were scheduled to undergo SRT, performed on an out-patient base with a dedicated Linac (Novalis; Brain-LABAG, Helmstetten, Germany), construction year 2003. Recruitment of patients took place between January 2009 and February 2012. Exclusion criteria were: prior treatment for metastatic brain tumors; insufficient mastery of the Dutch language; and Karnofsky Performance Status (KPS) score < 70 . The medical ethics committee of the institution approved the protocol. All patients provided written informed consent.

Procedures

The gross tumor volume (GTV) was contoured on a contrast-enhanced T1-weighted MRI. Planning target volume (PTV) was created by adding a 2-mm margin by 3D expansion to the clinical target volume (CTV), which was equal to the GTV. SRT treatment consisted of 21 Gy (PTV $< 8 \text{ cm}^3$) or 18 Gy (PTV $8\text{--}13 \text{ cm}^3$) in a single fraction or 24 Gy (PTV $> 13 \text{ cm}^3$ and metastases near the brainstem) in three fractions of 8 Gy.

The baseline evaluation of NCF and HRQoL was conducted in the week preceding SRT. Follow-up assessments took place 3 and 6 months after SRT. Patients' charts were examined to extract sociodemographic data and clinical variables, including primary tumor, treatment status and medication use. At all time points, MRI scans were made and the status of the primary disease and the use of medication were monitored. If patients showed intracranial progression during follow-up and underwent renewed SRT, provided the number of metastases was ≤ 3 , these patients remained in the study. Patients with intracranial progression who transitioned to WBRT were excluded from further assessment. Patients were included in the statistical analysis if they complied for assessment on NCF and/or HRQoL on at least baseline and 3 months, or 3 and 6 months.

Study instruments

Neurocognitive functioning

NCF was assessed with a standardized battery of validated neurocognitive tests found to be clinically relevant in brain tumor patients (Supplementary Table 1).²²⁻²⁹ Individual test scores were combined in seven neurocognitive domain scores: verbal memory, visual memory, attention, executive functioning, working memory, information processing speed and visuoconstruction. Raw individual test scores were converted into standardized z-scores, by using means and standard deviations of individually matched healthy controls regarding age, gender, and education level, for four different domains (verbal memory, attention, executive functioning and information processing

speed).³⁰⁻³² Published norms were used, corrected for age and education, for the three other domains (visual memory, working memory and visuoconstruction).^{33,34} A change in z-score of ≥ 1.5 standard deviation (SD) was considered to be clinically meaningful, in line with previous research in the same population.²¹

Health-related quality of life

HRQoL was evaluated with two validated self-assessment questionnaires, (1) the for cancer patients developed 30-item generic European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and (2) the 20-item brain tumor-specific EORTC QLQ-Brain Cancer Module (QLQ-BN20).^{35,36} A selection of HRQoL scales has been made, based on previous findings,³⁷ comprising six QLQ-C30 scales (global health status, physical functioning, emotional functioning, role functioning, cognitive functioning, and fatigue) and two BN20 scales (motor dysfunction and communication deficits). Global health status was rated on a 7-point Likert scale, ranging from 'very poor' to 'excellent'; the functioning and symptom scales were rated on a 4-point Likert scale, ranging from 'not at all' to 'very much'. Raw scores were converted linearly into standardized scores ranging from 0 to 100. A higher score on the global health status and the functioning scales indicates better HRQoL, while on symptom-oriented scales a higher score indicates worse HRQoL. Difference or change score ≥ 10 points on any given scale were considered to be clinically meaningful.³⁸

Statistical analysis

To assess changes in HRQoL and NCF, differences in scores over time were calculated on (1) a domain/scale level and (2) patient level. Above described cut-off scores were used to determine an improvement, deterioration or stable score. Changes in scores were calculated for two different time periods: baseline–3 months, and 3–6 months. A cluster analysis, using R, was performed to identify whether specific HRQoL scales clustered.

Statistical analyses were performed using SPSS version 23.0. Statistical significance for intergroup differences were tested using the χ^2 test for categorical variables, the Student's *t*-tests or Mann–Whitney U-test for two-level continuous variables (depending on the distribution of the data), and the Kruskal–Wallis test for continuous variables with more than two levels. Kaplan–Meier curves were used for analyses of OS, and a log rank test to assess differences in survival. A *p*-value of < 0.05 was considered statistically significant.

Domain/scale level

For both time periods (baseline–3 months, and 3–6 months), patients were assigned to one of three categories: (1) deterioration, (2) stable score or (3) improvement,

separately for each neurocognitive domain and HRQoL scale. For NCF, improvement and deterioration were defined as an increase or decrease in score ≥ 1.5 SD, respectively, and stable score as < 1.5 SD change. For HRQoL, improvement and deterioration were defined as ≥ 10 points increase or decrease respectively, and stable score as < 10 points increase or decrease.

Patient level

At patient level, patients were categorized into four categories, separately for NCF and HRQoL, applying the same cut-off scores as in the domain/scale level. These four categories were as follows: (1) decline, (2) improvement, (3) both and (4) stable. Decline and improvement were defined as deterioration or increase in NCF/HRQoL on at least one domain/scale respectively, while other domains/ scales remained stable. The category 'both' included both a decline and improvement, whereas 'stable' was defined as no detectable change in any neurocognitive domain or HRQoL scale. Moreover, changes in KPS score, SRT dose received (biologically higher [single fraction 21 or 18 Gy] versus lower dosis [8 Gy in three fractions]), total tumor volume (as a proxy for GTV), intracranial progression and active systemic disease were assessed for the four categories, separately for the two time periods.

Results

Fifty-five out of the original 97 (57%) patients were eligible for analyses, because they had sufficient data. Baseline sociodemographic and clinical characteristics of the study population are summarized in Table 1. These baseline sociodemographic and clinical characteristics were compared between patients with and without sufficient NCF/HRQoL data. At baseline, patients without sufficient data had more often a lower KPS score (median of 80 [inter quartile range (IQR) = 70–80] vs. 80 [IQR = 80–90]; $p = 0.002$) and shorter OS (median of 3.8 months [IQR = 1.6–6.4] vs. 12.0 months [IQR = 8.2–12.0]; $p < 0.001$) when compared to patients with NCF/HRQoL data. NCF and HRQoL scores over time in our subpopulation were similar to the results as previously reported in the original study population (data not shown).

Patient characteristics

The mean age of the 55 included patients was 63 years (SD = 9) and the primary tumor was most frequently located in the lung (49%). Although the MRI scan showed a fourth metastasis in two patients, these patients received SRT because of the small size (< 0.5 cm³) and were therefore also included. The median total tumor volume at baseline was 7.3 cm³ (IQR = 3.4–12.8) and the 1-year survival rate was 48%, with all patients still alive after 3 months and 87% after 6 months from initial SRT.

Table 1. Baseline sociodemographic and clinical characteristics of the patient population

	Patients with NCF/HRQoL data	Patients without NCF/HRQoL data	Original study population
Patients included, no. (%)	55	42	97
Age in years, mean $\pm$ SD	63 $\pm$ 9	64 $\pm$ 12	63 $\pm$ 11
Sex, no. (%)			
Male	25 (45%)	21 (50%)	46 (47%)
Female	30 (55%)	21 (50%)	51 (53%)
Educational level ^a , median (IQR)	3 (2–4)	2 (2–4)	2 (2–4)
Brain metastases, no. (%)			
1	21 (38%)	22 (52%)	43 (44%)
2	23 (42%)	8 (19%)	31 (32%)
3	9 (16%)	9 (21%)	18 (19%)
4	2 (4%)	3 (7%)	5 (5%)
Tumor volume by patient (cm ³)			
Median (range)/ (IQR)	7.3 (0.12–63.9)/ (3.4–12.8)	10.2 (0.15–32.0)/ (3.6–15.9)	7.8 (0.12–63.9)/ (3.5–14.2)
Missing	1 (2%)	0 (0%)	1 (1%)
Primary cancer, no. (%)			
Non-small cell lung	27 (49%)	20 (49%)	48 (50%)
Renal cell carcinoma	11 (20%)	1 (2%)	12 (13%)
Melanoma	4 (8%)	5 (12%)	9 (9%)
Colorectal cancer	3 (5%)	6 (15%)	9 (9%)
Breast cancer	3 (5%)	5 (12%)	8 (8%)
Other	7 (13%)	4 (10%)	10 (10%)
Missing	0 (2%)	1 (2%)	1 (1%)
Active systemic disease, no. (%)			
Yes	31 (56%)	21 (50%)	52 (54%)
No	24 (44%)	21 (50%)	45 (46%)
Chemotherapy, no. (%)			
Yes	6 (11%)	6 (14%)	12 (12%)
No	47 (85%)	33 (50%)	80 (82%)
Missing	2 (4%)	3 (7%)	5 (5%)
Extracranial metastases, no. (%)			
Yes	29 (53%)	25 (60%)	54 (56%)
No	25 (45%)	16 (38%)	41 (42%)
Missing	1 (2%)	1 (2%)	2 (2%)
Use of corticosteroids, no. (%)			
Yes	48 (87%)	37 (38%)	85 (88%)
No	4 (7%)	4 (10%)	8 (8%)
Missing	3 (5%)	1 (2%)	4 (4%)

Table 1. Baseline sociodemographic and clinical characteristics of the patient population (*continued*)

	Patients with NCF/HRQoL data		Patients without NCF/HRQoL data		Original study population
Use of AEDs, no. (%)					
Yes	12	(22%)	9	(21%)	21 (22%)
No	40	(73%)	32	(76%)	72 (74%)
Missing	3	(5%)	1	(2%)	4 (4%)
KPS					
Median (IQR)	80	(80–90)	80	(70–80)	80 (70–90)
KPS ≥ 90, No. (%)	25	(46%)	9	(21%)	34 (35%)
Missing	1	(2%)	0	(0%)	1 (1%)
Survival in months, median (IQR)	12.0	(8.2–12.0)	3.8	(1.6–6.4)	7.7 (3.9–12)

Due to rounding, not all percentages add up to 100%; ^aLevel 1–8, NCF neurocognitive functioning, HRQoL health-related quality of life, SD standard deviation, IQR interquartile range, AEDs antiepileptic drugs, KPS Karnofsky performance status

Compliance

During follow-up, compliance dropped from 91% at baseline (n = 50) to 69% at 3 and 56% at 6 months for NCF, and from 98% at baseline (n = 54) to 93% at 3 and 85% at 6 months for HRQoL assessments (Supplementary Table 2). Patients had several reasons for non-compliance, such as progression of disease or the assessment being too demanding.

Neurocognitive functioning

Prior to SRT, half of the patients with neurocognitive data (25/50, 50%) showed impairments in at least one neurocognitive domain, of which verbal memory was most frequently affected (10/33, 30%).

Domain level

Three months after initial SRT, deterioration in the different neurocognitive domains was observed in 5/7 domains (3–8% of patients), while in two domains (verbal memory and visual memory) none of the patients showed deterioration (Figure 1a). A stable score was observed in all domains (78–100% of patients), most frequently in verbal memory and visual memory. Improvement was found in 4/7 domains (3–17% of patients) and was most profound for visuoconstruction. Similar results were observed between 3 and 6 months after initial SRT [deterioration in 4/7 domains, 8–20% of patients; stable score in all domains, 73–100% of patients; and improvement

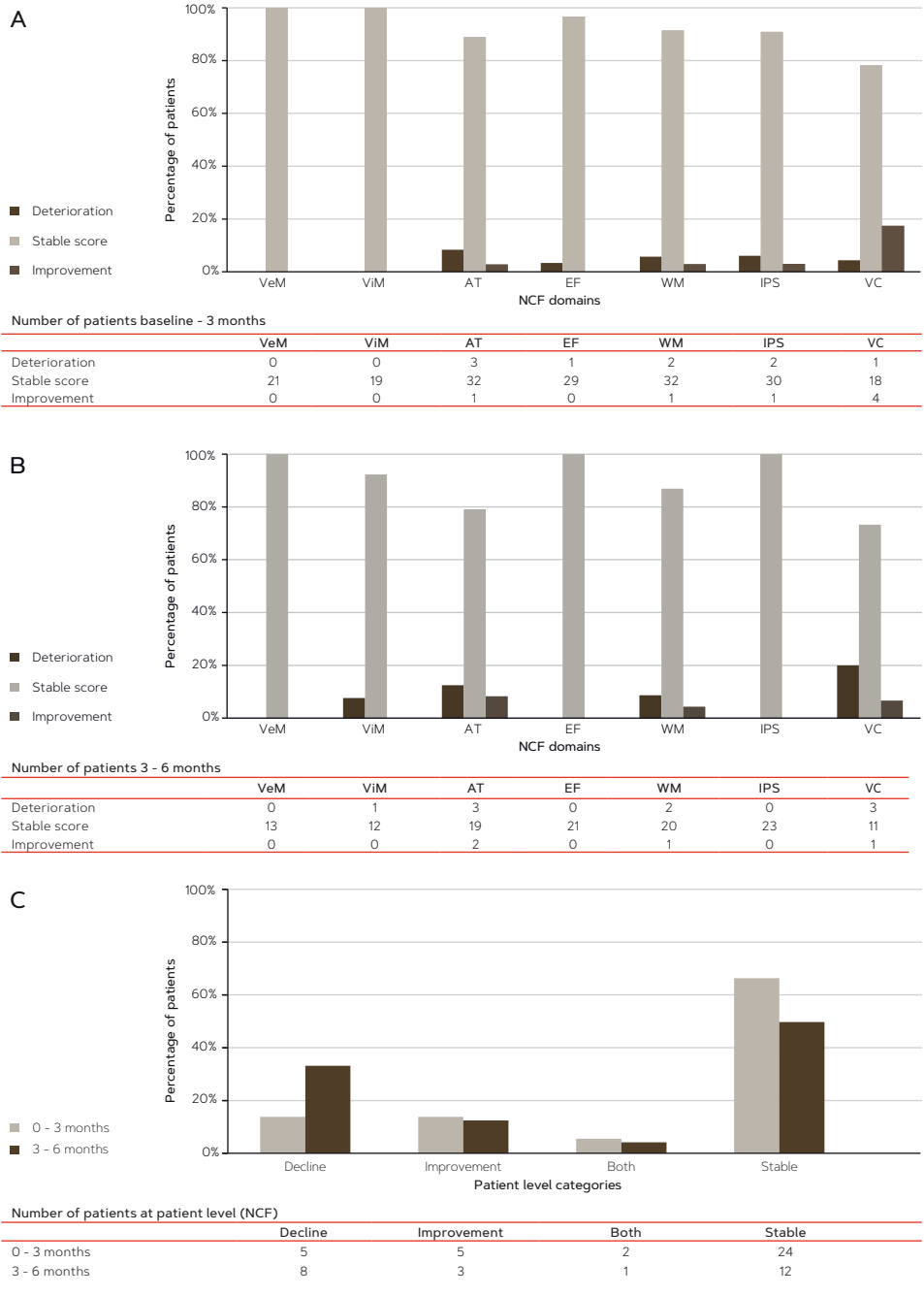


Figure 1. Changes in neurocognitive functioning (NCF) scores calculated from **A** baseline-3 months and **B** 3-6 months at domain level and **C** patient level. *VeM* verbal memory; *ViM* visual memory; *AT* attention; *EF* executive functioning; *WM* working memory; *IPS* information processing speed; *VC* visuoconstruction

in 3/7 domains, 4–8% of patients (Figure 1b)]. Post-hoc analysis using a less stringent cut-off, a change in z-score of ≥ 1.0 SD, revealed similar results (Supplementary Figure 1a; Supplementary Figure 1b).

Patient level

Three months after initial SRT, 14% of patients showed a decline in NCF, another 14% an improvement, 6% both a decline and an improvement, while 67% had stable NCF (Figure 1c). The period covering 3–6 months after initial SRT revealed similar results (decline 33%; improvement 13%; both 4%; and stable 50%). When using the ≥ 1.0 SD cut-off, scores differed from the original results, but still most patients remained stable or improved (Supplementary Figure 1c).

Changes in KPS scores (Supplementary Table 3), SRT dose received, total tumor volume, intracranial progression or active systemic disease in individual patients did not differ significantly between the four different categories from baseline to 3 months or from 3 to 6 months after initial SRT.

Health-related quality of life

Prior to SRT, the vast majority (48/54, 89%) of patients showed a clinically relevant and statistically significant impairment in at least one of the six QLQ-C30 scales when compared to the general population (no reference data available for the QLQ-BN20 scores),³⁹ of which physical functioning was most frequently affected (31/54, 57%).

Scale level

Three months after initial SRT, a decline in all eight different HRQoL scales was observed in 12–61% of patients, most often in fatigue (Figure 2a). 20–71% of patients had stable scores and an improvement was shown in 16–40% of patients most frequently in communication deficit and motor dysfunction, respectively. Comparable percentages were found between 3 and 6 months from initial SRT [deterioration 8–47% of patients; stable score 18–75% of patients; and improvement 11–34% of patients (Figure 2b)].

Patient level

A decline in HRQoL in the first 3 months was observed in 22% of patients, an improvement in 12%, both worsening and improvement in 64%, while only 2% had a stable score (Figure 2c).

Percentages were comparable 6 months after initial SRT (decline 21%; improvement 18%; both 58%; and stable 3%). Changes in KPS scores in individual patients differed significantly between the four categories from baseline to 3 months ($p = 0.001$) and from 3 to 6 months ($p = 0.036$) after initial SRT, with patients deteriorating in at least one HRQoL scale (in the 'both' and 'decline' category) showing most

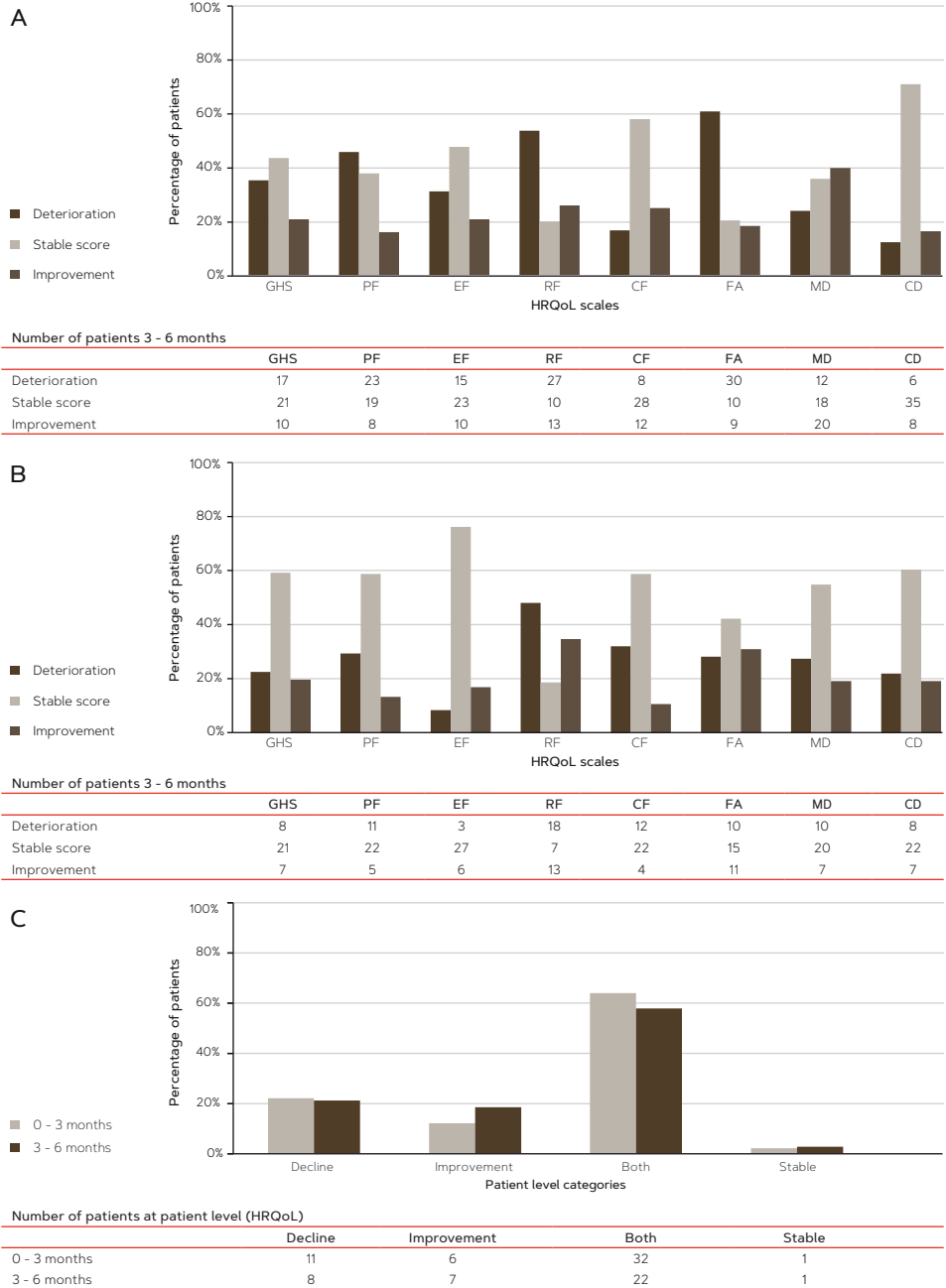


Figure 2. Changes in health-related quality of life (HRQoL) scores calculated from **A** baseline-3 months and **B** 3-6 months at domain level and **C** patient level. *GHS* global health status; *PF* physical functioning; *EF* emotional functioning; *RF* role functioning; *CF* cognitive functioning; *FA* fatigue; *MD* motor dysfunction; *CD* communication deficits

often worsening in performance status (Supplementary Table 3). No statistically significant differences between categories were found for SRT dose received, total tumor volume, intracranial progression or active systemic disease (data not shown).

Cluster analysis HRQoL

A heatmap was created to provide insight into changes in HRQoL at patient level (Figure 3). The most striking pattern is that fatigue, and to a lesser extent emotional functioning, were clustered with global health status, indicating that a change on one scale is likely to be accompanied by a similar change on the other (i.e. decline, improve, both or remain stable). In addition, physical and role functioning were clustered, as well as several brain tumor-specific symptoms, these were motor dysfunction, communication deficit and self-perceived cognitive functioning.

Discussion

The aim of this study was to evaluate changes in NCF and HRQoL at patient level 3 and 6 months after SRT, providing insight in the impact of treatment on the individual patient level. The overall results, in line with results at group level²¹ and several other studies in patients with limited brain metastases,^{19,40,41} indicate that most patients with brain metastases treated with SRT maintained their pre-treatment levels of NCF for at least 6 months. Although NCF and HRQoL at the group level showed little variation, this is not necessarily translated into little variation at domain/scale and patient level. Indeed, changes in scores on the different HRQoL scales did vary substantially within patients, and most individual patients showed both a decline and improvement in separate HRQoL scales in the first 6 months after initial SRT. This finding is in contrast with the HRQoL findings at group level, in which patients who deteriorated and improved most likely cancelled each other out. When informing patients about the impact of a certain treatment or monitor their disease status, it is not sufficient to have information at group level only, nor at the scale level. Clinicians should also be aware that the large majority of patients will experience both deterioration and improvement in HRQoL.

An explanation for the relatively unaffected NCF in brain metastases patients may be that our study population represents a highly selected group of patients with good functioning. Indeed, patients in our sample had a higher KPS score and longer survival compared to our patients without sufficient NCF/HRQoL data. This is also supported by the finding that prior to SRT, only 50% of patients had an impairment in at least one neurocognitive domain, which is considerably lower than in previous studies in metastatic brain tumor patients (67–92%).^{40,42} Particularly for neurocognitive testing, compliance rates decreased substantially over 6 months' time. Responsible for non-compliance, among other things, were poor neurological or physical functioning

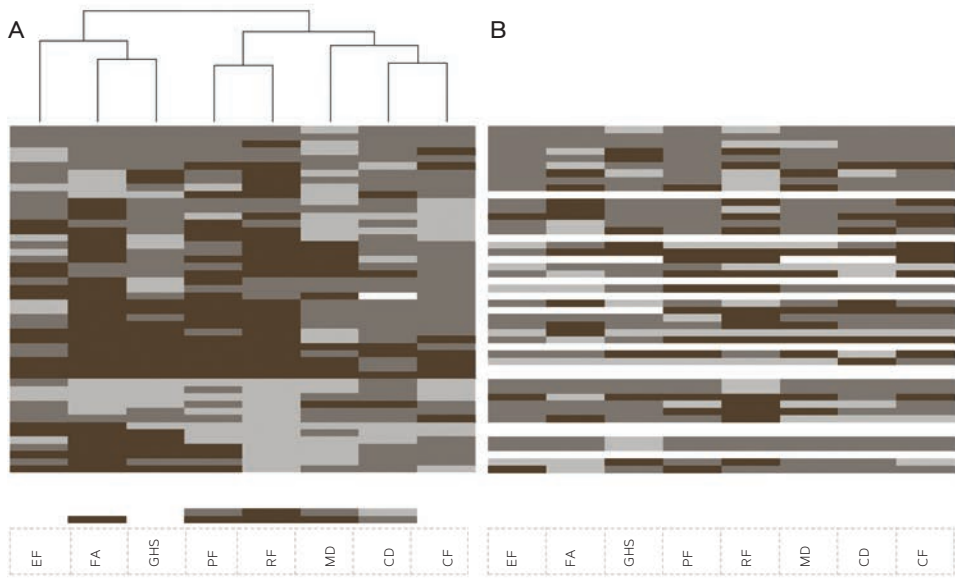


Figure 3. Cluster analysis of differences in health-related-quality of life scores between **A** baseline-3 months and **B** 3–6 months. Dark brown indicates deterioration; Medium brown a stable score; light brown improvement; and white a missing value. On the vertical axis all 55 patients included in this study are displayed. **A** Patients are also clustered, but dendrogram is not shown. **B** Patients and HRQoL scales are similarly ordered for comparison. *EF* emotional functioning; *FA* fatigue; *GHS* global health status; *PF* physical functioning; *RF* role functioning; *MD* motor dysfunction; *CD* communication deficits; *CF* cognitive functioning

and assessment considered too burdensome. Another explanation is the operational definition of objective neurocognitive decline, for which different cut-offs have been suggested.⁴³ Brown et al.,⁴⁴ using a ≥ 1.0 SD cut-off score, found considerably higher neurocognitive deterioration rates compared to our study, with most patients showing cognitive deterioration at 3 months after SRT. However, when using a ≥ 1.0 SD cut-off in our study, still the majority of patients showed no cognitive deterioration, meaning a different cut-off does only partially explains the difference in neurocognitive deterioration rates.⁴⁴ Taking into account the aforementioned explanations for the relatively unaffected NCF, maintenance of NCF over 6 months' time might have been overestimated in our biased sample and likely limits generalizability of the results to brain metastases patients with poor functioning.

Although average HRQoL remained stable at group level, except for physical functioning and fatigue, this did not hold true on scale level nor at patient level. On scale level, patients were relatively similarly distributed over the three different categories (deterioration; stable score; and improvement). At patient level, however, the majority of patients showed both deterioration and improvement in different HRQoL

scales after radiotherapy, which has been previously reported in patients with brain metastases, but comparison is difficult because the majority of patients received WBRT instead of SRT.^{45,46} Caissie et al.⁴⁵ reported that upon follow-up 1 month after radiotherapy significant improvement was seen in several HRQoL scales, including communication deficit.⁴⁵ On the contrary, Steinmann et al.⁴⁶ reported that upon follow-up 3 months after the start of radiotherapy patients showed a significant and clinically relevant deterioration in several preselected HRQoL scales, including global health status, physical functioning, fatigue, motor dysfunction and communication deficit, while other scales remained unchanged.⁴⁶ In our study, the majority of patients showed a clinically relevant deterioration between baseline and 3 months in physical functioning (46%), role functioning (54%) and fatigue (61%), reflecting the findings at group level.²¹ Nevertheless, considering the varying trajectories of changes in HRQoL after SRT, an important observation is that the majority of our patients showed both decline and improvement in separate HRQoL scales. An explanation for the varying trajectories of changes is that HRQoL measures vastly different concepts, encompassing physical, emotional, and social components, and that this outcome may be influenced by many factors, including comorbidity, marital status, heterogeneity of the primary tumor, SRT dose, total tumor volume, progression of the extracranial cancer and its corresponding supportive or anti-tumor treatment.⁴⁷ Although, SRT dose received, total tumor volume, intracranial progression and active systemic disease did not differ significantly between the four different categories at patient level, this result must be interpreted with caution due to our small sample size. As pointed out by Wilson and Cleary⁴⁸ in their model, more distal measures to the disease or the treatment (i.e. global health status and the functioning scales) are not only affected by health status but also by non-medical factors, as opposed to more proximal measures (i.e. symptoms).⁴⁸ NCF is a proximal measure, which is mainly influenced by the presence of brain metastases, or its treatment. Patients who deteriorated on at least one HRQoL scale did most often have decreased performance status, suggesting that especially the patients' overall functioning influences HRQoL. Moreover, Caissie et al.⁴⁹ found that fatigue and emotional functioning were the two strongest predictors of global health status in brain metastases patients, which is similar to the findings of our cluster analysis; deterioration in global health status clusters with increased fatigue and worse emotional functioning, suggesting fatigue may be a target for intervention to improve overall HRQoL.⁴⁹

To conclude, in accordance with previous results at group level, this study showed that most patients with brain oligometastases treated with SRT maintained their pre-treatment NCF for at least 6 months. However, changes in scores for the various HRQoL scales differed considerably between and within patients, suggesting that overall functioning is determined by complex underlying mechanisms which should be further analyzed.

References

1. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698-2705.
2. Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol*. 2012;14(7):910-918.
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14(1):48-54.
4. Soffietti R, Rudà R, Trevisan E. Brain metastases: current management and new developments. *Curr Opin Oncol*. 2008;20(6):676-684.
5. Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. *Neuro Oncol*. 2016;18(8):1043-1065.
6. Kamar FG, Posner JB. Brain metastases. *Semin Neurol*. 2010;30(3):217-235.
7. Day J, Gillespie DC, Rooney AG, et al. Neurocognitive Deficits and Neurocognitive Rehabilitation in Adult Brain Tumors. *Curr Treat Options Neurol*. 2016;18(5):22.
8. Kaal EC, Niël CG, Vecht CJ. Therapeutic management of brain metastasis. *Lancet Neurol*. 2005;4(5):289-298.
9. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
10. Pectasides D, Pectasides M, Economopoulos T. Brain metastases from epithelial ovarian cancer: a review of the literature. *Oncologist*. 2006;11(3):252-260.
11. Dirven L, Reijneveld JC, Taphoorn MJB. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? *Semin Oncol*. 2014;41(4):541-552.
12. Schagen SB, Klein M, Reijneveld JC, et al. Monitoring and optimising cognitive function in cancer patients: Present knowledge and future directions. *EJC Suppl*. 2014;12(1):29-40.
13. Müller-Riemenschneider F, Bockelbrink A, Ernst I, et al. Stereotactic radiosurgery for the treatment of brain metastases. *Radiother Oncol*. 2009;91(1):67-74.
14. Halasz LM, Rockhill JK. Stereotactic radiosurgery and stereotactic radiotherapy for brain metastases. *Surg Neurol Int*. 2013;4(Suppl 4):S185-191.
15. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys*. 2015;91(4):710-717.
16. Gavrilovic IT, Posner JB. Brain metastases: epidemiology and pathophysiology. *J Neurooncol*. 2005;75(1):5-14.
17. Soliman H, Das S, Larson DA, Sahgal A. Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases. *Oncotarget*. 2016;7(11):12318-12330.
18. Scoccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. *Radiother Oncol*. 2012;102(2):168-179.
19. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA*. 2006;295(21):2483-2491.
20. Regine WF, Huhn JL, Patchell RA, et al. Risk of symptomatic brain tumor recurrence and neurologic deficit after radiosurgery alone in patients with newly diagnosed brain metastases: results and implications. *Int J Radiat Oncol Biol Phys*. 2002;52(2):333-338.
21. Habets EJ, Dirven L, Wiggeraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with

- stereotactic radiotherapy for brain metastases: a prospective study. *Neuro Oncol.* 2016;18(3):435-444.
22. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4. New York: Oxford University Press; 2004.
 23. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery*. 2000;47(2):324-333.
 24. Saan RJ, Deelman BG. De 15-woordentest A en B (een voorlopige handleiding) [The 15 words test A and B (a preliminary manual)]. In: Afdeling Neuropsychologie, AZG, Groningen; 1986.
 25. Uterwijk JMR. WAIS-III Nederlandstalige bewerking. Technische handleiding. David Wechsler [WAIS-III Dutch revision. Technical manual. David Wechsler] Wechsler Adult Intelligence Scale III [Dutch revision. Technical manual]. In: Lisse: Swets Test Publishers; 2000.
 26. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess.* 2006;18(4):424-432.
 27. Krabbendam L, Kalf AC. *The Behavioural Assessment of the Dysexecutive Syndrome: Dutch Version*. Lisse: Swets and Zeitlinger; 1998.
 28. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning*. New York: Psychology Press, Inc.; 2003:159-173.
 29. Osterreith PA. Le test de copie d'une figure complexe [A test regarding a complex figure]. *Archives de Psychologie/ The Clinical Neuropsychologist*. 1944;30/ 7:206/ 209-356/ 215.
 30. Jolles J, Van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr*. 1998;29(3):120-129.
 31. de Bie SE. [Proposal for uniformisation of questions regarding background variables and interviews]. Leiden: Leiden University Press; 1987.
 32. van der Elst W. *The neuropsychometrics of aging: normative studies in the Maastricht Aging Study*. In: Maastricht: University of Maastricht; 2006.
 33. Fastenau PS, Denburg NL, Hufford BJ. Adult norms for the Rey-Osterrieth Complex Figure Test and for supplemental recognition and matching trials from the Extended Complex Figure Test. *Clin Neuropsychol*. 1999;13(1):30-47.
 34. Kessels RP, Nys GM, Brands AM, van den Berg E, van Zandvoort MJ. The modified Location Learning Test: norms for the assessment of spatial memory function in neuropsychological patients. *Arch Clin Neuropsychol*. 2006;21(8):841-846.
 35. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res*. 1996;5(1):139-150.
 36. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
 37. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013;31(1):65-72.
 38. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139-144.
 39. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC

- QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer*. 2011;47(5):667-675.
40. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery*. 2007;60(2):277-283; discussion 283-274.
 41. Minniti G, Esposito V, Clarke E, et al. Stereotactic radiosurgery in elderly patients with brain metastases. *J Neurooncol*. 2013;111(3):319-325.
 42. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol*. 2004;22(1):157-165.
 43. Jak AJ, Bondi MW, Delano-Wood L, et al. Quantification of five neuropsychological approaches to defining mild cognitive impairment. *Am J Geriatr Psychiatry*. 2009;17(5):368-375.
 44. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA*. 2016;316(4):401-409.
 45. Caissie A, Nguyen J, Chen E, et al. Quality of life in patients with brain metastases using the EORTC QLQ-BN20+2 and QLQ-C15-PAL. *Int J Radiat Oncol Biol Phys*. 2012;83(4):1238-1245.
 46. Steinmann D, Paelecke-Habermann Y, Geinitz H, et al. Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. *BMC Cancer*. 2012;12:283.
 47. Reeve BB, Potosky AL, Smith AW, et al. Impact of cancer on health-related quality of life of older Americans. *J Natl Cancer Inst*. 2009;101(12):860-868.
 48. Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *JAMA*. 1995;273(1):59-65.
 49. Caissie A, Culleton S, Nguyen J, et al. What QLQ-C15-PAL Symptoms Matter Most for Overall Quality of Life in Patients With Advanced Cancer? *World J Oncol*. 2011;2(4):166-174.

Supplementary data

Table S1. Neurocognitive domain and the corresponding neurocognitive test(s)

Neurocognitive domain	Neurocognitive test(s)
Verbal memory	Rey Auditory Verbal Learning Test (immediate recall, delayed recall and delayed recognition) ¹
Visual memory	Rey Complex Figure Test (delayed recall) ²
Attention	Stroop Color-Word Test ³
Executive functioning	Digit Span forward and backward, a subtest of Wechsler Adult Intelligence Scale III ⁴
	Concept Shifting Test ⁵
	Word fluency (category and letter fluency) ³
Working memory	Key-search test, a subtest of the behavioural Assessment of the Dysexecutive Syndrome ⁶
	Digit Span forward and backward, a subtest of Wechsler Adult Intelligence Scale III ⁴
Information processing speed	Stroop Color-Word Test ³
	Letter Digit Substitution Test ³
Visuoconstruction	Rey Complex Figure Test (copying) ²

Table S2. Compliance with NCF and HRQoL assessments

	No. of Forms/ Assessments Expected ^a	No. of forms completed/ Assessments performed	
		NCF	HRQoL
Baseline	55	50 (91%)	54 (98%)
3 months	55	38 (69%)	51 (93%)
6 months	48	27 (56%)	41 (85%)
Baseline, 3 and 6 months	48	23 (48%)	37 (77%)

^aBased on alive participating patients, NCF neurocognitive functioning; HRQoL health-related quality of life

Table S3. Changes in KPS scores from baseline - 3 months and 3 - 6 months, with respect to changes in NCF and HRQoL at patient level

	Changes in KPS scores (0-3 months, n=36; 3-6 months, n=24)					
	Deterioration		Stable		Improvement	
	0-3 months	3-6 months	0-3 months	3-6 months	0-3 months	3-6 months
NCF, No. (%)						
Decline	1 (3)	1 (4)	3 (8)	5 (21)	1 (3)	2 (8)
Both	1 (3)	0 (0)	0 (0)	0 (0)	1 (3)	1 (4)
Stable	14 (39)	4 (17)	6 (17)	6 (25)	4 (11)	2 (8)
Improvement	1 (3)	0 (0)	1 (3)	2 (8)	3 (8)	1 (4)
HRQoL, No. (%)						
Decline	10 (20)	4 (11)	0 (0)	4 (11)	1 (2)	0 (0)
Both	15 (30)	6 (16)	12 (24)	13 (34)	5 (10)	3 (8)
Stable	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Improvement	0 (0)	0 (0)	1 (2)	3 (8)	5 (10)	4 (11)

KPS Karnofsky Performance Status; NCF neurocognitive functioning; HRQoL health-related quality of life

Note: Due to rounding, not all percentages add up to 100%

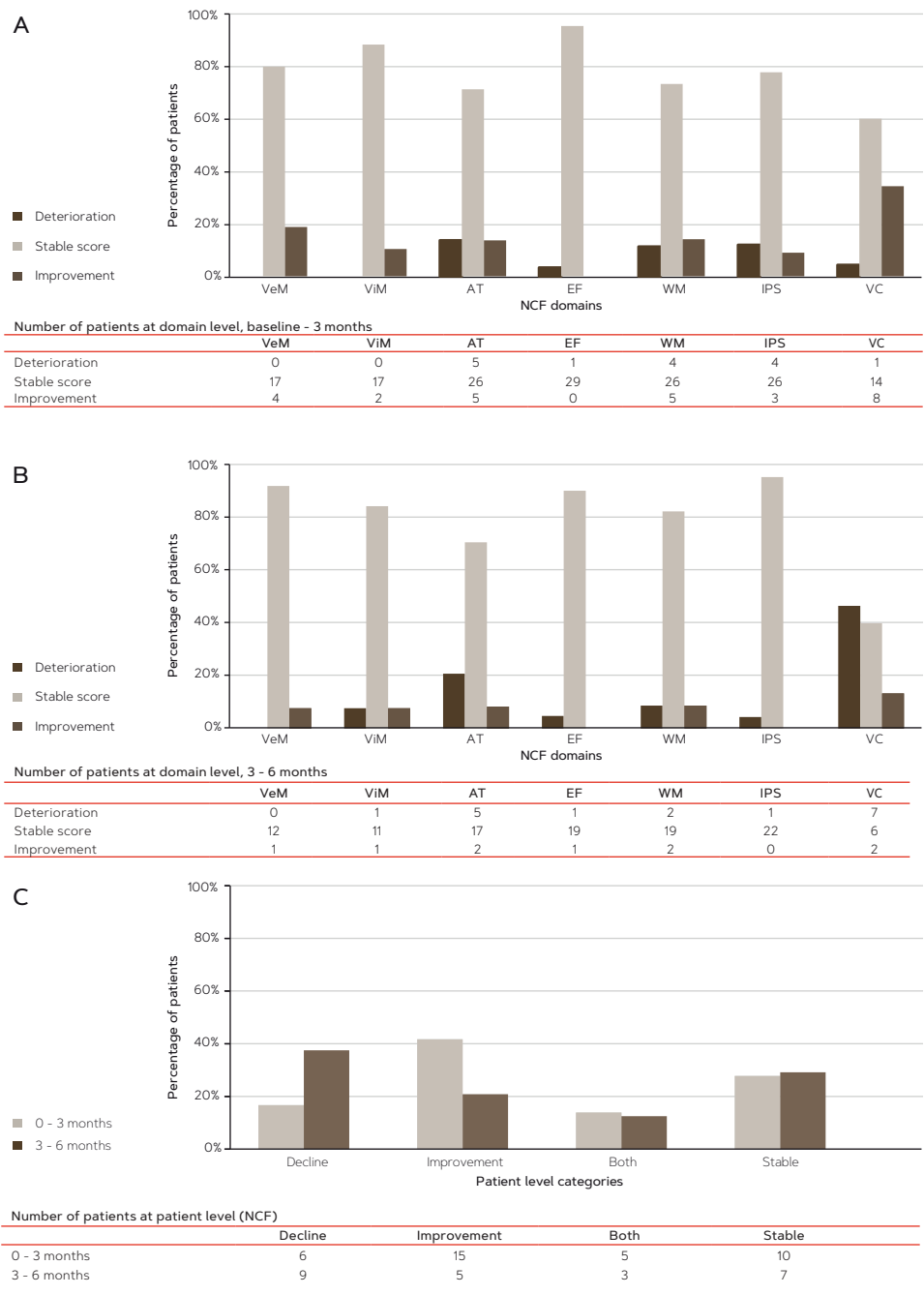


Figure S1. Changes in neurocognitive functioning (NCF) scores, using a change in z-score of ≥ 1.0 SD, at domain level calculated from **a** baseline - 3 months and **b** 3 - 6 months, and **c** patient level. *VeM*, verbal memory; *ViM*, visual memory; *AT*, attention; *EF*, executive functioning; *WM*, working memory; *IPS*, information processing speed; *VC*, visuoconstruction

References

1. Schmand B, Lindeboom J, Van Harskamp F. [*The 15 words test A and B (a preliminary manual)*]. Groningen: Afdeling Neuropsychologie, AZG; 1992.
2. Osterreith PA. Le test de copie d'une figure complexe [A test regarding a complex figure]. *Archives de Psychologie/ The Clinical Neuropsychologist*. 1944;30/ 7:206/ 209-356/ 215.
3. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4. New York: Oxford University Press; 2004.
4. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual]*. Lisse2000.
5. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Concept Shifting Test: adult normative data. *Psychol Assess*. 2006;18(4):424-432.
6. Krabbendam L, Kalff AC. *The Behavioural Assessment of the Dysexecutive Syndrome: Dutch Version*. Lisse: Swets and Zeitlinger; 1998.

5

Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors

Journal of Neuro-Oncology

2014 Jan;116(1):161-168.

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Abstract

Background: Overall survival of patients with anaplastic oligodendrogial tumors has been improved due to the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy to radiotherapy (RT), especially in 1p/19q-codeleted tumors. With improved survival, quality of survival becomes pivotal. We evaluated cognitive functioning and health-related quality of life (HRQoL) in a cohort of long-term anaplastic oligodendroglioma survivors.

Methods: Thirty-two out of 37 long-term survivors included in European Organisation for Research and Treatment of Cancer (EORTC) study 26951 in the Netherlands and France participated. Cognition was assessed using neuropsychological tests for 6 domains, and HRQOL with the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) and Brain Cancer Module (EORTC QLQ-BN20). Fatigue and mood were evaluated. Results were compared to healthy controls and to patients' own HRQOL 2.5 years following initial treatment.

Results: At the time of assessment, median survival for the patients was 147 months, 27 were still progression-free since initial treatment. Of progression-free patients, 26% were not, and 30% were severely cognitively impaired; 41% were employed and 81% could live independently. Patients' HRQoL was worse compared to controls, but similar to 2.5 years after initial treatment. Initial treatment (RT versus RT + PCV) was not correlated with cognition or HRQoL.

Conclusions: Cognitive functioning in long-term anaplastic oligodendroglioma survivors is variable. However, most patients function independently. In progression-free patients, HRQoL is relatively stable during the disease course. In this small sample, no effect of the addition of PCV on cognition or HRQoL was identified.

Introduction

Although anaplastic glioma still is an incurable disease, recent data have shown a considerable gain in overall survival with the addition of procarbazine, lomustine and vincristine (PCV) chemotherapy to radiotherapy (RT) for newly diagnosed anaplastic oligodendroglioma patients with combined 1p/19q loss.^{1,2} With (neo)adjuvant PCV, survival in this subgroup increased from 9 years to still not reached after 12 years of follow-up in the European Organisation for Research and Treatment of Cancer (EORTC) 26951 study, and from 7 to 14 years in the Radiation Therapy Oncology Group (RTOG) 9402 study.^{1,2} Median survival of all anaplastic glioma patients was between 2.5 and 4.7 years.^{1,2} A formal definition of long-term survival in anaplastic oligodendroglioma is missing. Five year survival varies from 16 to 32%.^{3,4} Patients surviving more than 8 years can therefore be considered as long-term survivors.

With improved survival, the quality of survival becomes essential. If treatment for effective tumor control results in neurotoxicity with cognitive impairments and worse health-related quality of life (HRQoL), longer survival may be less meaningful for patients. Proper information on HRQoL and cognition on the long run might influence the choice of postoperative treatment.

Data regarding long-term functioning in terms of cognitive functioning and HRQoL in high-grade glioma patients are scarce. Results vary from normal cognitive functioning to cognitive impairments in all studied patients, partly related to follow-up time and measures used.⁵⁻⁷ HRQoL was found to be of acceptable level, namely in the mid upper range, within 2.5 years after diagnosis in anaplastic oligodendroglioma patients.^{7,8} Unfortunately, due to a too low percentage of compliance, analyses beyond 2.5 years after treatment were no longer meaningful.⁸

Because of the lack of data on long-term functioning of anaplastic glioma patients and the growing number of long-term survivors, we evaluated HRQoL and cognitive functioning in long-term survivors with anaplastic oligodendroglioma and oligoastrocytoma with 1p/19q codeletion and non-1p/19q deletion.

Methods

Patients and procedure

We identified all long-term survivors included in EORTC study 26951 treated in centers in the Netherlands and in the largest accruing center in France. EORTC 26951 was initiated to study the efficacy of additional PCV to RT in newly diagnosed anaplastic oligodendroglial tumors; accrual was completed in 2002.

Evaluations were conducted between May and November 2011. Neurocognitive assessment took place at the patient's home or at the hospital. HRQoL

questionnaires were filled in by the patients and, separately, by their proxies, preceding the neurocognitive assessment. The study was approved by the Medical Ethical Committees of the VU University Medical Center Amsterdam and the Groupe Hospitalier Pitié-Salpêtrière Paris. All participants gave informed consent.

Primary outcome measures

Cognitive functioning

We assessed cognitive functioning by a battery of standardized neuropsychological tests, covering a wide range of cognitive functions found to be affected in glioma patients.⁹⁻¹¹ This battery consists of the letter-digits modalities test, concept shifting test, Stroop color-word test, visual verbal learning test, memory comparison test and categoric word fluency.¹² These tests cover six cognitive domains: information processing speed, psychomotor function, attention, verbal and working memory and executive functioning.¹² We compared patients' test performance with performance of healthy controls from a database of the Maastricht University, The Netherlands.¹³ These controls were individually matched with respect to age, sex, and educational level.¹⁴ Individual patient's test scores were converted into standardized z scores with use of mean and *SD* of the matched healthy controls on that test, and then combined into domain summary measures for the patients.

HRQoL

We assessed HRQoL of patients with self-report questionnaires specifically designed for (brain) tumor patients: the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) and the EORTC QLQ- Brain Cancer Module (EORTC QLQ-BN20).^{15,16} Raw scores were transformed into scaled scores with range 0-100.¹⁷ Mood and fatigue were evaluated through the Center for Epidemiologic Studies Depression Scale (CES-D)¹⁸ and the Checklist Individual Strength (CIS),¹⁹ respectively. Because HRQoL of high-grade glioma patients as evaluated by their proxies can be of use,²⁰ the QLQ-BN20 was also completed by the proxy regarding his/her opinion about functioning of the patient. We compared scores on the QLQ-C30 and QLQ-BN20 with the patients' own scores on average 2.5 years after initial treatment.⁸ Patients' scores on the QLQ-C30 were also compared with normative data from healthy persons,²¹ and on the QLQ-BN20 with patient-by-proxy scores. Scores on the CIS and CES-D were compared with published normative data. A CIS score of >76 was considered problematic fatigue,²² and a CES score of ≥ 16 was indicative of a clinical depression.²³

Secondary outcome measures

Secondary parameters were level of functioning and employment. We assessed level of functioning with the Karnofsky Performance Status (KPS).^{24,25} A patient with a KPS score of ≥ 70 is considered independent in activities of daily living and self-care.²⁴

Statistical analysis

According to accepted neuropsychological practice, an individual z-score of ≥ 1.5 SD below the mean of controls on a domain was defined as a clinically significant cognitive impairment.²⁶ We defined impairment as mild to moderate if one to three domains out of six were affected, and severe if four or more domains were affected.

Statistical analyses were performed with SPSS (version 17). Pearson χ^2 tests or Mann-Whitney test for independent samples were used to compare differences in sociodemographic and clinical characteristics between participating and non-participating patients. Because of expected differences in cognitive functioning and HRQoL between patients who never experienced progressive disease and patients with recurrent disease, we analyzed the outcome measures in both patient groups separately.^{27,28}

Kolmogorov-Smirnov test for independent samples was used to analyze differences between patients and healthy controls. We analyzed changes in HRQoL over time by Wilcoxon signed rank tests for related samples. Associations between cognitive functioning or HRQoL and initial treatment (RT versus RT + PCV), tumor location, genetic status (1p/19q codeletion versus non-1p/19q-codeletion), epilepsy in the last year, use of anti-epileptic drugs (AEDs), and use of medication which could impact the cognitive assessments (steroids, antidepressants, sedatives, analgesics) were analyzed with Spearman's rho or Mann-Whitney tests. The level of significance was set at $p < 0.05$. We corrected for multiple testing.

Results

Patients' characteristics

Of the 368 patients included in EORTC 26951, 217 were included by centers in The Netherlands and Paris.²⁹ Twenty-five of the 28 alive Dutch patients (89%) gave informed consent. Two patients expected participation to be too burdensome and one was in poor condition. Seven of the 9 alive French patients (78%) gave informed consent. One patient refused participation and one patient was in poor neurological condition.

Of the 32 patients included, two patients could not be tested neuropsychologically, due to severe neurological and cognitive condition in one patient, and to mutism in the other (both progression-free). In three other patients neurocognitive testing was incomplete, due to aphasia (one patient, with recurrent disease), problems in understanding the test instructions or visual disorder (both one patient, progression-free). The administered tests of these patients were included in the analyses. Patients in whom (complete) neuropsychological assessment was not possible due to poor cognitive condition, were considered severely cognitively impaired in further

analyses. Two patients were not able to fill in the questionnaires due to cognitive and neurological impairments. Four patients could not fill in the questionnaires on their own, because of e.g. aphasia or physical impairments, but completed (most of) the HRQoL questionnaires with (verbalized) help of the neuropsychologist who administered the neurocognitive tests. Furthermore, two proxies did not fill in the HRQoL questionnaires.

Table 1 shows the sociodemographic and clinical characteristics of the patient group. Non-participating patients did not differ from patients who participated regarding age, sex, education or KPS. Sixty-nine percent of patients received RT + PCV treatment, 50% had a 1p/19q-codeleted tumor. Five patients had been diagnosed with recurrent disease; three of them were treated with RT only, two with RT + PCV. Median survival since randomization was 147 months (range 112-170).

Primary outcome measures

Cognitive functioning

Cognitive domain summary measures are depicted in Figure 1. Within the group of patients that never experienced progressive disease ($n = 27$), we found no cognitive impairment in 26%, mild to moderate impairment in 44%, and severe impairment in 30% of patients. Of the patients with recurrent disease ($n = 5$), one had no cognitive impairment, one had mild to moderate impairment and three had severe impairment.

Because we considered the group of patients with recurrent disease too small to analyze cognitive functioning in relation to treatment, location, seizures, and use of medications, further analyses were restricted to patients who never progressed.

Compared to healthy controls, patients who never progressed had lower working memory capacity, information processing speed, psychomotor functioning, attention and executive functioning. We found no difference in cognitive impairments between patients treated with RT only ($n = 7$) and patients treated with RT + PCV ($n = 20$). No association was found between hemispheric location or genetic status or the presence of seizures and cognitive performance. Scores on the cognitive domains did not differ between patients using AEDs ($n = 17$) and patients not using AEDs ($n = 10$). Because only few patients used other medications, no analyses could be performed regarding the influence of these medications on cognitive functioning.

HRQoL

For the group of patients that never progressed, scores on the QLQ-C30 questionnaire were lower than of healthy controls. Differences were significant on emotional ($p = 0.003$), social ($p = 0.017$) and cognitive functioning scales ($p = 0.000$), as was also observed 2.5 years after initial treatment. On the symptom scales, patients experienced more fatigue ($p = 0.006$) and financial difficulties ($p = 0.037$) than healthy controls (Figure 2a, b). We could compare long-term QLQ-C30 and

Table 1. Sociodemographic and clinical characteristics of the study patients

	Patients (n = 32)	
	No. of patients	%
Age, years; mean $\pm$ SD	56.7 $\pm$ 8.3	
Sex		
Male/female	19/13	59/41
Educational level ^a ; mean $\pm$ SD	4 $\pm$ 1.9	
Tumor histology		
Anaplastic oligodendroglioma	22	69
Anaplastic oligoastrocytoma	10	31
Genetic status		
1p/19q codeletion	16	50
Non-codeletion	14	44
Unknown	2	6
Tumor hemisphere		
Left	13	41
Right	18	56
Bilateral	1	3
Tumor localization		
Frontal/non-frontal	17/15	53/47
EORTC- treatment		
RT	10	31
RT + PCV	22	69
Recurrent disease		
No recurrence	27	84
One recurrence	3	10
> One recurrence	2	6
Additional tumor treatment		
No additional treatment	28	88
Additional chemo (PCV/TMZ)	1/1	3/3
Additional surgery + TMZ	1	3
Additional surgery, PCV, RT	1	3
Epilepsy in <1 year	5	16
Use of anti-epileptics (AEDs)	22	69
Use of other medications		
Steroids	1	3
Anti-depressants	3	9
Sedatives	2	6
Analgesics (e.g. paracetamol)	4	13
Others (anti-Parkinson or antipsychotic)	2	6
Functional status		
KPS <70 / $\geq$ 70	7/25	22/78
Employment	10	31
Survival in months		
Mean $\pm$ SD / median	146 $\pm$ 16.5/147	
Range	112-170	

SD standard deviation; RT radiotherapy; PCV procarbazine/lomustine/vincristine; TMZ temozolomide; AEDs anti-epileptic drugs; KPS Karnofsky Performance Status; ^aCode 1-8¹⁴

QLQ-BN20 follow-up (present study) and follow-up 2.5 years after initial treatment in 22 out of 27 patients who never progressed. Although for several subscales scores at long-term follow-up tended to be lower than at 2.5 years follow-up, we found no significant differences in QLQ-C30 scores between both assessments. On the QLQ-BN20 questionnaire, patients reported significantly more problems in motor functioning ($p = 0.03$) than at 2.5 years follow-up. There was no significant difference between the scores of patients and patient-by-proxies on BN20 scales, although patient-by-proxies tended to report more symptoms (Figure 2c).

Initial treatment (RT versus RT + PCV) and genetic status were not related to differences in QLQ-C30 and BN20 scores of patients who never progressed. Patients with right-sided tumors experienced more fatigue ($p = 0.047$), insomnia ($p = 0.035$) and diarrhea ($p = 0.043$) than patients with left-sided tumors. Current seizures and use of AEDs were not associated with worse HRQoL. Cognitive impairment was only correlated with lower physical functioning (ρ ; $p = 0.01$), social functioning (ρ ; $p = 0.016$) and future uncertainties (ρ ; $p = 0.041$).

Due to the small size of the group with recurrent disease, no analyses on HRQoL measures could be performed in this subgroup. However, the few patients with recurrent disease tended to have lower HRQoL measures compared to patients who never progressed, and compared to their own scores 2.5 years after treatment.

On the CES-D, scores of 11% of patients who never progressed and of 60% of patients with recurrent disease were indicative of depressive mood. Fifty percent of patients who never progressed and 60% of patients with recurrent disease reported problematic fatigue on the CIS.

Secondary outcome measures

Measured by KPS score, 85% of patients who never progressed and 40% of patients with recurrent disease were independent in activities of daily living and self-care ($KPS \geq 70$). Institutionalized care was needed in 19% of patients who never progressed. In three patients this was due to frontal dysfunction, and in two because of poor neurological condition. Institutionalized care was needed in 40% of patients with recurrence, due to poor neurological status or frontal dysfunction (both one patient). Of the patients who never progressed and had not reached normal retirement age ($n = 22$), 41% were employed. Some patients worked fewer hours or did adjusted work after their diagnosis. Patients who had better cognitive functioning, tended to be more often employed compared to cognitively worse functioning patients, but differences were non-significant. Of the patients with recurrent disease who had not reached normal retirement age ($n = 4$), one patient was employed.

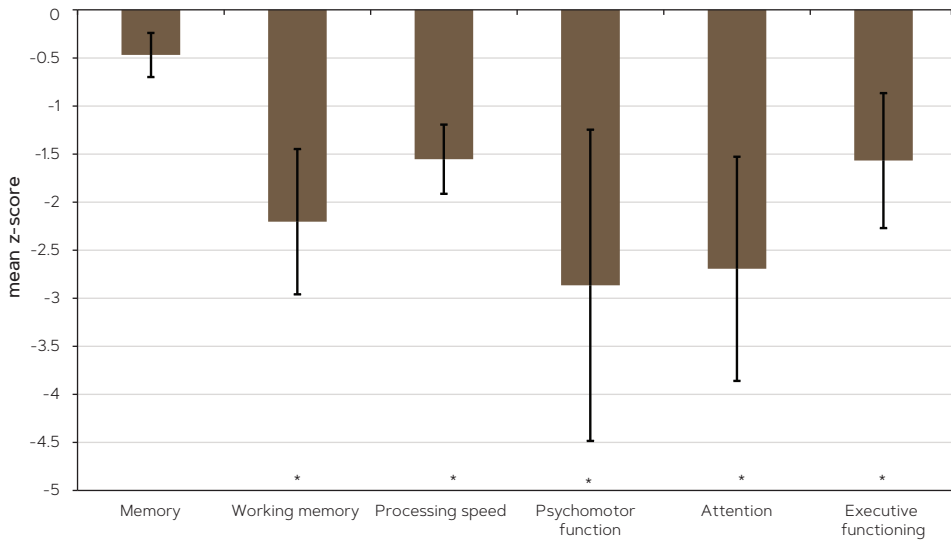


Figure 1. Mean z-scores and standard error mean (SEM) of patients who never progressed for each cognitive domain. The patients' performance is compared to age, sex-, and education-matched healthy controls (represented by the 0- line). A score closer to 0 means a better performance. * Significant at the 0.05 level

Discussion

We found highly variable cognitive functioning in long-term anaplastic oligodendroglioma survivors, with 74% of progression-free patients having at least some cognitive impairment. Long-term HRQoL did not differ significantly from measures 2.5 years after initial treatment in progression-free patients.

Very little data exist on quality of long-term survival in high-grade glioma patients. Cognitive dysfunction in glioma patients is partly related to the tumor itself.³⁰ A rapid cognitive decline is often seen with progressive disease,^{7,27} and this was confirmed in our study, although we included only few patients with progression. Surprisingly, left-sided tumors were not associated with more cognitive impairments compared to right-sided tumors in our study, which is a robust finding in studies on cognition in glioma patients with shorter survival.^{31,32} Unfortunately, we could not account for tumor size or extent of resection. We found no differences in cognition between patients with and without 1p/19q-codeleted tumors.

Treatment may also negatively influence cognitive functioning in glioma patients, and cognitive deterioration may continue for many years after treatment.^{5,12,33,34} Long-term low-grade glioma survivors who did not have had radiotherapy had stable

cognitive status, whereas patients who received radiotherapy showed a progressive decline in attention.^{12,34} Three years after initial treatment 40% of GBM patients, the vast majority without tumor recurrence, performed abnormal on a neurocognitive test measuring attention, (working) memory and language.⁶ Most of these GBM patients could function independently,⁶ in line with our observations. Two other studies however concluded that more than 5 years after initial treatment (nearly) all high-grade glioma patients suffered from cognitive deficits and only few functioned fully independently, despite the fact that only a minority had had recurrent disease.^{5,33} In these studies irradiation and chemotherapy treatment regimens differed from current standards.^{5,33}

In the absence of chemotherapy-treated patients only, we cannot assess to what extent the patients in our study suffered from delayed effects of RT on cognition, but this is plausible on the basis of previous reports. Regarding PCV chemotherapy, unfortunately, no data exists on cognitive effects of standard PCV such as our patients received,²⁹ and our patient sample was perhaps too small to detect possible effects.

Our findings that HRQoL measures of patients were lower than of healthy controls is in accordance with previous research with shorter follow-up in high-grade glioma.⁵⁻⁸ In earlier studies, HRQoL of anaplastic oligodendroglioma patients was considerably impaired compared to healthy controls before treatment, and showed a transient decline during and shortly after (neo)adjuvant PCV treatment.^{7,8} In the period after treatment, an improvement was found and up to 2.5 years after diagnosis, HRQoL was stable and of acceptable level.^{7,8} We found that the impact of anaplastic glioma is largest on HRQoL domains related to mental (i.e. social, cognitive and emotional) functioning. Our findings that HRQoL does not substantially change in the long term in patients without tumor progression might indicate patients have found a satisfactory way of living with their disease. But as on several subscales a trend towards a lower long-term HRQoL compared to 2.5 years after initial treatment was observed, our patient sample might have been too small to detect subtle changes in HRQoL. Also in patients not able to fill in the questionnaire, a decline in HRQoL might be expected. The observed differences in HRQoL between right- and left-sided tumors might be caused by the small sample size. Although our patient subgroup with progressive disease was small, recurrent disease tended to be associated with lower HRQoL, in accordance with earlier findings.²⁸ In other studies a (considerable) decline in HRQoL was seen in the year before death.⁷

Limitations of this study are related to the relatively small sample size, the inclusion of patients from a clinical trial and from a selected number of centers participating in EORTC 26951. Also, few patients could not be included due to severe condition. However, compliance of the alive patients was high and not limited to well-functioning patients. Due to the small sample size, no predictors of poor cognitive functioning or

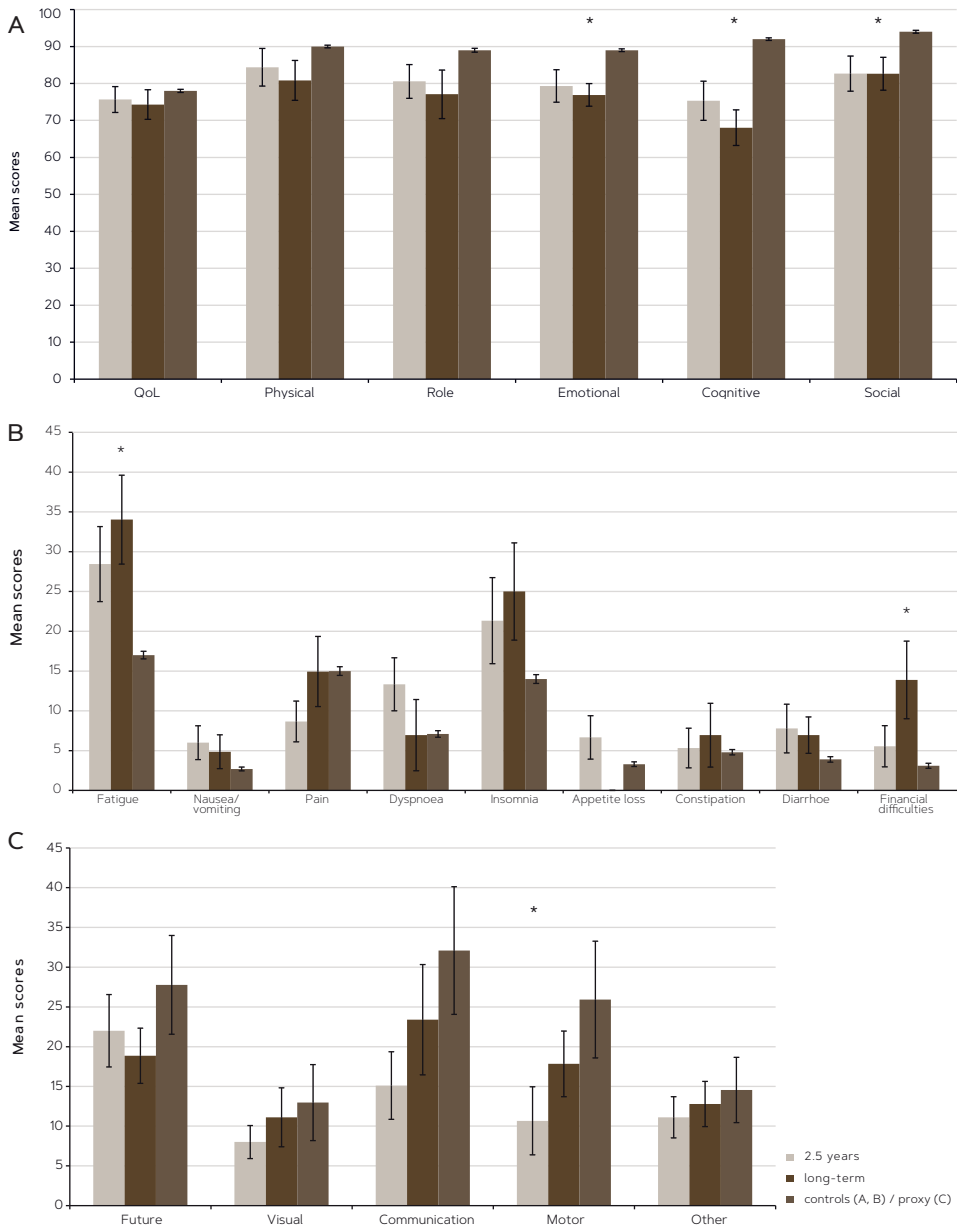


Figure 2. Mean scores and SEM of patients without progressive disease and controls on EORTC QLQ-C30 functional scales and global quality of life **A**, with higher score meaning better functioning; of patients without progressive disease and controls on EORTC QLQ-C30 symptom scales and single items **B**, higher score meaning more symptoms; of patients without progressive disease and patient-by-proxies on EORTC BN20 scales **C**, higher score meaning more symptoms. * Significant differences ($p < 0.05$) between long term follow-up and controls (A, B); * Significant differences ($p < 0.05$) between 2.5 years follow-up and long-term follow-up (C)

HRQoL could be identified. Another limitation is that cognition has not been evaluated extensively earlier in the disease course of these patients, and we could therefore not compare our long-term results with baseline cognition.

In conclusion, the present results suggest that long-term progression-free survival of patients with anaplastic oligodendroglioma is attended with relatively stable HRQoL, but that a substantial proportion of survivors suffers from cognitive impairment. We have no indication that the addition of chemotherapy negatively influences HRQoL and cognition, but we realize that our sample size is very small. In order to draw more definitive conclusions, prospective studies with much larger sample size are necessary. Our results illustrate the need to include cognitive functioning and HRQoL as outcome measures in studies on high-grade glioma patients,³⁵ and to continue evaluation of these measures in patients after tumor progression has occurred. With identification of potential adverse influences on cognition and HRQoL, interventions and (cognitive) rehabilitation programs³⁶ to preserve long term quality of survival in high-grade glioma patients, can be more adequately administered.

References

1. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013;31:344-350.
2. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol.* 2013;31:337-343.
3. Hamlat A, Saikali S, Chaperon J, et al. Proposal of a scoring scale as a survival predictor in intracranial oligodendrogliomas. *J Neurooncol.* 2006;79:159-168.
4. Sant M, Minicozzi P, Lagorio S, Borge JT, Marcos-Gragera R, Francisci S. Survival of European patients with central nervous system tumors. *Int J Cancer.* 2012;131:173-185.
5. Steinbach JP, Blaicher HP, Herrlinger U, et al. Surviving glioblastoma for more than 5 years: the patient's perspective. *Neurology.* 2006;66:239-242.
6. Flechl B, Ackerl M, Sax C, et al. Neurocognitive and sociodemographic functioning of glioblastoma long-term survivors. *J Neurooncol.* 2012;109:331-339.
7. Wang M, Cairncross G, Shaw E, et al. Cognition and quality of life after chemotherapy plus radiotherapy (RT) vs. RT for pure and mixed anaplastic oligodendrogliomas: radiation therapy oncology group trial 9402. *Int J Radiat Oncol Biol Phys.* 2010;77:662-669.
8. Taphoorn MJ, van den Bent MJ, Mauer ME, et al. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. *J Clin Oncol.* 2007;25:5723-5730.
9. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery.* 2000;47:324-333.
10. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol.* 2001;19:4037-4047.
11. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical Neuropsychology and Cost Outcome Research: A Beginning*. New York: Psychology Press, Inc.; 2003: 159-173.
12. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8:810-818.
13. Jolles J, van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr.* 1998;29:120-129.
14. de Bie SE. *Voorstellen voor uniformering van vraagstellingen naar achtergrondkenmerken en interviews* [Proposal for uniformisation of questions regarding background variables and interviews]. Leiden: Leiden University Press; 1987.
15. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365-376.
16. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res.* 1996;5:139-150.
17. Fayers PM, Aaronson NK, Bjordal K, et al. *The EORTC QLQ-C30 Scoring Manual*. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
18. Schroevens MJ, Sanderma R, van SE,

- Ranchor AV. The evaluation of the Center for Epidemiologic Studies Depression (CES-D) scale: depressed and positive affect in cancer patients and healthy reference subjects. *Qual Life Res.* 2000;9:1015-1029.
19. Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res.* 1994;38:383-392.
 20. Sneeuw KC, Aaronson NK, Osoba D, et al. The use of significant others as proxy raters of the quality of life of patients with brain cancer. *Med Care.* 1997;35:490-506.
 21. van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer.* 2011;47:667-675.
 22. de Vries J, Michielsen HJ, Van Heck GL. Assessment of fatigue among working people: a comparison of six questionnaires. *Occup Environ Med.* 2003;60 Suppl 1:i10-i15.
 23. Ensel WM. Measuring depression: the CES-D scale. In: Lin N, Dean A, Ensel WM, eds. *Social Support, Life Events and Depression*, Orlando: Academic Press Inc.; 1986: 51-70.
 24. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM, eds. *Evaluation of Chemotherapeutic Agents*, New York: Columbia University Press; 1949: 191-205.
 25. Sachsenheimer W, Piotrowski W, Bimmler T. Quality of life in patients with intracranial tumors on the basis of Karnofsky's performance status. *J Neurooncol.* 1992;13:177-181.
 26. Hannay HJ, Lezak ML. The neuropsychological examination: interpretation. In: Lezak MD, Howieson DB, Loring DW, eds. *Neuropsychological Assessment*, New York: Oxford University Press; 2004: 133-156.
 27. Bosma I, Vos MJ, Heimans JJ, et al. The course of neurocognitive functioning in high-grade glioma patients. *Neuro Oncol.* 2007;9:53-62.
 28. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol.* 2009;11:51-58.
 29. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol.* 2006;24:2715-2722.
 30. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3:159-168.
 31. Hahn CA, Dunn RH, Logue PE, King JH, Edwards CL, Halperin EC. Prospective study of neuropsychologic testing and quality-of-life assessment of adults with primary malignant brain tumors. *Int J Radiat Oncol Biol Phys.* 2003;55:992-999.
 32. Scheibel RS, Meyers CA, Levin VA. Cognitive dysfunction following surgery for intracerebral glioma: influence of histopathology, lesion location, and treatment. *J Neurooncol.* 1996;30:61-69.
 33. Archibald YM, Lunn D, Ruttan LA, et al. Cognitive functioning in long-term survivors of high-grade glioma. *J Neurosurg.* 1994;80:247-253.
 34. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet.* 2002;360:1361-1368.
 35. Reijneveld JC, Klein M, Taphoorn MJ, Postma TJ, Heimans JJ. Improved, personalized treatment of glioma necessitates long-term follow-up of cognitive functioning. *Pharmacogenomics.* 2012;13(15):1667-1669.
 36. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol.* 2009;27:3712-3722.

Part III

Association between
tumor location and
neurocognitive functioning

6

Association between tumor location and neurocognitive functioning using tumor localization maps

Journal of Neuro-Oncology

2019 Sep; 144(3):573-582.

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Abstract

Introduction: Patients with diffuse glioma often experience neurocognitive impairment already prior to surgery. Pertinent information on whether damage to a specific brain region due to tumor activity results in neurocognitive impairment or not, is relevant in clinical decision-making, and at the same time renders unique information on brain lesion location and functioning relationships. To examine the impact of tumor location on preoperative neurocognitive functioning (NCF), we performed MRI based lesion-symptom mapping.

Methods: Seventy-two patients (mean age 40 years) with a radiologically suspected glioma were recruited preoperatively. For each of the six cognitive domains tested, we used tumor localization maps and voxel-based lesion-symptom mapping analyses to identify cortical and subcortical regions associated with NCF impairment.

Results: Compared to healthy controls, preoperative NCF was significantly impaired in all cognitive domains. Most frequently affected were attention (30% of patients) and working memory (20% of patients). Deficits in attention were significantly associated with regions in the left frontal and parietal cortex, including the precentral and parietal-opercular cortex, and in left-sided subcortical fiber tracts, including the arcuate fasciculus and corticospinal tract. Surprisingly, no regions could be related to working memory capacity. For the other neurocognitive domains, impairments were mainly associated with regions in the left hemisphere.

Conclusions: Prior to treatment, patients with diffuse glioma in the left hemisphere run the highest risk to have NCF deficits. Identification of a left frontoparietal network involved in NCF not only may optimize surgical procedures but may also be integrated in counseling and cognitive rehabilitation for these patients.

Introduction

While patients with gliomas often experience impairment in physical and emotional functioning, specifically deficits in neurocognitive functioning (NCF) negatively affect daily life functioning and health-related quality of life.¹ These deficits can be caused by the tumor and surrounding edema, by epilepsy and anti-epileptic drugs, and by tumor treatment, including surgery, radiotherapy and chemotherapy.¹

There is substantial evidence that the tumor itself is the major cause of neurocognitive deficits in glioma patients. Prior to treatment, impairment in working memory,² memory,³ executive functioning,^{3,4} and language capacity^{4,5} have been observed.

Regarding surgery, usually the first step in treatment of these patients, detailed knowledge on the neuroanatomy-function associations is pivotal to attain an optimal balance between tumor control (e.g. OS) by resection and functional outcome (e.g. NCF). Although available data on the involvement of specific brain regions involved in language,⁵ and verbal or perceptual abilities⁶ certainly are of value, more detailed information regarding the involvement of specific cortical or subcortical brain regions and tracts on NCF is needed. To identify those brain regions critically involved in NCF, voxel-based lesion-symptom mapping⁷ is a promising tool that is well-established in stroke⁸ and traumatic brain injury.^{9,10} However, in brain tumor patients voxel-based lesion-symptom mapping has been applied in only a few postoperative^{11,12} and preoperative¹³ studies, with a focus on one specific neurocognitive function or specific brain regions. The use of so-called tumor localization maps (TLMs) in order to voxel-wise link brain tumor location to NCF, can add pertinent information to the associations known from non-tumor lesion studies, as gliomas have differences in preference location, nature and infiltrative growth pattern compared to other, acute, lesions.¹³ Voxel-by-voxel lesion mapping has the advantage that a priori lesion location grouping is avoided^{7,14} and that white matter structures can additionally be identified.

The aim of the present study is to better understand the impact of brain tumor locations on distinct neurocognitive functions in glioma patients prior to surgery, by using voxel-based lesion-function mapping.

Methods

Patients

A retrospective observational cohort of consecutive de novo patients planned to undergo resective surgery for suspected glioma in Amsterdam UMC, a tertiary referral center for neuro-oncological surgery, was established. Adult patients (≥ 18 years) were included if they had a radiologically suspected glioma, no prior surgery, no radiotherapy or chemotherapy, preoperative neurocognitive assessment, and

preoperative MRI including 3D FLAIR and 3D T1 gadolinium. Neuropsychological assessment and MRI were part of routine clinical care. Exclusion criteria were history of neurological or severe psychiatric disorder potentially interfering with NCF, and insufficient command of the Dutch language.

Standard protocol approvals and patient consent

Approval of the study protocol by the institutional review board of the Amsterdam UMC was not required according to the Dutch law on Medical Research in Humans. All patients gave written informed consent for using clinically derived data, including neuropsychological and MRI data, for research purposes.

Neurocognitive assessment

NCF was assessed by standardized neuropsychological tests, covering the range of neurocognitive functions known to be affected in glioma patients.^{6,15} We combined test outcomes into six cognitive domain scores, based on previous studies and consensus in neuropsychological practice: information processing speed, attention, working , verbal and visual memory and executive functioning (Online Resource 1).^{15,16}

For each test, the patient's performance was compared to published normative data of healthy controls, corrected for age and educational level, or with performance of healthy controls from a database of the Maastricht Aging study, The Netherlands.¹⁷ These controls were individually matched to patients according to age, gender, and educational level.¹⁸ Individual patient test scores were converted into standardized z-scores with use of mean and standard deviation (SD) of the healthy controls on that test outcome. Domain summary measures were calculated for the patients, by dividing the total score of the test scores contributing to the domain, by the number of test outcomes of that domain. A domain score of ≥ 1.5 SD below the mean of controls was considered a clinically significant neurocognitive impairment.¹⁹

MRI scanning

All patients were scanned using a standardized neuro-oncology protocol. The protocol included a 3D FLAIR turbo spin-echo pulse-sequence and a 3D heavily T1-weighted gradient-echo pulse-sequence obtained after double-dose administration of intravenous gadolinium. Scans were available from various 1.5 and 3.0 T scanners (including GE Signa HDXT, Toshiba Titan, Siemens Avanto, and Philips Ingenia). All MRI images were acquired with ~1 mm isotropic resolution.

Voxel-based lesion mapping

For tumor localization mapping, we used the methodology described elsewhere.²⁰ Tumor regions were segmented in 3D on FLAIR images (smart brush tool of iPlan v3.0 software; BrainLAB AG, Feldkirchen, Germany) in case of a suspected low-grade

glioma (i.e. hyperintense signal abnormality) and on T1 post contrast images in case of a high-grade glioma (i.e. contrast-enhancement abnormality). The segmented volumes were verified and adjusted in reconstruction planes by two observers (EH and PW). The FLAIR scans were linearly registered to the T1 scans for further analysis using the image fusion tool. Perilesional edema was excluded from the segmentations. Subsequently, the segmented volumes were exported as binary masks registered to the T1 images. The resulting patient-specific T1 volume was non-linearly registered to 2x2x2 mm Montreal Neurological Institute brain template (MNI-152 space), i.e. standard brain space.²¹ This registration was done in sequential steps, with rigid, affine, B-spline regularization and symmetric diffeomorphic registration with cross-correlation as similarity metric.²² The registration was visually verified and repeated when necessary. The results were preoperative TLMs of all patients grouped together, aligned to MNI space for further analysis. The probability of tumor was calculated for each voxel that covered MNI space, by dividing the number of patients with a glioma at that voxel by the total number of patients.

Statistical analysis

For a detailed description of the statistical analysis of the TLMs we refer to our previous publication.²⁰ In short, to identify brain regions associated with cognitive impairment, for each neurocognitive domain we compared TLMs of patients with and without neurocognitive impairment in the presence of a glioma at a specific voxel using a voxel-wise randomization test. We restricted the analyses to brain regions affected by tumor in at least three patients. As test statistic per voxel, the fraction of patients with a tumor region among those with an impairment was divided by the fraction of patients with a tumor region among those without, providing a 'relative risk'. A higher test statistic corresponded to a higher rate of tumor location regions among patients with an impairment than among those without.

To evaluate the probability of the test statistics, we used a randomization test. The spatial dependency of the data was addressed by estimating the empirical null-distribution of relative risks for each voxel based on a permutation with relabeling of patients to one of the two cohorts. A subset of 4000 randomizations was randomly drawn without replacement to provide a reasonable estimate, as has been applied to analyze functional neuroimaging.²³⁻²⁵ The adjusted one-sided p -value per voxel was calculated by counting the number of equal or more extreme test statistics in the randomized null distribution, and dividing by the number of randomizations. Multiple hypothesis testing was controlled for type I error using the false discovery rate, expressed as q -value for each voxel. These q -values are the proportion of voxels with false differential probability of a glioma among all voxels declared differentially infiltrated, when the p -value of a voxel is called significant. To obtain the q -value for a voxel, we divided the estimated number of false discoveries by the number of

voxels declared significant. The estimated number of false discoveries given a specific adjusted p -value threshold was determined from the empirical null-distribution of 4000 randomizations per voxel. The number of voxels declared significant was determined from the distribution of observed p -values.^{23,25} This resulted in p - and q -value maps of differentially infiltrated brain regions that were superimposed on MNI-152 space for visual inspection. Because of the exploratory nature of our study, we considered $q < 0.4$ as informative, and $q < 0.2$ as significant. The correlation between the number of tumor voxels and the neurocognitive domain score (impaired versus not impaired) was analyzed using a non-parametric Spearman test. For further interpretation of the brain locations, we aligned our results with standard cortical²⁶ and white matter anatomy.²⁷ Statistical procedures were customized in R, v3.3.²⁸

Language functioning as reference measure

To ensure the validity of our map comparisons, as the use of TLMs is a relatively new approach in glioma patients, we used language functioning as a reference measure. A map calculating the association between preoperative tumor location and language impairment was added. Language function was tested during preoperative neurological examination and was characterized mainly by naming and (subjective) word finding problems.

Results

Sociodemographic and clinical data

Seventy-two patients were included (Table 1). Excluded were ten cases: three patients with incomplete neuropsychological assessment, two patients with a history of previous surgery, one patient with both previous surgery and radiotherapy, two patients with a cavernous malformation, one patient with an epidermoid and one patient with a hypothalamus hamartoma. The majority (60%) of patients, with a mean age of 40 years, was diagnosed with a glioma WHO grade II. Forty-one tumors were located in the left, and 31 in the right hemisphere. Epilepsy was the most frequently presenting symptom (62%), in 10% of cases in combination with neurocognitive impairment. Tumors were predominantly located in frontal, temporal and insular brain regions (Figure 1). In two patients with right sided tumor and left handedness, additional fMRI revealed right hemispheric dominance for language functions. In two left handed patients with tumor in the left hemisphere, fMRI showed right hemisphere dominance for language. For all other patients, left hemisphere was language dominant. The mean interval between preoperative MRI and neurocognitive assessment was 0.4 weeks (SD $\pm$ 9.2 weeks).

Table 1. Sociodemographic and clinical characteristics of the patient cohort

	No. of patients (n = 72)
Age ^a ; mean ± SD	39.8 ± 12.3
Sex; Male, no. (%)	45 (63%)
Educational level ^b ; mean ± SD	4.5 ± 1.9
Glioma WHO grade	
I	7 (10%)
II	43 (60%)
III	12 (16%)
IV	10 (14%)
Tumor location; left, no. (%)	41 (57%)
Presenting symptom(s), no. (%)	
Epilepsy	45 (62%)
Epilepsy and neurocognitive impairment	7 (10%)
Epilepsy and neurological impairment	5 (7%)
Neurocognitive deficits	4 (6%)
Neurological impairment	5 (7%)
Headache	1 (1%)
None	5 (7%)
Use of AEDs, no. (%)	48 (67%)
Use of corticosteroids, no. (%)	6 (8%)
Interval between neuropsychological examination and preoperative MRI ^c ;	
mean ± SD / median	0.4 ± 9.2/0
range	0-35.6

AEDs anti-epileptic drugs; ^aYears; ^bCode 1-8, ranging from lower general education to university education,¹⁸
^cWeeks

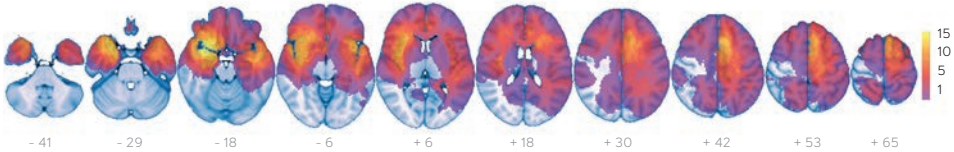


Figure 1. Glioma locations within the brain. Transversal sections are shown superimposed on standard brain space (MNI). See legend (right) with number of patients with glioma tissue at a voxel, lighter yellow indicating a higher number of patients.

Neurocognitive outcome

Attention and working memory capacity were the most frequently affected domains, in 30% and 20% of patients respectively. Fewer patients experienced impaired visual memory (14%), verbal memory (13%), information processing speed (11%), and executive functioning (8%) (Figure 2).

Brain regions associated with neurocognitive functions

Reference measure: language functioning

Only regions in the left hemisphere were found to be significantly associated with language functioning, including the frontal operculum, supra-marginal gyrus, arcuate fasciculus, superior- and middle frontal gyrus, superior temporal gyrus, and insular cortex (Online Resource 2). As the significant language regions and tracts in our sample are in accordance with earlier studies on naming and word retrieval processing in the brain,^{29,30} tumor location mapping can be considered a valid method to link NCF to brain regions.

Neurocognitive functions

Attentional performance was significantly associated with regions of the left frontal and parietal cortex (Figure 3a; Online Resource 3), including precentral and postcentral gyrus, central and parietal operculum (Figure 4). Moreover, significant regions were observed in the insular cortex, Heschl’s gyrus and the planum temporale, and in white matter tracts (arcuate fasciculus and corticospinal tract). In the right hemisphere, only

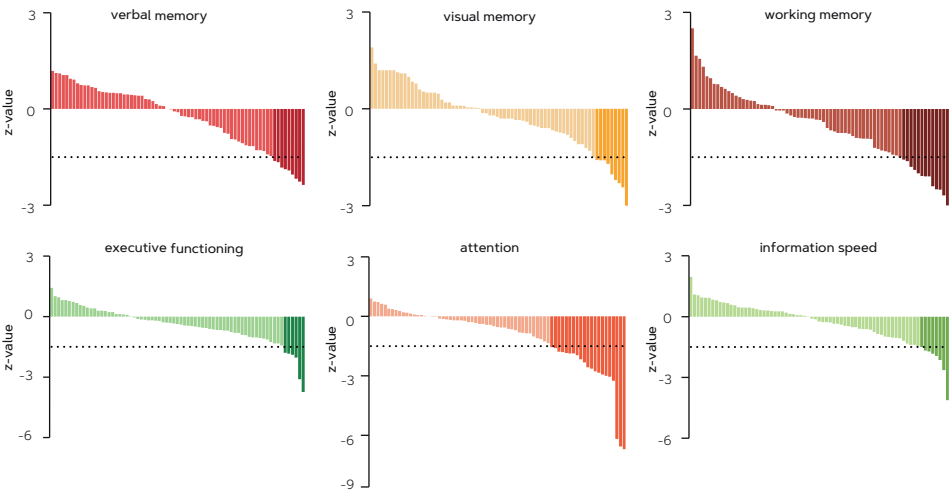


Figure 2. Distribution of neurocognitive functioning scores per domain (n = 72). Each bar represents one patient, with darker colors indicating scores below 1.5 SD of healthy controls (horizontal dotted line at -1.5 SD).

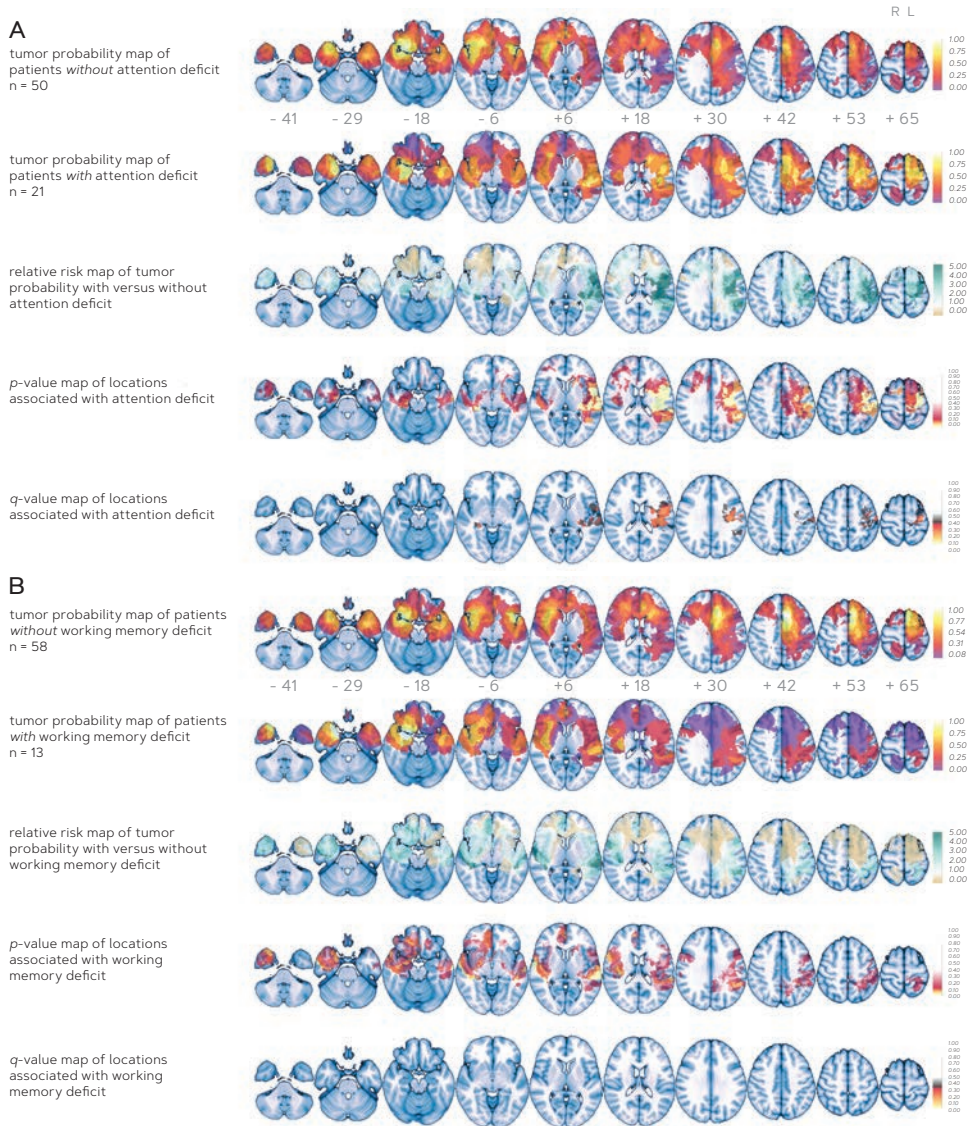
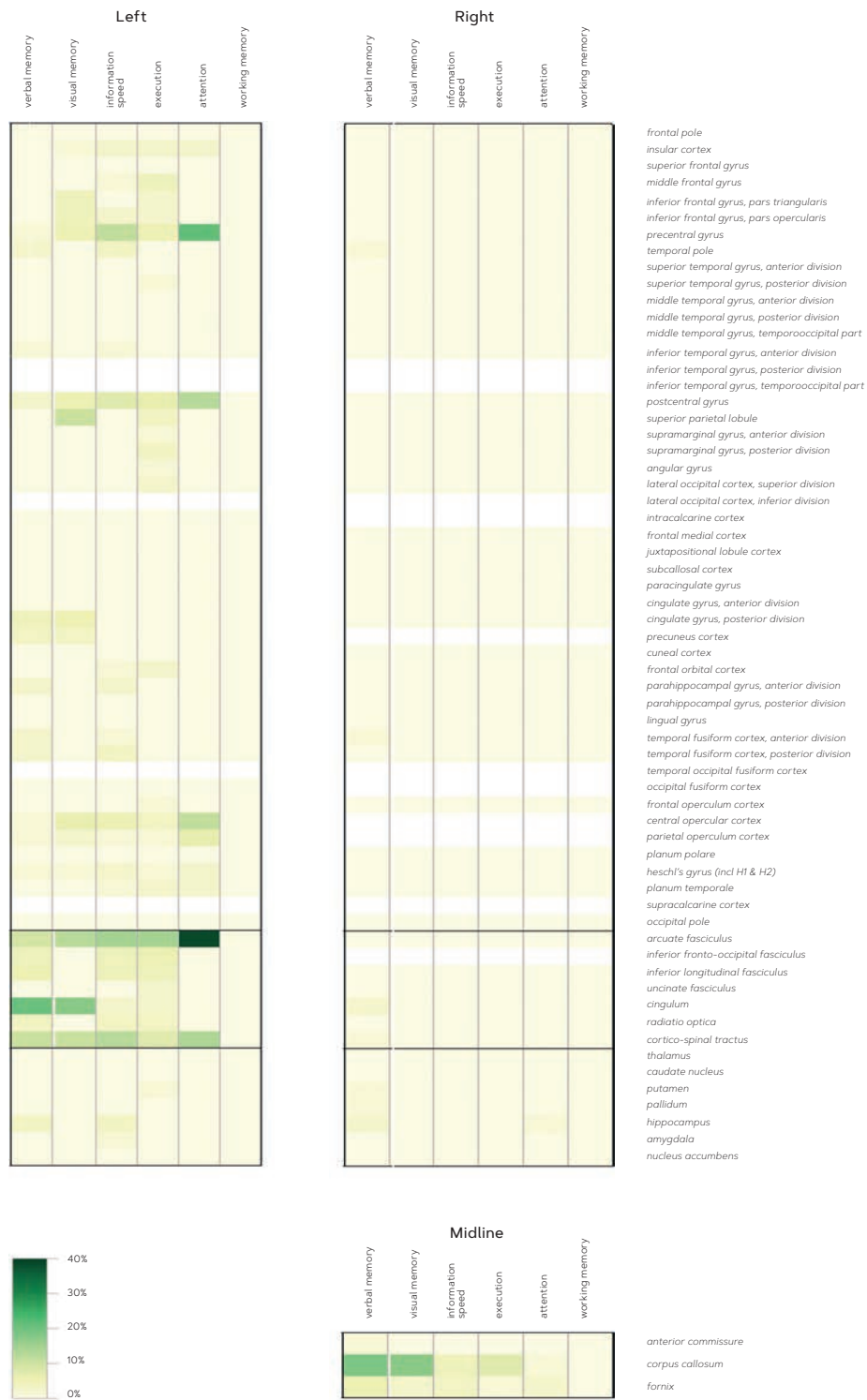


Figure 3. Tumor localization maps for the attention (**A**) and working memory (**B**) domains. For both domains, rows represent (1) TLM of patients with a tumor at that voxel without a deficit in the particular domain, (2) TLM of patients with a tumor and a deficit in that domain (lighter yellow indicates higher percentages), (3) relative risk map of tumor probability, i.e. the odds ratio at each voxel between tumor probabilities (1) and (2), with darker green indicating more deficits in presence of a tumor. The observed relative differences were voxel-wise tested for significance, resulting in an adjusted p-value map (4), taking spatial dependence into account (lighter yellow indicates lower p-values); (5) corrected q-value map to address multiple testing, displayed as the log odds ratios for the voxels with q-values below 0.4 presented in red and q-values below 0.2 in yellow. Voxel clusters with $q < 0.4$ were considered significant



<< **Figure 4.** Heat map with the association between anatomical brain structures and neurocognitive domains. The neurocognitive domains are shown in columns, grouped per hemisphere and the midline. Anatomical structures are displayed in rows, grouped per cortical region, subcortical white matter structure and subcortical nucleus. Horizontal orientation shows the percentage of significant voxels (with $q < 0.4$) per domain of the total number of significant voxels per anatomical structure, with darker shades of green indicating a stronger association. Absence of information in anatomical regions is displayed as white, while information of 0% is displayed as light yellow

a focal area of voxels in the parahippocampal gyrus exceeded the critical q -value.

For working memory, no significant clusters were identified (Figure 3B; Online Resource 4). P-values indicated bilateral parietal and frontal regions, predominantly in left hemisphere, possibly involved in working memory performance, but these were not identified in our q -value maps.

Visual memory, verbal memory, information processing speed, and executive functioning were also analyzed for associated brain regions, although these were involved in fewer patients. Overall, for these four domains, regions in left white matter structures, including arcuate fasciculus, corticospinal tract, and corpus callosum, and in left frontal and parietal cortex, including pre- and postcentral gyrus, were found to be significantly associated with performance (Figure 4; Online Resource 5-8). In addition, visual and verbal memory impairments were associated with regions in the left cingulum, left posterior cingulate gyrus and precuneus. For verbal memory and information processing speed, the hippocampus showed significant voxels. Many other regions were identified to be significantly associated with executive functioning, most importantly the inferior fasciculus and superior parietal lobe. Right-sided regions, including temporal pole, fusiform cortex and basal ganglia, were only associated with verbal memory.

Discussion

We aimed to better understand the association between tumor location and distinct neurocognitive functions in glioma patients prior to surgery. Attention and working memory were the most affected domains. Using voxel-based lesion mapping we observed brain structures associated with attention impairments to be localized in the left frontal and parietal cortex and left-sided white matter tracts. The neural basis for attentional functioning has been extensively studied. One of the most influential models is the three attentional networks model (alerting, orienting and executive control),^{31,32} which involves an extensive anatomical distribution including frontal and parietal regions with interconnecting pathways, the anterior cingulate

cortex and dorsolateral prefrontal cortex, and the thalamus with connections to the superior parietal lobe, temporo-parietal junction, the superior temporal lobe, and the frontal eye fields.^{31,33,34} Our results comply to some extent with this anatomical attentional network, i.e. we found significant regions in prefrontal and parietal areas. However, we could not replicate the involvement of the anterior cingulate cortex in executive control,^{34,35} nor did we observe regions associated with the orienting and alerting networks of attention.^{31,35} This could be due to an underrepresentation of gliomas in these regions or by the use of other attentional tasks than the ones used in Posner's model³⁴ that thus might have provoked activation in different brain regions. Contrasting with earlier studies, apart from the parahippocampal gyrus, we did not identify regions associated with aspects of attention in the right hemisphere,^{31,36} including the inferior frontal gyrus and medial temporal cortex found in stroke patients³⁷ and the caudal anterior cingulate in traumatic brain injury patients.³⁸ Nor did we observe bilateral activation in the thalamus^{35,39} and basal ganglia.³⁹ Perhaps we did not find associated regions in the right hemisphere because our testing protocol consisted of tasks requiring a verbal response, and did not assess spatial attention.

Surprisingly, we also observed sections of the white matter tracts, especially the arcuate fasciculus and the corticospinal tract, to be involved in attentional functioning. The corticospinal tract is mainly involved in motor function, which was not required in the applied tasks. The arcuate fasciculus is known for its role in language processing,³⁰ but scarce data also suggest a role in attentional processes and executive functioning, for example in patients with attention deficit hyperactivity disorder, using diffusion spectrum imaging tractography.⁴⁰ As the involvement of the arcuate fasciculus was also found for memory, speed and executive functioning, and most tasks were presented verbally and/or required a verbal response, glioma infiltrating in the arcuate fasciculus could have a subtle impact on neurocognitive performance.

No specific regions were identified to be associated with working memory, perhaps due to low statistical power. In the literature, many different structures within the prefrontal-parietal network have been associated with working memory performance in healthy and brain injured patients, partly depending on the type of working memory task. For example, impairments in complex span tasks were associated with lesions in the left inferior frontal gyrus.⁴¹ Other relevant regions, found in fMRI studies, include the bilateral posterior parietal cortex,^{42,43} premotor areas and posterior cingulate,⁴² insular cortex and middle temporal gyrus, the inferior longitudinal and fronto-occipital fasciculi, uncinate, and corpus callosum.⁴³

Our study evidently has some limitations. First, including low-grade glioma might have complicated the analysis, as these tumors do not show contrast enhancement on MRI and hence tumor boundaries are more difficult to identify. Also the behavior and biology of low- and high-grade glioma might affect the infiltration in brain tissue in a variable way,⁴⁴ complicating lesion mapping and therefore, according to

some authors, makes this method not applicable in glioma patients.⁴⁵ However, the tumor maps were also based on FLAIR images, and in accordance with others^{13,46} we are convinced that voxel-based lesion mapping is applicable in gliomas. Second, differences in the concept of brain plasticity might hamper interpretation of our results. For example, the higher growth rate associated with isocitrate dehydrogenase 1 wild type (IDH1-WT) tumors compared to IDH1-mutant tumors, might result in less efficient brain networks and less time for brain plasticity to compensate for functional loss.⁴⁷ Also, functional compensation might be better for cognitive functions that are represented in more widespread brain networks, such as language,⁴⁸ than for more basic functions such as spatial attention,¹³ although results in literature are partially contradictory.⁴⁹ As a result, we might have missed brain regions involved in specific neurocognitive functions seen in acute lesions. However, this does not negate that the regions we found to be associated with NCF are still of relevance. Third, due to unevenly distributed glioma over cortical and subcortical areas, not all regions could be included in our analysis. Therefore, perhaps not all brain structures relevant for the tested neurocognitive functions could be identified. Fourth, the interval between cognitive assessment and MRI scanning varied. In patients with a relatively long interval, the location, size and infiltration pattern of glioma tissue, as observed on MRI, could have been different from the glioma at time of the neurocognitive assessment. However, especially high-grade gliomas show rapid change and these patients were scanned within a relatively short interval. Fifth, we did not calculate Jaccard/Dice overlap scores between the two observers (EH and PW). The interrater agreement for tumor segmentation before surgery in general is known to be non-trivial.⁵⁰ Sixth, neuropsychological assessment was more routinely performed in WHO grade II glioma patients, who are typically young adults with an anticipated survival of many years. Cognitive performance is important for social and professional functioning during these years. For patients with WHO grade IV glioma, who still have a relatively short survival, extensive neuropsychological assessment was less well possible due to physical status or the necessity of planning the surgery at short notice. For this reason, high-grade glioma patients are underrepresented in our study cohort. Finally, because of the explorative nature of our study design, we did not examine the influence of epilepsy, use of anti-epileptic drugs, emotional changes, depression, anxiety and fatigue on NCF, while these factors are relevant in glioma patients and have an impact on cognition.⁵¹⁻⁵⁴

Our study has several implications. First, our finding regarding the involvement of the corticospinal tract in attention adds some information to the field of neuroscience. This observation should be confirmed in larger series. Second, as preoperative neurocognitive impairment in glioma patients is common, and mainly associated with disruption of the left frontoparietal network, assessment of attention and working memory prior to surgery, and informing patients regarding these impairments, should

be incorporated in clinical care. Third, during awake surgical procedures resective surgery can be optimized by intraoperative monitoring of attentional function. However, rigorous paradigms to test these functions are yet to be developed. Finally, with information regarding preoperative neurocognitive impairment, cognitive rehabilitation can be applied in an early stage and tailored to the individual patient.

References

1. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3(3):159-168.
2. Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. *J Neurooncol.* 2007;81(3):305-313.
3. Papagno C, Casarotti A, Comi A, Gallucci M, Riva M, Bello L. Measuring clinical outcomes in neuro-oncology. A battery to evaluate low-grade gliomas (LGG). *J Neurooncol.* 2012;108(2):269-275.
4. Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A. Cognitive functioning early after surgery of gliomas in eloquent areas. *J Neurosurg.* 2012;117(5):831-838.
5. Duffau H, Moritz-Gasser S, Mandonnet E. A re-examination of neural basis of language processing: proposal of a dynamic hodotopical model from data provided by brain stimulation mapping during picture naming. *Brain Lang.* 2014;131:1-10.
6. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol.* 2001;19(20):4037-4047.
7. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. *Nat Neurosci.* 2003;6(5):448-450.
8. Biesbroek JM, Kuijf HJ, van der Graaf Y, et al. Association between subcortical vascular lesion location and cognition: a voxel-based and tract-based lesion-symptom mapping study. The SMART-MR study. *PLoS One.* 2013;8(4):e60541.
9. Perlberg V, Puybasset L, Tollard E, Lehericy S, Benali H, Galanaud D. Relation between brain lesion location and clinical outcome in patients with severe traumatic brain injury: a diffusion tensor imaging study using voxel-based approaches. *Hum Brain Mapp.* 2009;30(12):3924-3933.
10. Barbey AK, Colom R, Solomon J, Krueger F, Forbes C, Grafman J. An integrative architecture for general intelligence and executive function revealed by lesion mapping. *Brain.* 2012;135(Pt 4):1154-1164.
11. Campanella F, D'Agostini S, Skrap M, Shallice T. Naming manipulable objects: anatomy of a category specific effect in left temporal tumours. *Neuropsychologia.* 2010;48(6):1583-1597.
12. Mandonnet E, De Witt Hamer P, Poisson I, et al. Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. *Neurosurgery.* 2015;76(4):382-389; discussion 389.
13. Shallice T, Mussoni A, D'Agostino S, Skrap M. Right posterior cortical functions in a tumour patient series. *Cortex.* 2010;46(9):1178-1188.
14. Rorden C, Karnath HO, Bonilha L. Improving lesion-symptom mapping. *J Cogn Neurosci.* 2007;19(7):1081-1088.
15. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning.* New York: Psychology Press, Inc.; 2003:159-173.
16. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810-818.
17. Jolles J, van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr.* 1998;29(3):120-129.
18. de Bie SE. [Proposal for uniformisation of questions regarding background variables and interviews]. Leiden: Leiden University Press; 1987.

19. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4. New York: Oxford University Press; 2004.
20. De Witt Hamer PC, Hendriks EJ, Mandonnet E, Barkhof F, Zwinderman AH, Duffau H. Resection probability maps for quality assessment of glioma surgery without brain location bias. *PLoS One*. 2013;8(9):e73353.
21. Fonov V, McKinstry R, Almlí C, Collins D. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *Neuroimage*. 2009;47:S102.
22. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008;12(1):26-41.
23. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*. 2002;15(1):1-25.
24. Nichols T, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat Methods Med Res*. 2003;12(5):419-446.
25. Schwartzman A, Dougherty RF, Lee J, Ghahremani D, Taylor JE. Empirical null and false discovery rate analysis in neuroimaging. *Neuroimage*. 2009;44(1):71-82.
26. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980.
27. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105-1132.
28. Team RC. R: A Language and Environment for Statistical Computing. In: Vienna, Austria: R Foundation for Statistical Computing; 2013.
29. Gleichgerrcht E, Fridriksson J, Bonilha L. Neuroanatomical foundations of naming impairments across different neurologic conditions. *Neurology*. 2015;85(3):284-292.
30. Dick AS, Tremblay P. Beyond the arcuate fasciculus: consensus and controversy in the connective anatomy of language. *Brain*. 2012;135(Pt 12):3529-3550.
31. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. *Annu Rev Neurosci*. 2012;35:73-89.
32. Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci*. 1990;13:25-42.
33. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci*. 2002;3(3):201-215.
34. Posner MI, Sheese BE, Odludas Y, Tang Y. Analyzing and shaping human attentional networks. *Neural Netw*. 2006;19(9):1422-1429.
35. Rinne P, Hassan M, Goniotakis D, et al. Triple dissociation of attention networks in stroke according to lesion location. *Neurology*. 2013;81(9):812-820.
36. Raz A. Anatomy of attentional networks. *Anat Rec B New Anat*. 2004;281(1):21-36.
37. Corbetta M, Ramsey L, Callejas A, et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. 2015;85(5):927-941.
38. Merkle TL, Larson MJ, Bigler ED, Good DA, Perlstein WM. Structural and functional changes of the cingulate gyrus following traumatic brain injury: relation to attention and executive skills. *J Int Neuropsychol Soc*. 2013;19(8):899-910.
39. Murakami T, Hama S, Yamashita H, et al. Neuroanatomic pathway associated with attentional deficits after stroke. *Brain Res*. 2014;1544:25-32.
40. Chiang HL, Chen YJ, Shang CY, Tseng WY, Gau SS. Different neural substrates for executive functions in youths with ADHD: a diffusion spectrum imaging tractography study. *Psychol Med*. 2016;46(6):1225-1238.
41. Ivanova MV, Dragoy O, Kuptsova SV, et al. Neural mechanisms of two different verbal working memory tasks: A VLSM study. *Neuropsychologia*. 2018;115:25-41.

42. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp.* 2005;25(1):46-59.
43. Palacios EM, Sala-Llanch R, Junque C, et al. White matter integrity related to functional working memory networks in traumatic brain injury. *Neurology.* 2012;78(12):852-860.
44. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro Oncol.* 2015;17(4):580-587.
45. Karnath HO, Steinbach JP. Do brain tumours allow valid conclusions on the localisation of human brain functions?--Objections. *Cortex.* 2011;47(8):1004-1006.
46. Duffau H. Do brain tumours allow valid conclusions on the localisation of human brain functions? *Cortex.* 2011;47(8):1016-1017.
47. Kesler SR, Noll K, Cahill DP, Rao G, Wefel JS. The effect of IDH1 mutation on the structural connectome in malignant astrocytoma. *J Neurooncol.* 2017;131(3):565-574.
48. Duffau H, Capelle L, Denvil D, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. *J Neurol Neurosurg Psychiatry.* 2003;74(7):901-907.
49. Charras P, Herbet G, Deverdun J, et al. Functional reorganization of the attentional networks in low-grade glioma patients: a longitudinal study. *Cortex.* 2015;63:27-41.
50. Visser M, Müller DMJ, van Duijn RJM, et al. Inter-rater agreement in glioma segmentations on longitudinal MRI. *Neuroimage Clin.* 2019;22:101727.
51. Klein M, Engelberts NH, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life. *Ann Neurol.* 2003;54(4):514-520.
52. Campanella F, Shallice T, Ius T, Fabbro F, Skrap M. Impact of brain tumour location on emotion and personality: a voxel-based lesion-symptom mapping study on mentalization processes. *Brain.* 2014;137(Pt 9):2532-2545.
53. van Coevorden-van Loon EMP, Coomans MB, Heijenbrok-Kal MH, Ribbers GM, van den Bent MJ. Fatigue in patients with low grade glioma: systematic evaluation of assessment and prevalence. *J Neurooncol.* 2017;133(2):237-246.
54. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.

Supplementary data

Online resource 1: Table 1. Cognitive domains and tests

Cognitive tests	Objective measures	Cognitive domains
Auditory verbal learning test ^{1,2}	Total of 5 trials (number correct: 0-75) * Delta score (number correct: 0-15) * Delayed recall (number correct: 0-15) * Delayed recognition (number correct: 0-30) *	Verbal memory (learning, delayed recall and delayed recognition)
Location Learning test ^{3,4}	Total of 5 trials (number incorrect: 0-∞) # Learning index (score 0-1) * Active delayed recall (number incorrect: 0- ∞) #	Visual memory (learning, delayed recall)
Rey Complex figure test ⁵	Delayed recall (number correct: 0-36) *	
Letter digit modalities test ^{2,6}	90 seconds writing and reading (both number correct: 0-125) *	Information processing speed
Stroop color word test ^{2,6}	Card I: word condition (time in seconds) * Card II: color condition (time in seconds) * Card III: color-word condition (time in seconds) * Interference #	Information processing speed; Attention
Trailmaking Test ⁶	Condition A and condition B (both time in seconds); B/A #	Information processing speed; Executive functioning
Digit span ⁷	Forward (number correct* span: 0-144) * Backward (number correct * span: 0-112) *	Attention; Working memory
Memory comparison test ²	Slope (time score) # Intercept (time score) #	Working memory
Categoric word fluency test ^{2,6}	Animals (number correct: 0- ∞)*	Executive functioning
Letter word fluency test ⁸	Letters D, A and T (numbers correct: 0- ∞) *	
Behavioral Assessment of the Dysexecutive Syndrome ^{9,10}	Subtest: rule shifting test (profile score: 0-4) *	Executive functioning (shifting abilities)

* higher score means better performance; # higher score means worse performance

Online resource 2: Video 1. Axial sections of tumor-infiltrated brain regions associated with language dysfunction. The results identify established language regions. Results are superimposed on MNI standard brain template: (1) tumor map of 46 patients without language dysfunction, (2) tumor map of 13 patients with language dysfunction, (3) relative risk map of tumor location with and without language dysfunction, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 3: Video 2. Axial sections of tumor regions associated with attention impairment. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 49 patients without impairment, (2) lesion map of 22 patients with attention impairment, (3) relative risk map of regions with and without attention impairment, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 4: Video 3. Axial sections of tumor regions associated with working memory impairment. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 57 patients without impairment, (2) lesion map of 14 patients with working memory impairment, (3) relative risk map of regions with and without working memory impairment, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 5: Video 4. Axial sections of tumor regions associated with visual memory impairment. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 60 patients without impairment, (2) lesion map of 10 patients with visual memory impairment, (3) relative risk map of regions with and without visual memory impairment, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 6: Video 5. Axial sections of tumor regions associated with verbal memory impairment. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 62 patients without impairment, (2) lesion map of 9 patients with verbal memory impairment, (3) relative risk map of regions with and without verbal memory impairment, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 7: Video 6. Axial sections of tumor regions associated with information processing speed impairment. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 63 patients without impairment, (2) lesion map of 8 patients with information processing speed impairment, (3) relative risk map of

regions with and without information processing speed impairment, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Online resource 8: Video 7. Axial sections of tumor regions associated with impairment in executive functioning. Results are superimposed on MNI standard brain template: (1) lesion map of regions of 65 patients without impairment, (2) lesion map of 6 patients with executive functioning impairment, (3) relative risk map of regions with and impairment in executive functioning, (4) p -value map of randomization tests, (5) q -value map of false discovery rate. The numbers indicate MNI z -values.

Movies can be found online in the Supplementary material that accompanies this article.

References

1. Schmand B, Lindeboom J, Van Harskamp F. [*The 15 words test A and B (a preliminary manual)*]. Groningen: Afdeling Neuropsychologie, AZG; 1992.
2. van der Elst W. *The neuropsychometrics of aging; normative studies in the Maastricht Aging Study*, Universiteit Maastricht; 2006.
3. Bucks RS, Willison JR. Development and validation of the Location Learning Test (LLT): A test of visuo-spatial learning designed for use with older adults and in dementia. *Clin Neuropsychol*. 1997;11(3):273-286.
4. Kessels RP, Nys GM, Brands AM, van den Berg E, van Zandvoort MJ. The modified Location Learning Test: norms for the assessment of spatial memory function in neuropsychological patients. *Arch Clin Neuropsychol*. 2006;21(8):841-846.
5. Osterreith PA. Le test de copie d'une figure complexe [A test regarding a complex figure]. *Archives de Psychologie/ The Clinical Neuropsychologist*. 1944;30/ 7:206/ 209-356/ 215.
6. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment*. Vol 4. New York: Oxford University Press; 2004.
7. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual]*. Lisse2000.
8. Schmand B, Groenink SC, van den Dungen M. Letter fluency: psychometric properties and Dutch normative data. *Tijdschrift voor gerontologie en geriatric*. 2008;39(2):64-76.
9. Wilson BA, Alderman N, Burgess PW. *Behavioural Assessment of the Dysexecutive Syndrome*. Bury St. Edmunds: ThamesValley Test Co; 1996.
10. Krabbendam L, Kalff AC. *The Behavioural Assessment of the Dysexecutive Syndrome: Dutch Version*. Lisse: Swets and Zeitlinger; 1998.

7

Linking late cognitive outcome with glioma surgery location using resection cavity maps

Human Brain Mapping

2018 May;39(5):2064-2074.

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Abstract

Background: Patients with a diffuse glioma may experience cognitive decline or improvement upon resective surgery. To examine the impact of glioma location, cognitive alteration after glioma surgery was quantified and related to voxel-based resection probability maps.

Methods: A total of 59 consecutive patients (range 18–67 years of age) who had resective surgery between 2006 and 2011 for a supratentorial non-enhancing diffuse glioma (grade I–III, WHO 2007) were included in this observational cohort study. Standardized neuropsychological examination and MRI were obtained before and after surgery. Intraoperative stimulation mapping guided resections towards neurological functions (language, sensorimotor function, and visual fields). Maps of resected regions were constructed in standard space. These resection cavity maps were compared between patients with and without new cognitive deficits (z-score difference >1.5 SD between baseline and one year after resection), using a voxel-wise randomization test and calculation of false discovery rates. Brain regions significantly associated with cognitive decline were classified in standard cortical and subcortical anatomy.

Results: Cognitive improvement in any domain occurred in 10 (17%) patients, cognitive decline in any domain in 25 (42%), and decline in more than one domain in 10 (17%). The most frequently affected subdomains were attention in 10 (17%) patients and information processing speed in 9 (15%). Resection regions associated with decline in more than one domain were predominantly located in the right hemisphere. For attention decline, no specific region could be identified. For decline in information speed, several regions were found, including the frontal pole and the corpus callosum.

Conclusion: Cognitive decline after resective surgery of diffuse glioma is prevalent, in particular, in patients with a tumor located in the right hemisphere without cognitive function mapping.

Introduction

Standard care for diffuse glioma of grade WHO I–III includes resective surgery, followed by radio- and/or chemotherapy, depending on tumor grade, subtype, and molecular markers, either adjuvant or delayed at recurrence. The incidence of diffuse glioma is 5 per 100,000; nearly half are of WHO grade I–III.¹ These tumors infiltrate the brain, recur, transform into higher grade gliomas, and are eventually lethal.²

Glioma surgery aims to improve survival by maximizing tumor removal,^{3,4} while preserving integrity of brain function.⁵ Nevertheless, glioma resections in general result in permanent neurological deficits in 7.1% of patients, mainly, motor and language dysfunction, which is 3.4% when neurological function mapping is applied.⁵ Cognitive outcome after glioma surgery has been less well studied, mainly focused on short-term outcome in WHO grade IV glioma with diverging results.^{6–8} Cognitive assessment in patients with brain tumors so far has demonstrated several factors contributing to cognitive functioning, such as tumor effects, seizures, medication, and oncological treatment.^{6,9} Cognitive functioning is of particular relevance for those patients diagnosed with WHO grade I–III gliomas, who are typically young adults with an anticipated survival of many years. Cognitive performance is important for social and professional functioning during these years. Consequently, here we focus on this population aiming to identify the relation between glioma surgery regions and late cognitive outcome. Knowledge on the relation between cognitive functioning and the resection site is important for patient counseling and surgical decision making.

Inherent to glioma resection is a locationalistic perspective on the brain: that some regions are more salient than others, surgical damage of which may induce brain dysfunction. At the same time, however, a more comprehensive framework consists of dynamic networks connected in parallel, and to which network theory applies.¹⁰ Several networks have been identified as relevant for cognitive functioning, and particular regions that are centrally located in the brain network, the so-called hubs.^{11–13} This framework may be important for surgical treatment to understand potential loss of brain function.

We set out to increase our understanding of cognitive decline after glioma surgery by pinpointing resected regions that are shared among patients with cognitive decline using the well-established method of lesion-function mapping, which has not been applied to this knowledge gap in glioma resections. Here we aim to quantify late cognitive outcome after glioma surgery and to link cognitive decline with resected regions.

Methods

Patients

An observational cohort of consecutive patients at our tertiary referral center for neuro-oncological care was identified. Standardized cognitive assessment and MR imaging were obtained as part of routine care.

Approval of the study protocol by the institutional review board (VU University Medical Center, Medical Ethical Research Committee, Amsterdam, The Netherlands) was not required according to the Dutch law on Medical Research in Humans. All patients provided informed consent for use of their clinical data for medical research. Data and imaging were analyzed after anonymization in accordance with the Personal Data Protection Act and the Code of conduct for responsible use of Human Tissue and Medical Research.

Patients were included, who (a) were over 17 years of age, (b) were diagnosed with a supratentorial glioma of grade I–II, or III with focal anaplasia—WHO 2007, (c) had a resection between 1/1/2006 and 31/12/2011, (d) had no prior radiotherapy to avoid MRI signal misinterpretation, (e) had pre- and postoperative cognitive assessment in seven cognitive domains, (f) had a pre- and postoperative MRI available, and (g) had stable disease between surgery and postoperative assessment. Furthermore, patients with another neurological or psychiatric disorder or with insufficient Dutch language skills were excluded, as this could have interfered with cognitive assessment.

Patients received standard care, including complete neurological examination by neurologists and neurosurgeons at presentation and during follow-up. Treatment decisions were made in consensus by experts in tumor board meetings. Preoperative MRIs included functional MRI and DTI when deemed necessary. A dedicated neurosurgical team applied intraoperative stimulation mapping under local anesthesia and neurophysiological monitoring using EMG and EEG corticography, as needed. A selection of neurological functions was mapped in 50 (85%) patients: language, sensorimotor function, visual fields, and line bisection. Cognitive functions were not mapped during surgery.

Cognitive assessment

Cognitive performance was quantified for each patient in seven domains before and after surgery using standardized neuropsychological tests, which are specific for cognitive tasks potentially affected in brain tumor patients and sensitive for detection over time (Table 1).^{14,15} These seven cognitive domain scores were based on previous studies and consensus in neuropsychological practice.^{9,16} For each test, the patient's score was compared to published normative data of healthy controls of similar age, gender, and educational level^{17–20} to calculate z-scores.

Table 1. Cognitive domains and tests

Cognitive domain	Cognitive test	Objective measure
Attention	Digit span	Subtest: forward (number correct 3 span: 0–144) ^a
	Stroop color word test	Subtests: card II: color condition, card III: color-word condition (both time in seconds) ^a and interference ^b
Information speed	Stroop color word test	Subtest: card I: word condition (time in seconds) ^b
	Trail making Test	Subtest: condition A (time in seconds) ^b
	Letter digit modalities test	90 seconds writing and reading (both number correct: 0–125) ^a
Visual construction	Rey complex figure test	Subtest: copy (number correct: 0–36) ^a
Verbal memory	Auditory verbal learning test	Total of 5 trials (number correct: 0–75) ^a Delta score (number correct: 0–15) ^a Delayed recall (number correct: 0–15) ^a Delayed recognition (number correct: 0–30) ^a
Visual memory	Location learning test	Total of five trials (number incorrect: 0–∞) ^b Learning index (score 0–1) ^a Active delayed recall (number incorrect: 0–∞) ^b
	Rey complex figure test	Subtest: delayed recall (number correct: 0–36) ^a
Working memory	Digit span	Subtest: backward (number correct 3 span: 0–112) ^a
	Memory comparison test	Slope (time score) ^b Intercept (time score) ^b
Execution	Trail making test	Subtest: condition B (time in seconds); B/A ^b
	Categoric word fluency test	Animals (number correct: 0–∞) ^a
	Letter word fluency test	Letters D, A, and T (numbers correct: 0–∞) ^a
	Behavioral assessment of the dysexecutive syndrome	Subtest: rule shifting test (profile score: 0–4) ^a

^aHigher score means better performance; ^bHigher score means worse performance.

Subsequently, a performance score was calculated for every patient in each of seven cognitive domains using a combination of specific test z-scores (Table 1). A domain z-score was obtained by dividing the summed z-scores of the tests contributing to that domain, by the number of tests within the domain. For each patient, scores were acquired at two time-points: baseline measurement one week prior to surgery and postoperative after one year to avoid measurements during rehabilitation. These two time-points allowed calculation of alteration per cognitive domain for every patient by subtracting the follow-up from the baseline measurement. A decrease in z-score of more than 1.5 was defined as cognitive decline; an increase of more than 1.5 as cognitive improvement.²¹ Hence, we classified each patient in every domain as cognitively stable, improved, or declined.

To identify the patients with worst—most clinically relevant—cognitive performance in our analysis, we distinguished between those with more than one and those with at most one cognitive domain decline.

MR-scanning

Patients were scanned before and after resective surgery using a standardized neuro-oncology protocol. For analysis, we used the scans scheduled at 4 months postoperatively to avoid surgical artefacts. The protocol included a 3D FLAIR turbo spin-echo pulse-sequence and a 3D heavily T1-weighted gradient-echo pulse-sequence obtained after double-dose administration of intravenous gadolinium. MR scans were available from various 1.5 and 3.0 T scanners (including GE Signa HDXT, Toshiba Titan, Siemens Avanto, and Philips Ingenia). All MR images were acquired with ~1 mm isotropic resolution.

Voxel-based maps of resected regions

The resected regions were segmented in 3D on the postoperative FLAIR images (smart brush tool of iPlan v3.0 software; BrainLAB AG, Feldkirchen, Germany). The segmented volumes were verified and adjusted in reconstruction planes by two observers (EH and PW). The FLAIR scans were linearly registered to the T1 scans for further analysis using the image fusion tool. The segmented volumes were exported as binary masks registered to the T1 images. To bring these objects to MNI-152 space,²² the T1 images were nonlinearly registered in sequential steps, including rigid, affine, B-spline regularization, and symmetric diffeomorphic registration with cross-correlation as similarity metric.²³ The segmented objects were then aligned as binary images to MNI-152 using these patient-specific nonlinear transformations, resulting in maps of resected regions. Voxel-based resection cavity maps of patient subgroups with and without cognitive decline could then be analyzed. The images and derived maps were downsampled to 2 x 2 x 2 mm for further analysis.

Statistical analysis to compare resection maps

To identify the brain regions that were associated with cognitive alteration upon resection, we set out to compare resection cavity maps of patients with and without a cognitive alteration using a voxel-wise randomization test. We restricted the analysis to brain regions that were resected in at least 3 patients. As test statistic per voxel, we divided the fraction of patients with a resection region among those with an alteration by the fraction of patients with a resection region among those without, thus providing a “relative risk.” A higher test statistic corresponded to a higher rate of resection regions among patients with an alteration than among those without. To evaluate the probability of the test statistics, we used a randomization test. To estimate the empirical distribution under the null hypothesis of no difference by randomization, patient labels of cognitive alteration were randomized 4,000 times without replacement, as has been applied to analyze functional neuroimaging.^{24–26} To obtain one-sided p -values per voxel, the number of equal or more extreme test statistics in the randomized null distribution were counted and divided by the number of randomizations. Next, to obtain q -values per voxel to account for multiple testing, we divided the expected number of false-discoveries based on the empirical null distribution by the number of discoveries across all voxels, if a voxel’s p -value would be declared significant.^{24,26,27} These q -values can be interpreted as false discovery rates. Because of the exploratory nature of our research question, we deemed q -values up to 40% of interest. Statistical procedures were customized in R (v3.3; R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, September, 2013). For visual inspection, the p - and q -values were presented as overlays on MNI-152. For further interpretation of the brain locations, we aligned our results with standard cortical anatomy²⁸ and white matter anatomy.²⁹

Results

Patient characteristics

Out of 68 eligible adults with a diffuse glioma, 9 were excluded due to prior therapy or early progression. The final cohort included 59 patients with a mean age of 39 (SD 11; range 18–67) years, of whom 25 (42%) were female. Patients presented with seizures in 54 (92%) or with an incidental finding in 5 (8%). At presentation language deficits were present in 13 (22%) and motor deficits in 5 (8%). Two (3%) patients were left-handed.

The gliomas had an average volume of 71 (SD 67) mL and were located in the left hemisphere in 32 (54%). WHO grade II was diagnosed in 43 (73%, oligodendroglioma in 21, astrocytoma in 14, oligo-astrocytoma in 8), grade III due to focal anaplasia in

10 (17%, anaplastic oligodendroglioma in 5, anaplastic astrocytoma in 4, anaplastic oligo-astrocytoma in 1), and of grade I in 6 (10%, ganglioglioma in 4, pilocytic astrocytoma in 1, dysembryoplastic neuroepithelial tumor in 1).

The mean postoperative residual volume was 17 (*SD* 38) mL, and the mean extent of resection was 81% (*SD* 20%). Less than 10 mL residual tumor was observed in 35 (59%); more than 90% extent of resection was observed in 24 (41%). None of the patients had a permanent severe neurological deficit. In 5 (8%) a minor motor deficit of at least Medical Research Council grade 4 weakness was observed, in 2 (3%) a minor language deficit, dysnomia, was reported. Adjuvant radiotherapy was initiated in 13 (18%) and adjuvant temozolomide in 2 (3%).

Baseline performance in cognitive domains deviated from normative data (baseline *z*-score < -1.5 *SD*) in 29 (49%) patients. Twelve (20%) patients deviated in one of seven domains. Seventeen (28%) deviated in more than one domain. Low scores at baseline were observed in 19 (32%) patients for attention, in 11 (19%) for working memory, in 8 (14%) for verbal memory, in 8 (14%) for visual memory, in 6 (10%) for information speed, in 4 (7%) for execution, and in one (2%) for visual construction.

Cognitive outcome per domain

The differences between patients' *z*-scores at follow-up and baseline are plotted in Figure 1, indicating that the strict thresholds indeed identified outliers.

Cognitive improvement was observed in one or more domains in 10 (17%) patients. Cognitive decline manifested in one domain in 15 (25%) patients, of whom 4 had normal cognitive performance preoperatively. More than one domain declined in 10 (17%) patients, of whom 5 had normal cognitive performance preoperatively. No clustering profiles of cognitive alteration patterns were identified (Figure 2).

Cognitive improvement was observed for working memory in 6 (10%) patients, in other domains only incidentally. Cognitive decline was observed in attention in 10 (17%) patients, in information processing speed in 9 (15%), in visual construction in 7 (12%), in both visual and verbal memory in 6 (10%), and in both working memory and execution in 4 (7%).

Language deficits linked to tumor infiltration as positive control

To ensure the robustness of our map comparison, we compared tumor localization maps of the patients with and without a language deficit at presentation (Supporting Information, Movie 1).

All identified regions were in the left hemisphere and were focused on the arcuate fasciculus, the dorsal part of the superior temporal gyrus, the ventral premotor cortex, and the dorsolateral premotor cortex. This confirmation³⁰ adds support to the validity of our approach.

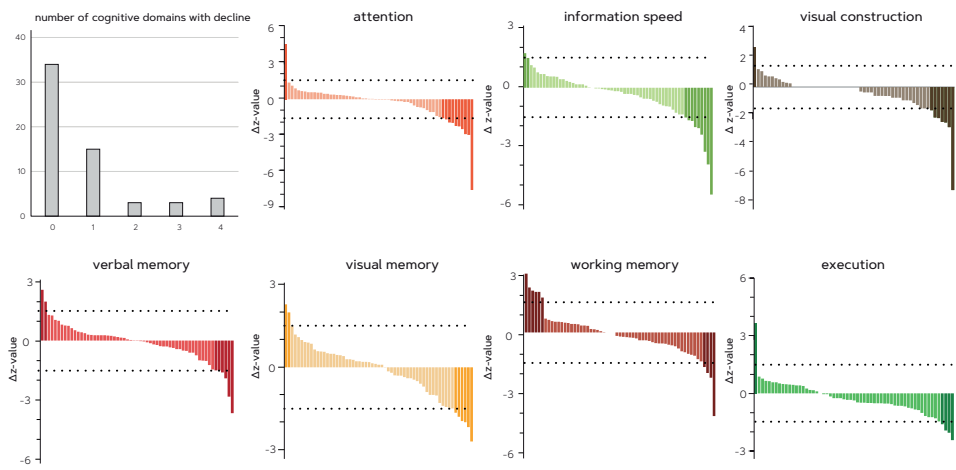


Figure 1. Cognitive alteration per domain between follow-up and baseline neuropsychological assessment (n = 59). Upper-left: Histogram of number of patients by number of cognitive domains with decline. Bar plots of change in z-score values in decreasing order of change for each of seven cognitive domains. Each bar represents one patient. Positive values correspond with cognitive improvement; negative values with cognitive decline. The horizontal dotted lines are drawn at +1.5 and -1.5 SD as arbitrary thresholds for classification as improvement (far-left dark-colored) or decline (far-right dark-colored), or unchanged (light-colored)

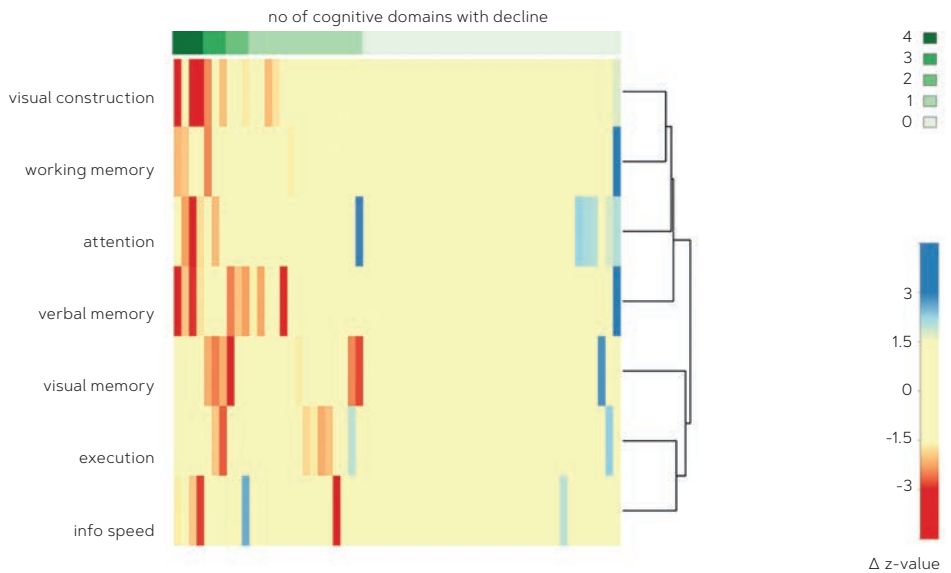
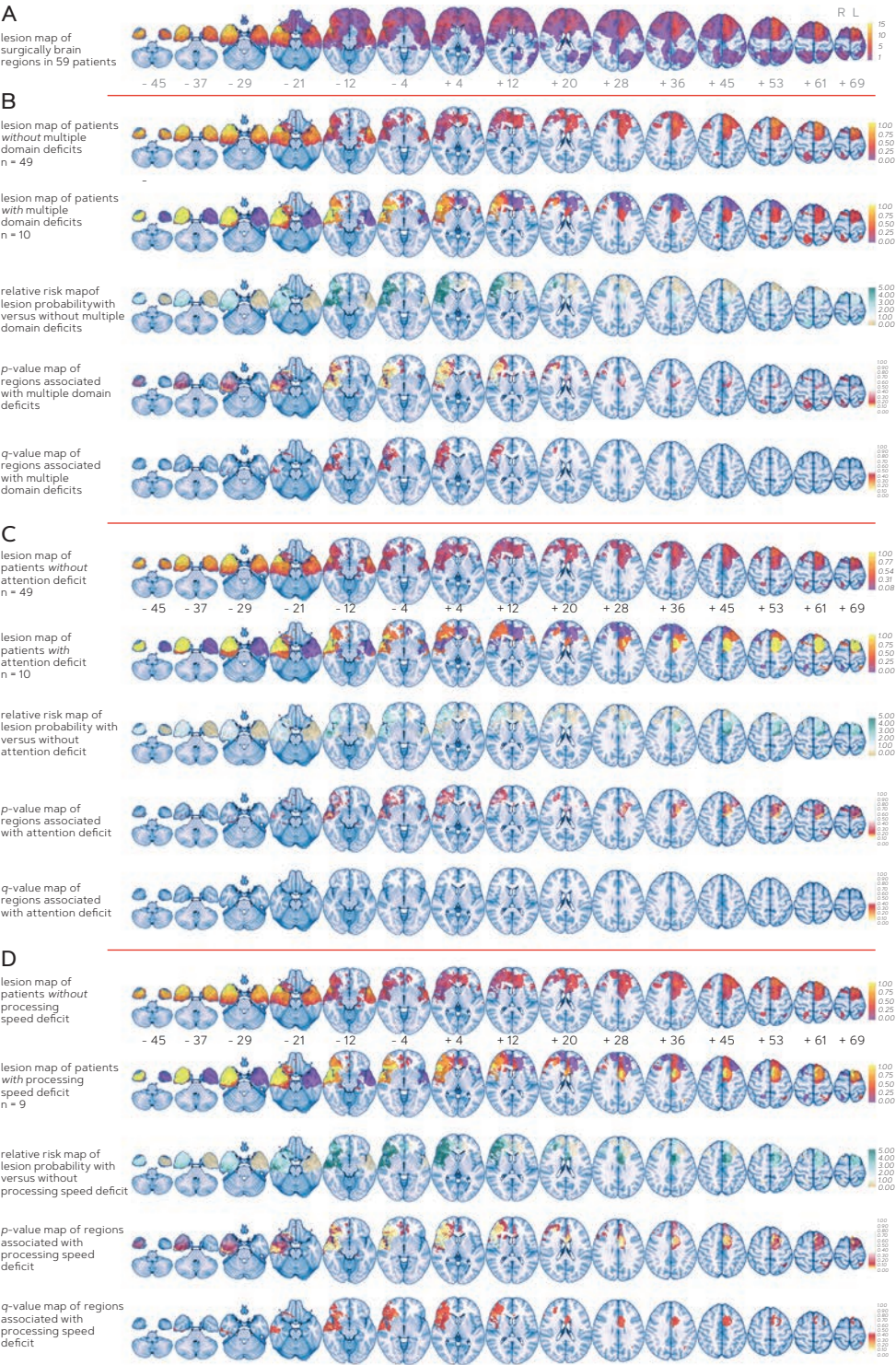


Figure 2. Heat map of cognitive alteration in 59 patients in columns by cognitive domain in rows. Patients are ordered by number of cognitive domains with decline (green color coding on top right). Domains are ordered by unsupervised clustering. No clustering profiles are identified. Cognitive decline is shown in shades of red; cognitive improvement in shades of blue; and unchanged cognitive performance in yellow (see bottom right color legend)



<< **Figure 3.** Brain result maps of (A) lesions, here surgically removed regions as resection cavity map, in the study population, demonstrating temporal and frontal preferential locations, with a maximum of 15 patients at a voxel, (B) patients without and with two or more declined cognitive domains, (C) patients without and with an attention decline, and (D) patients without and with a processing speed deficit. For (B–D), rows represent (1) a resection cavity map of the patients without a decline, (2) a resection cavity map of the patients with a decline, (3) a relative risk map with larger differences in resected regions represented by deeper turquoise, (4) a randomized p -value map with lower p values represented by lighter colors, and (5) a q -value map with lower false discovery rates represented by lighter colors for visual interpretation of other thresholds. All results are superimposed on MNI's standard brain, z -values are plotted below slices in the first rows. Laterality as indicated

Brain regions associated with cognitive decline

We then determined the resection map across all 59 patients, corresponding to the preferential locations of gliomas (Figure 3A).

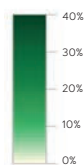
We aimed to pinpoint the critical brain locations for overall cognitive decline upon surgical removal. Therefore, maps of resected regions were compared between the 10 patients with cognitive decline in more than one domain and the 49 patients with decline in at most one domain (Figure 3B; Supporting Information, Movie 2). All identified regions were located in the right hemisphere, and were centered around the insular cortex, the fronto-orbital cortex, and the perisylvian cortex, including the inferior frontal gyrus, the superior temporal gyrus, and opercular cortex (Figure 4). This also included peri-Sylvian white matter structures, such as the inferior fronto-occipital fasciculus, the uncinate fasciculus, and the inferior longitudinal fasciculus.

As attention was the most-frequently affected cognitive domain, we proceeded to evaluate the associated brain regions. Resection cavity maps were compared between the 10 patients with an attention decline and the 49 patients with unchanged attention performance (Figure 3C; Supporting Information, Movie 3). No regions were identified with q -values <40%.

As information processing speed was the next most frequently affected domain, we also compared the maps of resected regions between the 9 patients with a reduction in information processing speed and the 50 patients with unchanged information processing (Figure 3D; Supporting Information, Movie 4).

Associated brain regions were located in both hemispheres and in the midline, and focused on the right frontal pole, the left cingulum, and the corpus callosum (Figure 4). This also included the right insular cortex, the frontal orbital cortex and peri-Sylvian white matter structures, such as the inferior fronto-occipital fasciculus, the uncinate fasciculus, and the inferior longitudinal fasciculus.

The other domains were also analyzed for associated brain regions, although these were involved in fewer patients. Results show that a decline in executive functioning



<< **Figure 4.** Heat map of percentage of voxels (shades of green) with a q -value < 0.4 in a cognitive domain in columns per anatomical region in rows. The anatomical regions are grouped by laterality and midline structures, and subdivided by horizontal black bars in cortical regions, subcortical white matter pathways, and subcortical grey nuclei. No brain regions were identified for decline in attention, verbal memory, visual memory, and working memory, and therefore, these rows are empty. Absence of information in anatomical regions is demonstrated as white, whereas information of 0% is demonstrated as light yellow

may be particularly associated with surgical removal of the right pars triangularis of the inferior frontal gyrus and the right superior and middle temporal gyrus (Figure 4). A selection of individual tests was also analyzed for the executive functioning domain. Declines in the trail making test A, B, and B-A, or categoric word fluency score were not associated with surgically removed brain regions at a q -value $< 40\%$.

Discussion

The main findings of this study are that (a) cognitive alterations after resective surgery of diffuse (nonenhancing) glioma are rather prevalent with 17% of patients declining in more than one domain and 10% improved in at least one domain, (b) attention and information processing speed are the most frequently declined cognitive domains, and (c) the brain regions most vulnerable for cognitive decline after surgery are located in the right hemisphere.

Few studies have reported on cognitive alteration after glioma resection based on pre- and postoperative neuropsychological examination.^{7,8,31-36} Cognitive decline varied between 24% and 60% in these studies and reported different affected domains. Postoperative testing was within 6 weeks of surgery in nearly all studies, whereas further cognitive improvement has been observed between 3 months and one year.⁷ Furthermore, these studies have included mainly patients with WHO grade IV glioblastoma, in whom tumor mass-effect on the brain and subsequent surgical relief of compression is likely different from removal of tumor-infiltrated brain regions in patients with lower grade gliomas. In addition, in these studies, the difference between mean test scores before and after surgery was analyzed for the study group, instead of the frequency of relevant cognitive alterations which, in our opinion, is more informative for patient counseling and clinical decision-making. Some studies aimed to identify brain locations associated with decline in a specific test, such as in working memory,³⁷ personality,³⁸ and mentalization.³⁹ We decided to analyze composite domain scores rather than individual tests, in line with previous reports,^{9,40} because of the presumed higher robustness against noise of individual test scores. This is supported by the finding that the executive functioning domain

score identified brain regions that are vulnerable to cognitive decline, whereas individual test scores, that is, the trail making test and the categoric word fluency score, did not. Other studies aimed to detect cognitive alterations after glioma surgery in specific brain regions, such as the temporal lobes,³⁴ the insula,³³ or eloquent areas.³² Here, we investigated cognitive changes one year after surgery, using a combination of tests to cover a variety of domains in a homogeneous population of adults with slow-growing diffuse gliomas to isolate surgical impact on cognition.

Patients often declined in attention after glioma resection in our series. The attention network is usually divided into an alerting, an executive, and an orienting component. The anatomical distributions of these networks are extensive. The alerting attention network has been localized in frontal and parietal regions with their interconnecting path-ways, particularly in the right hemisphere, the executive attention network in the anterior cingulate cortex with connections to the dorso-lateral prefrontal cortex, and the orienting network in the thalamus with connections to the superior parietal lobe, temporo-parietal junction, the superior temporal lobe, and the frontal eye fields.⁴¹ In a neuro-imaging meta-analysis of 173 experiments with normal subjects, activation was observed during attention tasks in bilateral fronto-parietal pathways, such as the anterior insula, inferior frontal gyrus, dorsolateral prefrontal cortex, dorsal premotor cortex, and intraparietal sulcus.⁴² Lesion mapping studies in patients within two weeks after stroke identified loci associated with declined attention in the peri-Sylvian cortex, prefrontal and premotor cortical regions, and the thalamus.⁴³⁻⁴⁵ Many of these regions were indicated by our *p*-value maps, although we were unable to pinpoint associated brain regions in our *q*-value maps. The extensiveness of the attention network may explain why this domain was most frequently involved in our study.

Our patients also declined in information processing speed after glioma resection. This domain represents efficiency of overall cognition measured by timing of performances. A decline in information processing speed during aging was associated with global white matter changes,⁴⁶ and with fractional anisotropy alterations in the corpus callosum, superior longitudinal fasciculus and the inferior fronto-occipital fasciculus.⁴⁷ In stroke, decline of information processing speed was associated with cortical lesions in the left supramarginal and angular gyri and with the superior longitudinal fasciculus.⁴⁸ In cerebral small vessel disease, reduced processing speed was associated with the anterior corpus callosum and right anterior thalamic radiation.^{49,50} The connectivity of the mediodorsal nucleus of the thalamus with the frontal and temporal regions⁵¹ may explain why distant lesions can be associated with the same processing speed decline. In our data, similar regions were associated with speed reduction, indicating a disconnection of the projections between the right thalamus and prefrontal and insular cortical regions. The left cingulum was also associated with reduced processing speed in our data. In normal aging, processing speed decline

has previously been linked with fractional anisotropy changes of the left cingulum.⁵²

Voxel-based lesion mapping is one established method to relate brain location to brain function.⁵³ This has contributed considerably to clinical knowledge of brain function, such as language deficit recovery after stroke.^{54,55} Nevertheless, this technique has limitations, which may result in mislocalization of function. First, mislocalization of functional focal points in the brain may result from spatial bias, introduced in lesion-deficit mapping by the specific lesion architecture of gliomas. For instance, lesion-deficit mapping analysis of ischemic lesions may well reflect differences in vascular territories rather than the true functional organization of the brain.⁵⁶ The equivalent in glioma may be the location of origin of different molecular glioma subtypes.⁵⁷ Second, more complex and unpredictable interactions between lesions and deficits may arise when tumor is located in many locations or when a function is distributed over many critically functional areas in the brain.^{56,58} As a consequence, two patients with the same cognitive deterioration and with damage to the same functional network may have had resections at entirely different brain locations. Or symptoms may arise from anatomically intact brain regions in connection with the lesion-induced disconnected regions. Third, spatial resolution of lesion mapping may differ from the resolution of functional individual neurons and networks in the brain. Fourth, nonlinear registration is a potential source of mislocalization. This was verified by visual inspection for all patients and the potential error was considered minimal.

In our voxel-based mapping, we have used resection cavities as lesions to obtain resection cavity maps for lesion-function mapping. These should be distinguished from resection probability maps that capture the resectability of tumors in patient populations, that have been previously used to estimate the expected residual tumor volume,⁵⁹ to evaluate the potential for brain plasticity^{60,61} to compare resection results between surgical teams.⁶²

Our approach has several strengths. First, the study cohort was homogeneous consisting of young adults with a slowly infiltrative diffuse glioma who had standardized imaging and neuropsychological follow-up. Second, an established voxel-based lesion-symptom mapping methodology was applied without presumptions to the association between brain location and function. Third, the assumption-free randomization test with quantification of false discoveries was used as robust analysis. This is illustrated by the verification of the established brain regions involved in language in our data.^{63,64}

This study has some limitations as well. First, the power to detect associations between resected brain and cognitive deterioration follows the preferential locations of glioma, and is therefore, not distributed evenly in the brain. Second, whereas we attempted to isolate the association between resections and cognition, several other factors may have contributed to cognitive alterations, such as psychological burden of disease, early effects of radiotherapy in some patients,⁶ or surgery-related

ischemia. Cognitive deterioration is associated with late, rather than early, effects of radiotherapy.⁹ New post-operative diffusion-restricted regions, that is, surgical ischemia, were excluded from our segmentations, but may have contributed to cognitive decline, similar to acquired neurological deficits.⁶⁵ Third, according to most clinical settings, application of different scanner vendors and field strengths is a commonly known concern, and this could have potentially influenced our voxel-based lesion mapping analysis.

The clinical relevance of the observed cognitive alterations is difficult to answer because cognition does not correlate with quality of life.^{66,67} Nevertheless, our findings can have clinical implications. Patient counseling should include information on cognitive alterations after glioma resection, in particular for attention and information processing speed, which seems to be at risk after surgery in the right hemisphere. In addition, surgery of the right-sided peri-Sylvian cortex and subcortical connections may benefit from mapping of attention tasks. Similarly, surgery of the frontal cortex, cingulum, and the anterior corpus callosum may benefit from mapping of information processing tasks. Intraoperative mapping beyond language and motor functions of specific cognitive tasks has been demonstrated to be feasible.^{68,69} Our observations may contribute to identify the patients who can benefit most from these techniques.

References

1. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012. *Neuro Oncol.* 2015;17 Suppl 4:iv1-iv62.
2. Ricard D, Idbaih A, Ducray F, Lahutte M, Hoang-Xuan K, Delattre JY. Primary brain tumours in adults. *Lancet.* 2012;379(9830):1984-1996.
3. Capelle L, Fontaine D, Mandonnet E, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. *J Neurosurg.* 2013;118(6):1157-1168.
4. Jakola AS, Myrnes KS, Kloster R, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. *JAMA.* 2012;308(18):1881-1888.
5. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. *J Clin Oncol.* 2012;30(20):2559-2565.
6. Klein M. Neurocognitive functioning in adult WHO grade II gliomas: impact of old and new treatment modalities. *Neuro Oncol.* 2012;14 Suppl 4:iv17-24.
7. Satoer D, Visch-Brink E, Smits M, et al. Long-term evaluation of cognition after glioma surgery in eloquent areas. *J Neurooncol.* 2014;116(1):153-160.
8. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.
9. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol.* 2009;8(9):810-818.
10. De Benedictis A, Duffau H. Brain hodotopy: from esoteric concept to practical surgical applications. *Neurosurgery.* 2011;68(6):1709-1723; discussion 1723.
11. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci.* 2009;29(6):1860-1873.
12. Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci.* 2013;16(9):1348-1355.
13. Power JD, Schlaggar BL, Lessov-Schlaggar CN, Petersen SE. Evidence for hubs in human functional brain networks. *Neuron.* 2013;79(4):798-813.
14. Klein M, Taphoorn MJ, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol.* 2001;19(20):4037-4047.
15. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. *J Clin Oncol.* 2006;24(8):1305-1309.
16. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning*. New York: Psychology Press, Inc.; 2003:159-173.
17. Jolles J, Van Boxtel MP, Ponds RW, Metsemakers JF, Houx PJ. [The Maastricht aging study (MAAS). The longitudinal perspective of cognitive aging]. *Tijdschr Gerontol Geriatr.* 1998;29(3):120-129.
18. Kessels RP, Nys GM, Brands AM, van den Berg E, van Zandvoort MJ. The modified Location Learning Test: norms for the assessment of spatial memory function in neuropsychological patients. *Arch Clin Neuropsychol.* 2006;21(8):841-846.
19. Schmand B, Groenink SC, van den Dungen M. Letter fluency: psychometric properties and Dutch normative data. *Tijdschrift voor gerontologie en geriatrie.* 2008;39(2):64-76.

20. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual]*. Lisse; 2000.
21. Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological assessment*. 5 ed. New York: Oxford University Press; 2012.
22. Fonov V, McKinstry R, Almlí C, Collins D. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *Neuroimage*. 2009;47:S102.
23. Avants BB, Epstein CL, Grossman M, Gee JC. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. *Med Image Anal*. 2008;12(1):26-41.
24. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp*. 2002;15(1):1-25.
25. Nichols T, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat Methods Med Res*. 2003;12(5):419-446.
26. Schwartzman A, Dougherty RF, Lee J, Ghahremani D, Taylor JE. Empirical null and false discovery rate analysis in neuroimaging. *Neuroimage*. 2009;44(1):71-82.
27. Langers DR, Jansen JF, Backes WH. Enhanced signal detection in neuroimaging by means of regional control of the global false discovery rate. *Neuroimage*. 2007;38(1):43-56.
28. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980.
29. Catani M, Thiebaut de Schotten M. A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*. 2008;44(8):1105-1132.
30. Banerjee P, Leu K, Harris RJ, et al. Association between lesion location and language function in adult glioma using voxel-based lesion-symptom mapping. *Neuroimage Clin*. 2015;9:617-624.
31. Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir (Wien)*. 2014;156(8):1451-1459.
32. Mandonnet E, De Witt Hamer P, Poisson I, et al. Initial experience using awake surgery for glioma: oncological, functional, and employment outcomes in a consecutive series of 25 cases. *Neurosurgery*. 2015;76(4):382-389; discussion 389.
33. Wu AS, Witgert ME, Lang FF, et al. Neurocognitive function before and after surgery for insular gliomas. *J Neurosurg*. 2011;115(6):1115-1125.
34. Noll KR, Weinberg JS, Ziu M, Benveniste RJ, Suki D, Wefel JS. Neurocognitive Changes Associated With Surgical Resection of Left and Right Temporal Lobe Glioma. *Neurosurgery*. 2015;77(5):777-785.
35. Racine CA, Li J, Molinaro AM, Butowski N, Berger MS. Neurocognitive Function in Newly Diagnosed Low-grade Glioma Patients Undergoing Surgical Resection With Awake Mapping Techniques. *Neurosurgery*. 2015;77(3):371-379; discussion 379.
36. Dallabona M, Sarubbo S, Merler S, et al. Impact of mass effect, tumor location, age, and surgery on the cognitive outcome of patients with high-grade gliomas: a longitudinal study. *Neuro-Oncology Practice*. 2017;4(4):229-240.
37. Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. *J Neurooncol*. 2007;81(3):305-313.
38. Campanella F, Fabbro F, Ius T, Shallice T, Skrap M. Acute effects of surgery on emotion and personality of brain tumor patients: surgery impact, histological aspects, and recovery. *Neuro Oncol*. 2015;17(8):1121-1131.
39. Duffau H. The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. *Cortex*. 2014;58:325-337.

40. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet*. 2002;360(9343):1361-1368.
41. Raz A, Buhle J. Typologies of attentional networks. *Nat Rev Neurosci*. 2006;7(5):367-379.
42. Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neurosci Biobehav Rev*. 2015;48:22-34.
43. Corbetta M, Ramsey L, Callejas A, et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. 2015;85(5):927-941.
44. Murakami T, Hama S, Yamashita H, et al. Neuroanatomic pathway associated with attentional deficits after stroke. *Brain Res*. 2014;1544:25-32.
45. Rinne P, Hassan M, Goniotakis D, et al. Triple dissociation of attention networks in stroke according to lesion location. *Neurology*. 2013;81(9):812-820.
46. Kuznetsova KA, Maniega SM, Ritchie SJ, et al. Brain white matter structure and information processing speed in healthy older age. *Brain Struct Funct*. 2016;221(6):3223-3235.
47. Kerchner GA, Racine CA, Hale S, et al. Cognitive processing speed in older adults: relationship with white matter integrity. *PLoS One*. 2012;7(11):e50425.
48. Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *Neuroimage*. 2008;42(2):1032-1044.
49. Duering M, Zieren N, Hervé D, et al. Strategic role of frontal white matter tracts in vascular cognitive impairment: a voxel-based lesion-symptom mapping study in CADASIL. *Brain*. 2011;134(Pt 8):2366-2375.
50. Duering M, Gesierich B, Seiler S, et al. Strategic white matter tracts for processing speed deficits in age-related small vessel disease. *Neurology*. 2014;82(22):1946-1950.
51. Behrens TE, Johansen-Berg H, Woolrich MW, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci*. 2003;6(7):750-757.
52. Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci*. 2013;7:32.
53. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. *Nat Neurosci*. 2003;6(5):448-450.
54. Kümmerer D, Hartwigsen G, Kellmeyer P, et al. Damage to ventral and dorsal language pathways in acute aphasia. *Brain*. 2013;136(Pt 2):619-629.
55. Price CJ, Seghier ML, Leff AP. Predicting language outcome and recovery after stroke: the PLORAS system. *Nat Rev Neurol*. 2010;6(4):202-210.
56. Mah YH, Husain M, Rees G, Nachev P. Human brain lesion-deficit inference remapped. *Brain*. 2014;137(Pt 9):2522-2531.
57. Ellingson BM, Lai A, Harris RJ, et al. Probabilistic radiographic atlas of glioblastoma phenotypes. *AJNR Am J Neuroradiol*. 2013;34(3):533-540.
58. Boes AD, Prasad S, Liu H, et al. Network localization of neurological symptoms from focal brain lesions. *Brain*. 2015;138(Pt 10):3061-3075.
59. Mandonnet E, Jbabdi S, Taillandier L, et al. Preoperative estimation of residual volume for WHO grade II glioma resected with intraoperative functional mapping. *Neuro Oncol*. 2007;9(1):63-69.
60. Herbet G, Maheu M, Costi E, Lafargue G, Duffau H. Mapping neuroplastic potential in brain-damaged patients. *Brain*. 2016;139(Pt 3):829-844.

61. Ius T, Angelini E, Thiebaut de Schotten M, Mandonnet E, Duffau H. Evidence for potentials and limitations of brain plasticity using an atlas of functional resectability of WHO grade II gliomas: towards a "minimal common brain". *Neuroimage*. 2011;56(3):992-1000.
62. De Witt Hamer PC, Hendriks EJ, Mandonnet E, Barkhof F, Zwinderman AH, Duffau H. Resection probability maps for quality assessment of glioma surgery without brain location bias. *PLoS One*. 2013;8(9):e73353.
63. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18-27.
64. Tate MC, Herbet G, Moritz-Gasser S, Tate JE, Duffau H. Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited. *Brain*. 2014;137(Pt 10):2773-2782.
65. Jakola AS, Berntsen EM, Christensen P, et al. Surgically acquired deficits and diffusion weighted MRI changes after glioma resection--a matched case-control study with blinded neuroradiological assessment. *PLoS One*. 2014;9(7):e101805.
66. Boele FW, Douw L, Reijneveld JC, et al. Health-related quality of life in stable, long-term survivors of low-grade glioma. *J Clin Oncol*. 2015;33(9):1023-1029.
67. Wolf J, Campos B, Bruckner T, Vogt L, Unterberg A, Ahmadi R. Evaluation of neuropsychological outcome and "quality of life" after glioma surgery. *Langenbecks Arch Surg*. 2016;401(4):541-549.
68. Kinoshita M, Nakajima R, Shinohara H, et al. Chronic spatial working memory deficit associated with the superior longitudinal fasciculus: a study using voxel-based lesion-symptom mapping and intraoperative direct stimulation in right prefrontal glioma surgery. *J Neurosurg*. 2016;125(4):1024-1032.
69. Wager M, Du Boisgueheneuc F, Pluchon C, et al. Intraoperative monitoring of an aspect of executive functions: administration of the Stroop test in 9 adult patients during awake surgery for resection of frontal glioma. *Neurosurgery*. 2013;72(2 Suppl Operative):ons169-180; discussion ons180-161.

Supplementary data

Movies can be found online in the Supplementary material that accompanies this article.

Part IV

Neurocognitive outcome
reporting in brain tumor trials

8

The level of reporting of neurocognitive outcomes in randomized controlled trials of brain tumor patients:

a systematic review

European Journal of Cancer

2018 Sep;100:104-125.

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Abstract

Background: Neurocognitive impairment is frequently present in brain tumor patients and is therefore considered an important outcome in brain tumor 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 randomized controlled trials (RCTs) in brain tumor 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 analyzed 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 generalizability 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.

Conclusion: Investigators involved in brain tumor 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.

Introduction

Brain tumors can be classified as either primary, such as gliomas and meningiomas which originate in the brain, or secondary, in which systemic tumors metastasize to the brain. The incidence of primary brain tumors ranges from 5.6 for women to 7.8 for men per 100,000.¹ With an incidence of cancer ranging between 306.3 to 429.9 per 100,000 persons, and 9-45% of cancer patients developing brain metastases, secondary brain tumors far outnumber primary brain tumors.^{1,2} Brain tumor 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 tumor patients and their proxies.⁴ This suggests that the negative impact of both the tumor and its treatment on NCF should be prevented as much as possible. Indeed, neurocognitive functioning has gained more attention in recent brain tumor research⁵ and has been included as a secondary outcome in a growing number of randomized controlled trials (RCTs) in brain tumor 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 tumors 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 tumor 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 standardized neurocognitive test batteries, instead of screening instruments, for which proposals have been published¹²⁻¹⁵ 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 tumor patients and assessed whether high level reporting RCTs did indeed impact clinical decision-making.

Methods

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 tumors', 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

Inclusion and exclusion criteria

RCTs were included concerning adult (≥ 18 years) patients with an intracranial tumor, both those with brain tumors 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 tumor patients and patients with other diagnoses were included because of possible difficulties in interpreting NCO results related specifically to brain tumor patients.

Data extraction and definition of high-quality reporting of neurocognitive outcome study

From the eligible articles, the following data was extracted: study design, sample size, population characteristics, types of interventions, type of instrument used to assess neurocognitive functioning, main NCO and various clinical outcomes.

The level of NCO reporting was assessed using the recommendations by the International Society for Quality of Life Research (ISOQOL).¹⁸ Although the criteria were developed for assessment of the level of patient reported outcome reporting, we felt that most criteria were also applicable to reporting of NCOs. The original

ISOQOL checklist consists of 17 items that should be reported in all RCTs, irrespective of the type of outcome and whether the outcome is a primary or secondary end-point. When the outcome is a primary end-point, an additional 11 items should be reported.¹⁸ In line with Dirven et al. (2014),¹⁹ we divided the item about 'missing data' into two items (extent of missing data and statistical approaches to deal with missing data). By this, we could better investigate the possible differences between reporting of actual missing NCO data and reporting of statistical methods to address this issue. Moreover, we discarded the items about 'statement of validity and reliability of NCO instrument', 'NCO in protocol and post-hoc analysis' and 'a copy of the instrument should be included' because we considered these items not to be useful for our research question.

To determine the potential impact of NCO evidence on clinical decision-making, we defined that at least two-thirds of the recommended ISOQOL criteria should be met in order to be classified as 'high-quality' evidence. This cut-off is based on previous literature²⁰ and implicates that studies with NCO as primary outcome should at least meet 18/26 items, and studies with NCO as secondary outcome 11/16 items. For high-quality studies, we also assessed the level of the used neurocognitive test battery, based on criteria set up for glioma research and including sensitivity and availability of parallel test versions of the measures.²¹ Clinical impact was evaluated by combining outcome data on survival and on NCF.

In addition, for all eligible studies, we assessed risk of bias, based on the Cochrane Risk of Bias Tool.²² Types of bias assessed were selection bias, performance bias, detection bias, attrition bias and reporting bias. Three categories were used to judge risk of bias: low, unclear and high risk of bias.²² In short, low risk was defined as adequate randomization, no ability to foresee the group assignment, blinding or no impact of lack of blinding on the outcomes, balanced or use of adequate methods in case of missing data and reporting of all pre-specified outcomes. High risk of bias was defined in case the study did not fulfill the criterium for low risk, and unclear risk was defined in case of insufficient data or reporting, or when the study did not address that specific type of bias.²²

Results

The literature search yielded 1889 unique records published until August 2017. A total of 77 eligible articles were identified, comprising 65 RCTs representing over 14,000 brain tumor patients. The selection procedure is shown in Figure 1.

Study demographics and NCO assessment

The main characteristics of the included trials are displayed in Table 1, and in more detail in supplementary file 2. Table 2 shows the level of NCO reporting according to the ISOQOL criteria. In 14/65 (22%) RCTs, NCO was a primary end-point. The included brain tumor types varied, with 20 RCTs studying glioma patients (31%) and 17 studying brain metastatic patients (26%) only. Radiotherapy and chemotherapy were the most studied treatments (both in 31% of studies). In five studies (8%), rehabilitation of neurocognitive impairments was investigated. Regarding NCO measures used, 26 studies (40%) included only a cognitive screening instrument, mainly the Mini-Mental State Examination (MMSE). In 38 studies (59%) a short ($n=23$, 35%), medium ($n=12$, 18%) or extensive ($n=3$, 5%) cognitive test battery was used. In one study (2%), it remained unclear which instrument was used. In 19 studies (29%), NCO differed between treatment arms, most often in memory functioning (9/19 studies).

Quality of NCO reporting

Twenty out of the 65 RCTs (31%) met the pre-defined ISOQOL criteria to be classified as 'high-quality' evidence (Table 3). Of these, eight RCTs included NCO as a primary end-point. Overall, 'primary NCO studies' were of higher quality reporting (8/14; 57%) than 'secondary NCO studies' (12/51; 23%).

Major limitations in reporting included the lack of documentation of details on missing data: statistical approaches for dealing with missing data were not stated in 79% of studies with NCO as primary end-point and in 73% studies with NCO as secondary end-point (see Table 2). Reasons for missing data were not explained in 57% and 80% for primary and secondary NCO studies, respectively. Similarly, the documentation of limitations of NCO components of the trial was poor, lacking in 79% of primary and 73% of secondary NCO studies. On the other hand, most studies identified NCO as outcome in the abstract (100% for primary and 86% for secondary NCO), documented the extent of missing data (71% versus 65%, respectively), and stated whether NCO was either a primary or secondary end-point (71% versus 67%). Compared to studies with NCO as secondary end-point, more studies with NCO as primary end-point reported a hypothesis (25% versus 79%, respectively), described methods of collecting data (24% versus 57%), and provided a flow diagram on patient inclusion (45% versus 71%).

Regarding criteria exclusively for primary NCO studies, in 43% of studies no referral to NCO was made in the title, and the windows for valid NCO responses were specified in only 36%. The power size calculation and reporting of all NCO domains were both documented in 79% of studies.

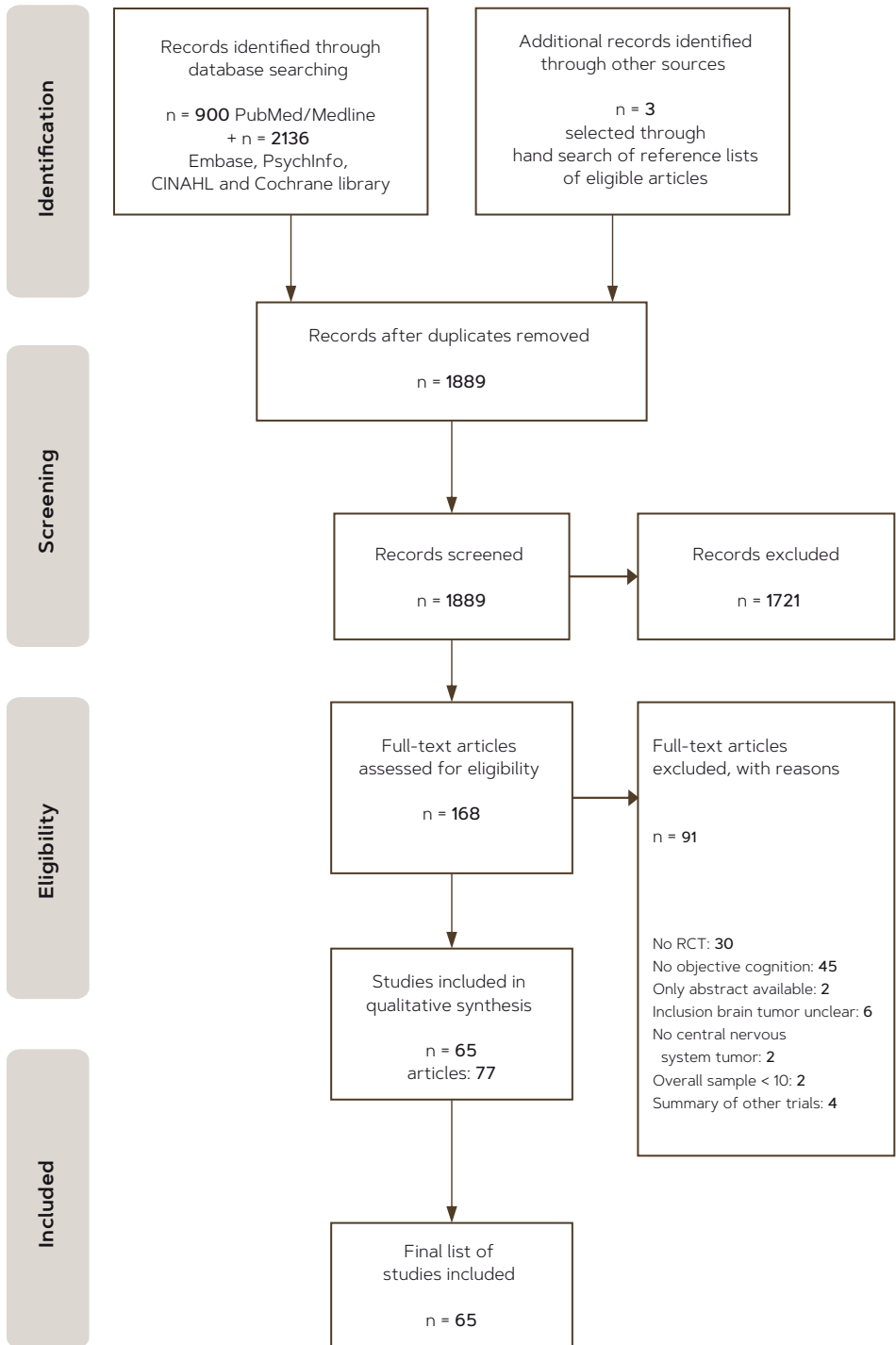


Figure 1. Schematic breakdown of literature search results of brain tumor randomized controlled trials

Risk of bias

High risk of bias was especially observed regarding blinding of participants and personnel (i.e. performance bias): 76% in low-quality NCO reporting studies and 70% in high-quality reporting studies (Figure 2). Attrition bias (i.e. incomplete outcome data) was high in 15% of both higher and lower quality studies, with unclear bias in 56% of the latter group. On the other hand, we classified bias regarding blinding of outcome assessment (detection bias) as low risk in all studies. Overall, lower quality reporting NCO studies did not have more high risk of biases compared to higher quality reporting studies.

Treatment recommendations based on high-quality NCO reporting studies

The 20 high-quality NCO studies that we defined most informative to determine the net clinical benefit of a treatment are summarized in Table 3. In six RCTs, described in 10 articles, both overall and/or progression-free survival and NCO did not differ significantly between the treatment groups. This was found for studies including high-grade glioma,^{23,24} low-grade glioma^{6,25-28} and in patients with brain metastases or candidates for PCI.²⁹⁻³¹ In these studies, the test battery was not of high quality, and no clear conclusions in favor of one of the treatments studied could be made on both the high-quality reporting NCO evidence and survival outcomes. In two of these six RCTs, baseline cognitive impairments were found to be predictors of (poorer) survival, suggesting NCO could possibly be used as a prognostic factor.^{6,23,25-27} In one rehabilitation study including adequate measures, investigating the effect of armodafinil on fatigue, also no difference in NCO was found between the experimental and placebo group.³²

In two studies, overall or progression-free survival (PFS) improved significantly with the experimental treatment, with no differences in cognitive performance observed when using an insensitive cognitive measure.^{7,33} These NCO results resulted in the authors' conclusion to treat low-grade and high-grade glioma patients, especially those with 1p/19q-codeletion, with radiotherapy (RT) + procarbazine, lomustine and vincristine (PCV) chemotherapy instead of RT alone.^{7,33} In two studies on brain metastases with NCO as primary end-point,^{9,34} survival was comparable between patients treated with stereotactic radiosurgery (SRS) with or without whole brain radiotherapy (WBRT) and in patients treated with SRS or WBRT, but NCO, measured by an extended test battery, was in favor of patients treated with SRS alone.

>> **Caption Table 1:** TTF tumor treating fields; MMSE Mini-Mental State Examination; SOMCT short orientation memory concentration test. ^a primary with or without metastatic brain tumor; ^b due to rounding up not exactly 100%; ^c more domains per study possible

Table 1. Randomized Controlled Trial (RCT) demographic characteristics of studies identified.

Variable	Category	Overall number, n= 65; n (%)
<i>Basic RCT demographics</i>		
International	Yes	20 (31)
	No	45 (69)
Industry supported (fully or in part)	Yes	22 (34)
	No	43 (66)
Overall study sample size (regardless of patients included in the NCO analysis)	<200	43 (66)
	>200	22 (34)
Type of tumor	Glioblastoma	11 (17) ^b
	High-grade glioma (grade III-IV)	4 (6)
	Low-grade glioma (grade II)	3 (5)
	Glioma (combination low- and high-grade)	2 (3)
	Brain metastases	17 (26)
	Cerebral lymphoma	3 (5)
	Meningioma	1 (2)
	Prophylactic	8 (12)
	Different brain tumors ^a ; histology described	5 (8)
	Different brain tumors ^a ; incl. unknown histology	7 (11)
	Brain tumor type not specified	4 (6)
Experimental treatment type	Radiotherapy (including PCI)	20 (31) ^b
	Chemotherapy	20 (31)
	Target therapy and immunotherapy	2 (3)
	Other medication (incl. modafinil & melatonin)	8 (12)
	Anesthesia	7 (11)
	Other therapy (surgery, boswelvia, TTF)	3 (5)
	Rehabilitation	5 (8)
Difference between treatment arms in the primary end-point (including NCO as primary outcome)	Yes	24 (37)
	No	37 (57)
	Unclear	4 (6)
Overall survival (OS) difference favoring experimental treatment	Yes	5 (8)
	No difference	38 (58)
	N/A	19 (29)
	Unclear	3 (5)
<i>NCO-related basic characteristics</i>		
NCO instrument used	Screening (MMSE, SOMCT)	26 (40)
	Short test battery (< 5 tests)	23 (35)
	Medium test battery (5-15 tests)	12 (18)
	Extensive test battery (>15 tests)	3 (5)
	Unclear	1 (2)
NCO difference between treatment arms	Yes	19 (29)
	No	34 (52)
	N/A	7 (11)
	Unclear	5 (8)
If statistically different NCO, in these domains ^c	Memory	9 (14)
	Attention	3 (5)
	Executive functioning	6 (9)
	Information processing speed	6 (9)
	Overall cognitive score	3 (5)
	Screening instrument	5 (8)
Length of NCO follow-up during RCT	Up to 6 months	28 (43)
	Up to 1 year	6 (9)
	More than 1 year	27 (42)
	Unknown	4 (6)
NCO as primary end-point	Yes	14 (22)
	No	51 (78)

Table 2. Level of NCO reporting

Criterion		Primary end-point, n = 14; n (%)	Secondary end-point, n = 51; n (%)
Title and abstract			
The title of the paper should be explicit as to the RCT including NCO	Yes	8 (57)	n/a
	No	6 (43)	
NCO should be identified as an outcome in the abstract	Yes	14 (100)	44 (86)
	No	0 (0)	7 (14)
Introduction, background and objectives			
The introduction should contain a summary of NCO research that is relevant to the RCT	Yes	12 (86)	n/a
	No	2 (14)	
The NCO hypothesis should be stated and should specify the relevant NCO domain(s) if applicable	Yes	11 (79)	13 (25)
	No	3 (21)	38 (75)
Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment	Yes	11 (79)	n/a
	No	3 (21)	
Methods			
<i>Outcomes</i>			
The mode of administration of the NCO tool (i.e. performed by a health care professional trained in neuro-cognitive assessment) and the methods of collecting data (e.g. telephone, other) should be described	Yes	8 (57)	12 (24)
	No	6 (43)	39 (76)
A citation for the original development of the NCO instrument should be provided	Yes	7 (50)	n/a
	No	7 (50)	
The rationale for choice of the NCO instrument should be provided	Yes	8 (57)	19 (37)
	No	6 (43)	32 (63)
Windows for valid NCO responses specified and justified as appropriate for clinical context (i.e. range of scores)	Yes	5 (36)	n/a
	No	9 (64)	
The intended NCO data collection schedule should be provided	Yes	14 (100)	44 (86)
	No	0 (0)	7 (14)
Status of NCO as either primary or secondary outcome should be stated	Yes	10 (71)	34 (67)
	No	4 (29)	17 (33)
<i>Sample size</i>			
There should be a power/sample size calculation relevant to the NCO based on a clinical rationale (e.g. anticipated effect size)	Yes	11 (79)	n/a
	No	3 (21)	
<i>Statistical methods</i>			
There should be evidence of appropriate statistical analysis and tests of statistical significance for the NCO hypothesis tested (N/A if NCO hypotheses were not stated)	Yes	11 (79)	7 (14)
	No	0	6 (12)
	N/A	3 (21)	38 (74)
The manner in which multiple comparisons have been addressed should be provided	Yes	3 (21)	n/a
	No	11 (79)	
<i>Statistical methods (continued)</i>			
Extent of missing data should be stated ^a	Yes	10 (71)	33 (65)
	No	4 (29)	18 (35)
Statistical approaches for dealing with missing data should be explicitly stated ^a	Yes	3 (21)	14 (27)
	No	11 (79)	37 (73)

Table 2. Level of NCO reporting (*continued*)

Criterion	Primary end-point, n = 14; n (%)	Secondary end-point, n = 51; n (%)
Results		
<i>Participant flow</i>		
A flow diagram or a description of the allocation of participants and those lost to follow up should be provided for NCOs specifically	Yes 10 (71) No 4 (29)	23 (45) 28 (55)
The reason for missing data should be explained	Yes 6 (43) No 8 (57)	10 (20) 41 (80)
<i>Baseline data</i>		
The study patients' characteristics should be described, including baseline NCO scores	Yes 11 (79) No 3 (21)	30 (59) 21 (41)
<i>Outcomes and estimation</i>		
The analysis of NCO data should account for survival differences between treatment groups if relevant (otherwise N/A)	Yes 2 (14) No 0 N/A 12 (86)	n/a
Results should be reported for all NCO domains (if multi-dimensional) and items identified by the reference instrument (i.e., not just those that are statistically significant)	Yes 11 (79) No 3 (21)	n/a
The proportion of patients achieving predefined responder definitions should be provided where relevant (otherwise N/A)	Yes 9 (64) No 3 (21) N/A 2 (14)	n/a
Discussion		
<i>Limitations</i>		
The limitations of the NCO components of the trial should be explicitly discussed	Yes 3 (21) No 11 (79)	14 (27) 37 (73)
<i>Generalizability</i>		
Generalizability issues uniquely related to the NCO results should be discussed	Yes 8 (57) No 6 (43)	7 (14) 44 (86)
<i>Interpretation</i>		
The clinical significance of the NCO findings should be discussed	Yes 10 (71) No 4 (29)	22 (43) 29 (57)
The NCO results should be discussed in the context of the other clinical trial outcomes	Yes 9 (64) No 5 (36)	30 (59) 21 (41)

^a These items were originally combined in the ISOQOL recommended standards¹⁸ but have been split in our analysis to better investigate discrepancies between documentation of NCO missing data, and actual reporting of statistical methods to address this issue.

Table 3. Characteristics of RCTs classified as high-quality NCO reporting (n = 20) (page 160-173)

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Ahles et al. ²⁹	347	295	SCLC	Secondary	TMT B	No	PCI ± warfarin in patients treated with intensive doxorubicin, cyclophosphamide, etoposide (ACE)/ cisplatin, cyclophosphamide, etoposide (PCE) chemotherapy & RT
Aoyama et al. ³⁵	132	110	BM	Secondary	MMSE	No	SRS (18-25 Gy) ± WBRT (30 Gy)
Armstrong et al. ²³	833	191	GBM	Secondary	HVLT-R, TMT, COWA	Yes	6-12 cycles standard adjuvant Temozolomide (150-200 mg/m ² for 5 consecutive days of a 28-day cycle) versus dose dense adjuvant Temozolomide (75-100 mg/m ² for 21 consecutive days of a 28-day cycle)
Brown et al.; Brown et al.; Daniels et al.; and Laack et al. ^{6,25-27}	203		LGG	Secondary	MMSE, ^{6,25,26} MMSE, WAIS-R, Stroop, AVL, BVRT, TMT, COWA ²⁷	No	RT: 50.4 vs 64.8 Gy

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
No significant differences in response rates, survival, failure-free survival, disease-free survival or patterns of relapse between the warfarin treated and control groups. A landmark analysis at 8 months showed a median survival time after the landmark for complete responders of 33 months with warfarin treatment compared with <13.75 months for complete or partial responders not treated with warfarin ($p = 0.05$).	No differences on TMT B between patients with or without warfarin. TMT B showed improved performance from baseline to post-ACE chemotherapy (practice effect), but a significant worsening of TMT B scores post-RT compared with the pre-RT assessments ($p < 0.0001$).	The poorer TMT B performance post-RT suggested that this combination of chemotherapy and RT had a negative impact on cognitive functioning. Warfarin did not affect cognition.
No significant differences in median OS time and the 1-year actuarial survival rate, which were 7.5 months and 38.5% (95% CI 26.7%-50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% CI 17.6%-39.2%) for SRS alone ($p = 0.42$). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group ($p < 0.001$). Salvage brain treatment was less frequently required in the WBRT + SRS group ($n = 10$) than with SRS alone ($n = 29$) ($p < 0.001$).	Nearly significant higher rate of average deterioration in MMSE in SRS group (7.6 months) compared to WBRT + SRS (16.5 months) ($p = 0.05$)	Control of the brain tumor is the most important factor for stabilizing neurocognitive functioning. However, the long-term adverse effects of WBRT on neurocognitive function might not be negligible.
No statistically significant difference between standard arm and dose-dense arm for median OS (16.6 vs 14.9 months, respectively; hazard ratio [HR], 1.03; $p = 0.63$) or median PFS (5.5 vs 6.7 months; HR, 0.87; $p = 0.06$). MGMT methylation was associated with improved OS (21.2 vs 14 months; HR, 1.74; $p < 0.001$), PFS (8.7 vs 5.7 months; HR, 1.63; $p < 0.001$), and response ($p = 0.012$).	No between-arm differences in NCF: deterioration in HVLT-R total recall occurred in 27% vs 30% in standard dose arm vs dose-dense arm ($p = 0.78$); Delayed recall in 21% vs 24% ($p = 0.76$); Recognition in 24% and 19% ($p = 0.6$); TMT A in 20% vs 29% ($p = 0.35$); TMT B in 26% and 30% ($p = 0.69$); COWA in 7% and 16% ($p = 0.25$). Baseline and baseline to cycle 1 NCF tests were associated with OS and PFS.	Longitudinal collection of NCF/net clinical benefit (NCB) measures is feasible in cooperative group studies and provides an added dimension to standard outcome measures. Baseline and early change in NCB measures were associated with decreased rates of survival.
Non-significantly better survival with low-dose RT: survival at 2 and 5 years was 94% and 72%, respectively, with low-dose RT and 85% and 64%, respectively, with high-dose RT (log rank $p = 0.48$). The 2-year actuarial incidence of grade I to V radiation necrosis was 2.5% with low-dose RT and 5% with high-dose RT.	In patients without tumor progression, significant MMSE deterioration from baseline occurred at years 1, 2, and 5 in 8.2%, 4.6% and 5.3% of patients. Most patients with an abnormal baseline MMSE score (< 27) experienced significant increases. Baseline variables such as radiation dose, conformal versus conventional radiotherapy did not predict cognitive function changes. Extensive battery: Baseline test scores below normative means, with non-significant improvement at second assessment (practice effect). No differences in changes in cognition between groups.	Most LGG patients maintained a stable neurocognitive status after focal RT as measured by the MMSE. Patients with an abnormal baseline MMSE were more likely to have an improvement in cognitive abilities than deterioration after receiving RT. Only a small percentage of patients had cognitive deterioration after RT. Abnormal baseline MMSE was a predictor of worse OS and PFS. Extensive battery: no difference between groups in cognition at 3 years follow-up.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Brown et al. ³⁹	554	508	BM	Primary	MMSE, HVLT, TMT, COWA	Yes	WBRT (37.5 Gy) ± memantine/ placebo (24 weeks in escalating doses ([5 to 20 mg/day])
Brown et al. ⁹	213	213	BM	Primary	HVLT-R, Grooved Pegboard, TMT, COWA	Yes	SRS (18-24 Gy) ± WBRT (30 Gy)
Brown et al. ³⁴	194	194	Resected BM	Primary	HVLT-R, Grooved Pegboard, TMT, COWA	Yes	SRS (12-20 Gy) or WBRT (30-37.5 Gy)

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
NCF was primary end-point, no other outcomes reported.	Less decline in delayed recall in the memantine arm at 24 weeks ($p = 0.059$). The memantine arm had significantly longer time to cognitive decline (HR 0.78, 95% CI 0.62–0.99, $p < 0.01$); the probability of cognitive function failure at 24 weeks was 53.8% in the memantine arm and 64.9% in the placebo arm. Superior results were seen in the memantine arm for executive function at 8 ($p = 0.008$) and 16 weeks ($p = 0.0041$) and for processing speed ($p = 0.0137$) and delayed recognition ($p = 0.0149$) at 24 weeks.	Patients treated with memantine had better cognitive function over time: memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.
No significant difference in OS: 7.4 months for SRS + WBRT and 10.4 months for SRS alone (hazard ratio, 1.02; 95% CI, 0.75–1.38; $p = 0.92$)	Three months after treatment, patients in SRS alone group showed less cognitive deterioration (40/63 patients [63.5%]) than in the SRS + WBRT group (44/48 patients [91.7%]; difference –28.2%; 90% CI, –41.9% to –14.4%; $p < 0.001$). Differences were significant for immediate memory (30.4% vs 8.2%, difference 22.2%; 95% CI, 5.4%–39.1%; $p = 0.004$), delayed memory (51.1% vs 19.7%, difference 31.4%; 95% CI, 12.1%–50.7%; $p < 0.001$), and verbal fluency (18.6% vs 1.9%, respectively; difference 16.7%; 95% CI, 2.4%–31.0%; $p = 0.01$). For long-term survivors, the incidence of cognitive deterioration was lower after SRS alone at 3 months (5/11 [45.5%] vs 16/17 [94.1%]; difference –48.7%; 95% CI, –87.6% to –9.7%; $p = 0.007$) and at 12 months (6/10 [60%] vs 17/18 [94.4%]; difference –34.4%; 95% CI, –74.4% to 5.5%; $p = 0.04$).	In the absence of a difference in overall survival, the findings suggest that for patients with 1–3 brain metastases amenable to radiosurgery, SRS alone may be a preferred strategy.
No significant differences in median OS: 12.2 months (95% CI 9.7–16.0, 69 deaths) for SRS and 11.6 months (9.9–18.0, 67 deaths) for WBRT (HR 1.07 [95% CI 0.76–1.50]; $p = 0.7$).	Cognitive-deterioration free survival was longer in patients assigned to SRS (median 3.7 months [95% CI 3.45–5.06], 93 events) than in patients assigned to WBRT (median 3.0 months [2.86–3.25], 93 events; hazard ratio [HR] 0.47 [95% CI 0.35–0.63]; $p < 0.0001$). Cognitive deterioration at 6 months was less frequent in SRS patients than WBRT patients (28 [52%] of 54 evaluable SRS patients vs 41 [85%] of 48 evaluable patients assigned to WBRT; difference –33.6% [95% CI –45.3 to –21.8], $p < 0.00031$).	Decline in cognitive function was more frequent with WBRT than with SRS and there was no difference in OS between the treatment groups. After resection of a brain metastasis, SRS should be considered one of the standards of care as a less toxic alternative to WBRT for this patient population.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Chang et al., ⁸ Taychak-hoonayudh et al. ⁴⁴	58	58 ⁸ / 55 ⁴⁴	BM	Primary; secondary ^a	HVLT, WAIS III digit span and digit symbol, TMT, COWA, Grooved Pegboard	Yes	SRS ± WBRT
Gehring et al. ¹⁰ ; Gehring et al. ³⁸	140	140	Glioma (117 LGG, 23 HGG)	Primary; secondary	Stroop, digit span, LDST, MST*, TEA*, VVLT, CST*, letter fluency, categoric fluency*, BADS*	Yes	Rehabilitation (6 sessions of computer-based attention retraining and compensatory skills training of attention, memory, and executive functioning; CRP) vs care as usual

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
NCF was primary end-point, no other outcomes reported.	96% confidence that total recall at 4 months for SRS + WBRT (64% of patients deteriorated) was inferior to total recall for SRS alone (20% deteriorated). The total recall difference persisted at 6 months, with a mean posterior probability of decline of 28% for the SRS + WBRT group and 8% for the SRS alone group, with 90% confidence. Also HVLRT-R delayed recall and delayed recognition indicated that it was highly probable that patients had worse neurocognitive function in the SRS + WBRT than the SRS. NCF not significant associated with Time Trade-Off (TTO).	Patients treated with SRS + WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy in patients with newly diagnosed brain metastases. Lack of correlation between TTO utility and cognitive function suggests that patients' preferences for better health and for quantity of time are primary influenced by the expected length of time until death and not by their current health state.
NCF was primary end-point, no other outcomes reported.	Immediately post-treatment no difference in objective neuropsychological outcomes measures between groups. At 6 months follow-up, the CRP group performed significantly better than the control group on combined tests of attention ($p = 0.004$), with effect sizes ranging from 0.23 to 0.55, and combined tests of verbal memory ($p = 0.009$), and two of the three individual variables yielded significant results that favored the CRP group (effect sizes 0.48 and 0.43). The percentage of patients who no longer met criteria for cognitive impairment at the 6-month assessment was 39% in the intervention group vs 21% in the control group ($p = 0.027$). Reliable improvement in the intervention group was predicted by age ($p = 0.003$) and education ($p = 0.011$). Younger patients were more likely to benefit from the cognitive rehabilitation program ($p = 0.001$), and higher education was also associated with improvement in the control group ($p = 0.024$).	The cognitive rehabilitation program has a salutary effect on longer-term cognitive performance. Cognitive rehabilitation programs should take the patients' age into account and, if possible, adapt programs to increase the likelihood of improvement among older participants.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Gehring et al. ⁴¹	24	24	Primary brain tumor (3 grade II, 9 grade III, 9 grade IV, 3 other)	Primary	Digit span, digit symbol, TMT, HVLT, COWA, Grooved pegboard;	Yes	Methylphenidate (10 mg b.i.d. vs. 18 mg q.d. [AM]) vs. modafinil (200 mg q.d. [AM]) for 4 weeks.
Gondi et al., ³⁶ Gore et al., ⁴⁵ Sun et al. ^{37 b}	621; 340	583, ³⁶ 340 ^{37,45}	NSCLC (and SCLC)	Secondary	HVLT; ³⁶ MMSE, HVLT ^{37,45}	No	PCI (25 Gy vs 36 Gy) vs observation
Murray et al., ³⁰ Regine et al. ³¹	445	182 (1 arm AF); 359	BM	Secondary	MMSE	No	Accelerated hyperfractionated (AH) RT (54.4 Gy) vs accelerated fractionation (AF) (30 Gy) RT

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
NCF was primary end-point, no other outcomes reported.	After stimulant treatment, speed of processing ($p = 0.02$) and executive function requiring divided attention ($p = 0.02$) improved, while verbal memory ($p = 0.03$) and COWA ($p = 0.02$) declined. Patients with the greatest deficit in executive function at baseline appeared to derive the greatest benefit following stimulant therapy. Inconsistent, differential effects were found on a measure of attention ($p = 0.05$) in favor of MPH and on a measure of processing speed ($p = 0.05$) in favor of MOD, but without clinically significant improvement at the individual level.	The results from this small pilot study should be interpreted with caution, but appear to warrant additional research, in larger study samples, targeting fatigue, processing speed and executive function, and exploring different doses of stimulants. Future studies may also wish to explore the specific patient factors that may be associated with responsiveness to psychostimulant treatment.
The 1-year OS ($p = 0.86$; 75.6% vs 76.9% for PCI vs observation) and 1-year DFS ($p = 0.11$; 56.4% vs 51.2% for PCI vs observation) were not significantly different. The HR for observation vs PCI was 1.03 (95% CI, 0.77-1.36). The 1-year rates of BM were significantly different ($p = 0.004$; 7.7% vs 18.0% for PCI vs observation). Patients in the observation arm were 2.52 times more likely to develop BM than those in the PCI arm (unadjusted odds ratio, 2.52; 95% CI, 1.32-4.80).	HVLT-R decline at 6 and 12 months was associated with PCI ($p = 0.002$ and $p = 0.002$, respectively). At 1 year post treatment, no significant difference in MMSE ($p = 0.6$). For HVLT, there was greater decline in immediate recall ($p = 0.03$) and delayed recall ($p = 0.008$) in the PCI arm at 1 year.	The results of this study enable us to develop strategies that can potentially decrease the risks, such as decline in HVLT, associated with PCI. One such strategy is to test agents that protect NCF. Another strategy may be to develop a conformal PCI technique that may spare memory function or hippocampal avoidance. An additional strategy would be to closely observe patients with imaging and apply WBRT or focused stereotactic radiosurgery as needed.
OS not significantly different; 4.5 months in both arms	AF arm: AF appears to be associated with an improvement in MMSE. Pre-treatment MMSE score was a statistically significant factor for survival ($p = 0.0002$). Of the 88 patients in which improvement could be assessed, 48 (54.5%) demonstrated an improvement in their MMSE at any follow-up visit. In long-term survivors, 81% at 6 months and 66% at 1 year maintained a MMSE above 23. Decreasing baseline MMSE ($p = 0.003$) and primary site (breast vs lung vs other $p = 0.032$) were highly associated with time until death from brain metastases. The average change in MMSE at 2 and 3 months was a drop of 1.4 and 1.1, respectively, in the AF arm as compared to a drop of 0.7 and 1.3, respectively, in the AH arm ($p = ns$). At 3 months, the average change in MMSE score was a drop of 0.5 for those whose brain metastases were radiologically controlled as compared to a drop of 6.3 for those with uncontrolled brain metastases ($p = 0.02$).	MMSE is, besides gender and perhaps age, an important way of assessing a patient's outcome. The use of altered fractionation within this study design was not associated with a statistically detectable difference in neurocognitive function as measured by the MMSE in patients with unresectable brain metastases and limited survival. Control of brain metastases had a significant impact on MMSE.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Page et al. ³²	54	54	Primary brain tumor (33 GBM, 7 MG, 14 other)	Secondary	HVLT, Digit span, TMT, fluency	Yes	RT with armodafinil (150 mg/day) vs placebo
Peng et al. ⁴²	94	80	Brain tumor (21 LGG, 16 HGG, 35 MG, 8 other)	Primary	MMSE, IMCT (memory and concentration)	No	Lidocaine (1.5 mg/kg) vs placebo (normal saline) during anesthesia for surgery
Prabhu et al. ⁷	251	251	LGG (WHO grade II)	Secondary	MMSE	No	RT (54 Gy) ± PCV (6 cycles of post radiation procarbazine (60 mg/m ² per day on days 8-21 of each cycle), lomustine (110 mg/m ² orally on day 1 of each cycle), and vincristine (1.4mg/m ² on days 8 and 29 of each cycle). The cycle length was 8 weeks. Also comparison to observation arm.
Reijneveld et al. ²⁸	477	477	LGG (WHO grade II)	Secondary	MMSE	No	RT (50.4 Gy in 28 fractions) vs TMZ chemotherapy (12 cycles of 75 mg/m ² daily, for 21 of 28 days)

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
No statistically significant differences in end-RT or 4 weeks post-RT outcomes between armodafinil and placebo in fatigue. In participants with more baseline fatigue, those treated with armodafinil did better than those who received the placebo on the end-RT assessments for several outcomes. NCF was primary end-point, no other outcomes reported. Median OS and 5-year OS rates for RT vs RT + PCV were 7.5 years vs not reached and 63% vs 72%, respectively (HR; 0.72; 95% CI, 0.47-1.10; $p = 0.33$; log-rank $p = 0.13$). Median PFS time and 5-year PFS rates for RT vs RT + PCV were 4.4 years vs not reached and 46% vs 63%, respectively (HR, 0.6; 95% CI 0.41-0.86; $p = 0.06$; log-rank $p = 0.005$). OS and PFS were similar for all patients between years 0 and 2. After 2 years, OS and PFS curves separated significantly, favoring RT + PCV. For 2-year survivors ($n = 211$), the probability of OS for an additional 5 years was 74% with RT + PCV versus 59% with RT alone (HR, 0.52; 95% CI 0.30-0.90; log-rank $p = 0.02$). At a median follow-up of almost 48 months (IQR 31-56), PFS not significantly different between groups (TMZ: median 39 months [95% CI 35-44] vs RT 46 months [40-56]; HR 1.16, 95% CI 0.9-1.5, $p = 0.22$)	A non-significant improvement over time in both groups. No significant differences between treatment arms at the end of RT or at 4 weeks post RT for any of the tests. No significant difference in postoperative cognitive decline up to 6 months in the lidocaine group compared to the normal saline group. At 6 months, ≥ 1SD deficit on either the MMSE or IMCT occurred in 5 of 40 (12.5%) patients in the lidocaine group, and 5 of 40 (12.5%) patients in the saline group ($p = 1$). Few patients experienced significant decline in MMSE score. No significant differences in the proportion of patients with MMSE decline between the study arms at any time point. Both study arms experienced a significant gain in average MMSE score longitudinally over time, with no difference between arms. Compliance of MMSE was significantly higher in the TMZ group than in the RT group at 3 months (71% in RT group vs 81% in TMZ group; 95% CI 1.72-17.40, $p = 0.0026$) and at 6 months (63% in RT group vs 75% in TMZ; 95% CI 3.14-20.57, $p = 0.00014$). The baseline profile of patients who were non-compliant at 3 or 6 months did not differ significantly between the groups. No significant difference in longitudinal and overall analysis at any time point for MMSE between groups. At baseline, 32 (13%) of 239 patients who received RT and 32 (14%) of 236 patients who received TMZ had impaired MMSE scores. After randomization, five (8%) of 63 patients who received RT and three (6%) of 54 patients who received TMZ chemotherapy and could be followed up for 36 months had impaired MMSE scores.	None given for NCO. Intraoperative lidocaine does not significantly decrease incidence of postoperative cognitive decline in patients 6 months after supratentorial tumor surgery. The addition of PCV chemotherapy to RT improves PFS without excessive cognitive functioning detriment over RT alone for patients with low-grade glioma. These results do not support the choice of TMZ alone over RT alone in these patients.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Rapp et al. ⁴⁰	198	198	Primary (20 grade II, 38 grade III, 23 grade IV, 22 MG, 6 pilocytic, 21 other), BM (53), and PCI (15)	Primary	HVLT, Rey, TMT, COWA, Digit span, Grooved pegboard	Yes	Donepezil (5 mg/day for 6 weeks to 10 mg/day for 18 weeks) vs placebo after RT
Taylor et al. ²⁴	701	701	HGG (159 (grade III, 542 grade IV) (2 trials)	Secondary	MMSE	No	First trial: RT (60 Gy) + BCNU (200 mg/m ²) vs PCNU (100 mg/m ²), both every 7 weeks for 1 year, then every 10 weeks for the next year. Second trial: RT (64.8 Gy) and BCNU (200 mg/m ² , one dose); adjuvant BCNU (200 mg/m ² every 7 weeks, max. 6 cycles) vs. BCNU (150 mg/m ² every 7 weeks, max. 6 cycles) + interferon alfa (12 MU/m ² 3 days of weeks 1, 3, and 5 during each 7-week treatment cycle)
Wang et al. ³³	289	289	Grade III glioma	Secondary	MMSE	No	RT (59.4 Gy) ± PCV (prior to RT, up to 4 cycles every 6 weeks, lomustine 130 mg/m ² on day 1, procarbazine 75 mg/m ² on days 8-21, and vincristine 1.4mg/m ² on days 8 and 29)

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
NCF was primary end-point, no other outcomes reported	After 24 weeks of treatment, the composite scores did not differ significantly between groups ($p = 0.48$); but significant differences favoring donepezil were observed for memory (recognition, $p = 0.027$; discrimination, $p = 0.007$) and motor speed ($p = 0.016$). Significant interactions between pretreatment cognitive function and treatment were found for cognitive composite ($p = 0.01$), immediate recall ($p = 0.05$), delayed recall ($p = 0.004$), attention ($p = 0.01$), visuomotor skills ($p = 0.02$), and motor speed and dexterity ($p = 0.001$), with the benefits of donepezil greater for those who were more cognitively impaired before study treatment.	Treatment with donepezil did not result in an overall improvement in cognitive function. But there were modest improvements in several key cognitive functions, especially among patients with greater pretreatment cognitive impairment. Neurotransmitter regulators like donepezil can play a role in treating cognitive impairment associated with brain cancer and its treatments.
The median survival duration in each group was 47 weeks, and median time to progression was 28 weeks.	No difference between treatment arms. Decrease in MMSE in 13 of 119 non-progressors (10.9%; 95% CI 6.3%-18.9%) at 6 months, three of 54 non-progressors (5.5%; 95% CI 0.5%-12.8%) at 12 months, three of 30 non-progressors (10%; 95% CI 2.1%-26.5%) at 18 months, and four of 22 non-progressors (18.2%; 95% CI 5.2%-40.3%) at 24 months. No statistically significant increase in the percentage of patients who experienced a significant decrease in their MMSE score. Patients who demonstrated a significant decrease in their MMSE score were significantly older than those who did not ($p = 0.0017$) at 6 months and remained so throughout follow-up; these patients also had a significantly shorter time to progression and death. Performance status was strongly negatively correlated with MMSE score throughout the study, and MMSE score at all time intervals was correlated with baseline PS.	In this population of glioma patients receiving radiotherapy, there was no clear trend to cognitive worsening. Factors such as older age, poorer PS and subclinical tumor progression may be more significant factors in those patients who did demonstrate a significant cognitive decline.
Median OS was similar (4.9 years after PCV + RT vs 4.7 years after RT alone; HR = 0.90; 95% CI 0.66-1.24; $p = 0.26$). PFS time favored PCV + RT (2.6 years vs 1.7 years for RT alone; HR = 0.69; 95% CI, 0.52-0.91; $p = 0.004$), but 65% of patients experienced grade III or IV toxicity, and one patient died. Patients with tumors lacking 1p and 19q (46%) compared with tumors not lacking 1p and 19q had longer median survival times (> 7 vs 2.8 years, respectively; $p < 0.001$); longer PFS was most apparent in this subset.	For survivors, MMSE scores were similar longitudinally and between treatments ($p = 0.4752$). MMSE scores trended upwards over 5 years of follow-up for the PCV + RT group. For patients who died, MMSE scores remained stable initially and declined rapidly in the last year of life and similarly between groups. In the aggregate, scores decreased over time ($p = 0.0413$) and were superior with age < 50 years ($p < 0.001$) and KPS 80-100 ($p < 0.001$). After adjusting for patient factors and dropout, survival was longer after PCV + RT (HR = 0.66, 95% CI 0.49-0.9, $p = 0.0084$; HR=0.74, 95% CI 0.54-1.01, $p = 0.0592$) in models with MMSE and B-QOL. Higher MMSE scores predicted longer survival.	Younger, fitter patients had better MMSE and longer survival. Cognition among the more intensively treated PCV + RT group was indistinguishable from the RT group; both MMSE and B-QOL scores were stable in the upper range in both arms over time in surviving patients. Tumor growth is the main cause of decline in brain tumor patients.

Reference	Overall sample size	Baseline NCO sample size	Patient group	NCO end-point	NCO instruments used	Criteria test battery fulfilled ^c	Study treatment
Wefel et al. ⁴³¹⁶⁷	167		Recurrent GBM	Secondary	HVLT, TMT, COWA	Yes	BEV; 10 mg/kg) ± irinotecan (CPT-11; 340 mg/m ² or 125 mg/m ²) once every 2 weeks

SCLC: small cell lung carcinoma; BM: brain metastases; GBM: glioblastoma multiforme; HGG: high-grade glioma; LGG: low-grade glioma; NSCLC: non-small cell lung carcinoma; MG: meningioma; TMZ: temozolomide; PCV: procarbazine, lomustine, and vincristine; BCNU: carmustine; PCNU: 1-(2-chloroethyl)-3(2,6 dioxo-lpiperidyl)-l-nitrosourea; BEV: bevacizumab; RT: radiotherapy; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; PCI: prophylactic cranial irradiation; OS: overall survival; PFS: progression free survival; MMSE: mini-mental state examination; HVLT(-R): Hopkins verbal learning test (-revised); TMT: trail making test; COWA: controlled word association test; AVLT: auditory verbal learning test; BVRT: Benton visual >>

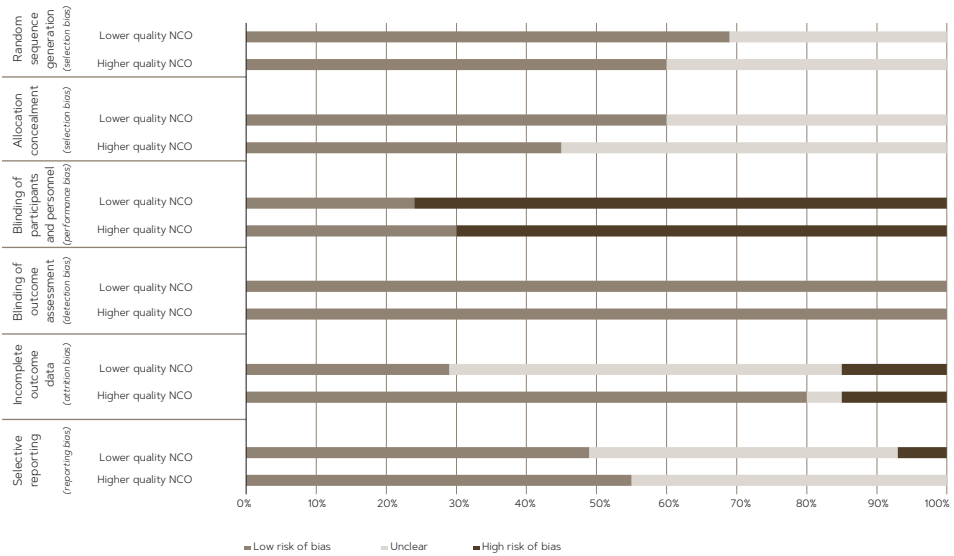


Figure 2. Risk bar chart showing risk of bias according to the Cochrane handbook for systematic reviews and interventions,²² across RCTs separately for higher and lower quality NCO reporting studies

Summary of main clinical results	Summary of NCO results	NCO treatment recommendations (according to the authors of the RCT)
The median PFS times were 4.2 months (95% CI 2.9-5.8 months) for the BEV group and 5.6 months (95% CI 4.4-6.2 months) for the BEV + CPT-11 group. The median OS times were 9.2 months (95% CI 8.2-10.7 months) for the BEV group and 8.7 months (95% CI 7.8-10.9 months) for the BEV + CPT-11 group. In the BEV-alone and the BEV + CPT-11 groups, estimated 6-month PFS rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively.	No comparisons between groups provided. Most patients with an objective response or PFS > 6 months had poorer NCF compared to the general population at baseline and had improved or stable NCF at the time of response (BEV: 75.0%; BEV+CPT-11: 60.7%) or at the 24-week assessment (BEV: 70.4%; BEV+CPT-11: 69.0%), on all tests relative to baseline. Most patients with progressive disease had neurocognitive decline at the time of progression.	Neurocognitive testing was an objective, valid, and feasible method of monitoring NCF in patients with recurrent GBM. Inclusion of a control or comparison arm in future studies will facilitate more detailed interpretations of these data.

<< retention test; WAIS: Wechsler adult intelligence scale; MST: memory scanning test; TEA: test of every day attention; CST: concept shifting test; VVLT: visual verbal learning test; LDST: letter digit substitution test; BADS: behavioral assessment of the dysexecutive syndrome; ^a In case NCO was both a primary and secondary end-point in different publications, it was included as primary end-point; ^b Studies describing overlapping trials; ^c Only applicable in 'high-quality' studies. Total number of criteria: 7. For studies with NCO as secondary outcomes, the level of the used test battery was judged adequate when all criteria were fulfilled. For studies with NCO as primary outcome, also longer than the advised 30-40 minutes assessment was judged acceptable²¹

According to the authors, this NCO evidence strongly supports the recommendation to treat patients with SRS alone, at the same time with close MRI monitoring to detect new brain metastases in an early stage. Another study,⁸ which included NCO as primary end-point but did not include survival, also supported the choice for SRS treatment, as the authors found that SRS preserves memory better than SRS + WBRT in brain metastatic patients. However, in an earlier study on this topic,³⁵ it was found that patients treated with SRS alone had a nearly higher rate of cognitive deterioration measured by the MMSE than patients treated with SRS + WBRT, which was deemed due to recurrent tumor elsewhere in the brain, with comparable survival. One study showed that patients treated with PCI had comparable survival but worse memory scores than patients not treated with PCI.^{36,37} These authors concluded that it is important to find strategies to overcome this negative effect of PCI.

In five studies including NCO as a primary end-point, the experimental treatments aimed at improving (existing impairments in) NCF. It was found that cognitive rehabilitation could be effective in reducing cognitive impairments in glioma patients,^{10,38} that memantine improved cognition in brain metastatic patients undergoing WBRT³⁹ and that donazepil improved neurocognitive functioning in brain tumor patients.⁴⁰ Although these results are encouraging and adequate neurocognitive measures

were used, these results have not led to inclusion of these treatments in standard patient care so far. Moreover, in a small sample, the effect of two types of stimulants on different cognitive functions was inconclusive,⁴¹ while the use of lidocaine after anesthesia induction during surgery did not reduce postoperative neurocognitive decline.⁴² In one study on bevacizumab with or without irinotecan for recurrent GBM, no comparison was made between the study treatments for NCO, but patients with a response or PFS >6 months had stable median standardized test scores across 24 weeks follow-up, while progressive disease was associated with neurocognitive decline at time of progression.⁴³

Discussion

In this systematic review, we found a substantial number of RCTs using NCO as end-point in brain tumor trials, underpinning the fact that neurocognitive functioning is an important outcome for brain tumor patients. Of the 65 eligible RCTs, 20 (31%) could be identified as 'high-quality' reporting for NCO. Not surprisingly, studies using NCO as primary end-point were more often classified as high-quality reporting (57%) than studies using NCO as secondary end-point (23%), which also reflects that the publication is mainly focused on NCO. Still, 43% of primary NCO studies did not fulfill the criteria to be classified as high-quality reporting.

It should be noted that in studies where the level of NCO reporting was classified as low, this does not necessarily mean the trial design of these studies was poor. Although the NCO reporting was not adequate, this does not exclude that both assessment and analysis of NCO could have been done correctly. Since the majority of the studies included NCO as secondary end-point, describing the NCO results in a separate publication can therefore also result in higher quality of reporting, and subsequently facilitate clinical decision-making.

Compared to a recent review on HRQoL reporting in brain tumor RCTs, in which only two of 14 RCTs (14%) were classified as high-quality,¹⁹ we did find a higher proportion of RCTs to be classified as 'high-quality' reporting. Regarding trials with high-quality NCO reporting, in most of these studies the NCO evidence was judged useful for clinical decision-making. This was particularly found for studies on radiotherapy treatment regimens in brain metastases, where NCO evidence supported the use of SRS over WBRT, as survival outcomes were similar but neurocognitive functioning was better with SRS alone.^{8,9,34} The only contradictory finding on this issue might be related to the use of a cognitive screening instrument instead of an appropriate test battery.³⁵ In studies on the addition of chemotherapy to radiotherapy in glioma patients, NCO results showed that cognition, although measured with MMSE only, was not negatively impacted by the addition of chemotherapy, while survival was

improved, supporting the choice for combined treatments.^{7,33}

In most high-quality reporting studies on the effect of cognitive rehabilitation or medication on NCF and with NCO as primary end-point, a (modest) beneficial effect of the experimental treatment on existing cognitive impairments was found.^{10,39,40} However, these results have not yet impacted clinical decision-making, as these treatments are currently not part of standard care. Although the study design, test battery and sample sizes of these studies were adequate overall, it could be that taking additional medication or participating in rehabilitation programs is too burdensome for patients already undergoing extensive anti-tumor therapy, and too costly for health care providers.

Also, studies in which both survival and NCO were not different between treatment strategies are worthwhile for clinical decision-making.^{6,23-31} Based on the findings that specific treatments do not result in survival or neurocognitive (dis)advantages, other outcomes related to the treatments could be important. For example, differences in HRQoL of these patients, or in the treatment burden or costs can instead impact clinical decision-making. However, it is more difficult to interpret these NCO results because these studies, as was the case in 40% of eligible studies, included the MMSE or another screening instrument as the only measure of neurocognitive functioning. The sensitivity of screening instruments is low for brain tumor patients:⁷ cognitive domains often affected by brain tumors, including memory, attention, information processing speed and executive functioning, are not well measured by the MMSE, and clinically meaningful changes in cognition are not detected. Still, due to the short length and simplicity of administration, the MMSE has been widely used in clinical trials on brain tumor patients, and as it is an objective measure of cognition, we did not exclude those RCTs. Nevertheless, in line with others, we think an extensive neurocognitive test battery is essential in using the results for clinical decision making in brain tumor research.^{5,21}

This review does have some limitations. First, the used ISOQOL-criteria were originally created for patient reported outcomes and not specifically for (objective) NCO.¹⁸ Therefore, we regarded not all items to be relevant or practically applicable. In addition, we may have missed relevant aspects of reporting on neurocognitive research. However, as to our knowledge, no criteria exist for NCO reporting specifically, using the ISOQOL-criteria seemed an appropriate method to study reporting of NCO. Second, results of the included studies might be biased as these were often based on test batteries not covering all relevant neurocognitive domains. Consequently, our conclusions regarding the net clinical benefit of the studies might be hampered.

To conclude, the level of reporting in about one third of RCTs including NCO could be classified as sufficiently high-quality to be useful for clinical decision-making. In most high-quality NCO reporting RCTs, the NCO evidence added to the authors recommended treatment. This systematic review indicates the need to pay attention to NCO reporting in brain tumor research, to obtain high-quality evidence which is necessary to determine the net clinical benefit of treatment strategies.

References

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.
2. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer*. 2002;94(10):2698-2705.
3. Posti JP, Bori M, Kauko T, et al. Presenting symptoms of glioma in adults. *Acta Neurol Scand*. 2015;131(2):88-93.
4. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3(3):159-168.
5. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol*. 2013;14(10):e407-e416.
6. Brown PD, Buckner JC, O'Fallon JR, et al. Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. *J Clin Oncol*. 2003;21(13):2519-2524.
7. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol*. 2014;32(6):535-541.
8. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
9. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA*. 2016;316(4):401-409.
10. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol*. 2009;27(22):3712-3722.
11. Zucchella C, Capone A, Codella V, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *J Neurooncol*. 2013;114(1):93-100.
12. Caine C, Mehta MP, Laack NN, Gondi V. Cognitive function testing in adult brain tumor trials: lessons from a comprehensive review. *Expert Rev Anticancer Ther*. 2012;12(5):655-667.
13. Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. *Neuro Oncol*. 2011;13(3):353-361.
14. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol*. 2011;12(6):583-593.
15. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703-708.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012.
17. Canney P, Murray E, Dixon-Hughes J, Lewsley LA, Paul J. A Prospective Randomised Phase III Clinical Trial Testing the Role of Prophylactic Cranial Radiotherapy in Patients Treated with Trastuzumab for Metastatic Breast Cancer - Anglo Celtic VII. *Clin Oncol (RCollRadiol)*. 2015;27(8):460-464.
18. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized

- clinical trials: development of ISOQOL reporting standards. *Qual Life Res.* 2013;22(6):1161-1175.
19. Dirven L, Taphoorn MJB, Reijneveld JC, et al. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: A systematic review. *Eur J Cancer.* 2014;50(14):2432-2448.
 20. Efficace F, Feuerstein M, Fayers P, et al. Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. *Eur Urol.* 2014;66(3):416-427.
 21. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol.* 2012;108(2):309-318.
 22. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions.* In:2011.
 23. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. *J Clin Oncol.* 2013;31(32):4076-4084.
 24. Taylor BV, Buckner JC, Cascino TL, et al. Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma. *J Clin Oncol.* 1998;16(6):2195-2201.
 25. Brown PD, Buckner JC, O'Fallon JR, et al. Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. *Int J Radiat Oncol Biol Phys.* 2004;59(1):117-125.
 26. Daniels TB, Brown PD, Felten SJ, et al. Validation of EORTC prognostic factors for adults with low-grade glioma: a report using intergroup 86-72-51. *Int J Radiat Oncol Biol Phys.* 2011;81(1):218-224.
 27. Laack NN, Brown PD, Ivnik RJ, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys.* 2005;63(4):1175-1183.
 28. Reijneveld JC, Taphoorn MJ, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1533-1542.
 29. Ahles TA, Silberfarb PM, Herndon J, et al. Psychologic and neuropsychologic functioning of patients with limited small-cell lung cancer treated with chemotherapy and radiation therapy with or without warfarin: a study by the Cancer and Leukemia Group B. *J Clin Oncol.* 1998;16(5):1954-1960.
 30. Murray KJ, Scott C, Zachariah B, et al. Importance of the mini-mental status examination in the treatment of patients with brain metastases: a report from the Radiation Therapy Oncology Group protocol 91-04. *Int J Radiat Oncol Biol Phys.* 2000;48(1):59-64.
 31. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys.* 2001;51(3):711-717.
 32. Page BR, Shaw EG, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro Oncol.* 2015;17(10):1393-401.
 33. Wang M, Cairncross G, Shaw E, et al. Cognition and quality of life after chemotherapy plus radiotherapy (RT) vs. RT for pure and mixed anaplastic oligodendrogliomas: radiation therapy oncology group trial 9402. *Int J Radiat Oncol Biol Phys.* 2010;77(3):662-669.
 34. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised,

- controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1049-1060.
35. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2007;68(5):1388-1395.
 36. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys*. 2013;86(4):656-664.
 37. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J Clin Oncol*. 2011;29(3):279-286.
 38. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoorn MM. Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. [Erratum appears in *J Int Neuropsychol Soc*. 2011 Mar;17(2):384]. *J Internat Neuropsychol Soc*. 2011;17(2):256-266.
 39. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429-1437.
 40. Rapp SR, Case LD, Peiffer A, et al. Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial. *J Clin Oncol*. 2015;33(15):1653-1659.
 41. Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol*. 2012;107(1):165-174.
 42. Peng Y, Zhang W, Zhou X, Ji Y, Kass IS, Han R. Lidocaine Did Not Reduce Neuropsychological-Cognitive Decline in Patients 6 Months After Supratentorial Tumor Surgery: A Randomized, Controlled Trial. *J Neurosurg Anesthesiol*. 2016;28(1):6-13.
 43. Wefel JS, Cloughesy T, Zazzali JL, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. *Neuro Oncol*. 2011;13(6):660-668.
 44. Taychakoonavudh S, Franzini L, Lal LS, et al. Comparison of time trade-off utility with neurocognitive function, performance status, and quality of life measures in patients with metastatic brain disease. *J Radiat Oncol*. 2014;3(2):215-221.
 45. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214.[Erratum appears in *J Clin Oncol*. 2011 Aug 10;29(23):3204]. *J Clin Oncol*. 2011;29(3):272-278.

Supplementary data

File 1. Search string

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OR ((carcinoma*[ti]) AND ("brain"[ti] OR "brains"[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR "carcinoma of brain"[tw] OR "carcinomas of brain"[tw] OR "carcinoma of the brain"[tw] OR "carcinomas of the brain"[tw] OR brain carcinoma*[tw] OR cerebral carcinoma*[tw] OR "intracerebral carcinoma"[tw] OR "intracerebral carcinomas"[tw] OR ((malignan*[ti]) AND (intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR cns malignan*[tw] OR central nervous system malignan*[tw] OR intracranial malignan*[tw] OR cerebral malignan*[tw] OR intracerebral malignan*[tw] OR ((("Neoplasm Metastasis"[Mesh] OR metasta*[ti] OR meta-sta*[ti]) AND ("brain"[ti] OR "brains"[ti] OR "cns"[ti] OR central nervous system*[ti] OR intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR metastasis of brain[tw] OR metastases of brain[tw] OR metastasis of the brain[tw] OR metastases of the brain[tw] OR brain metasta*[tw] OR metastasis of cns[tw] OR metastases of cns[tw] OR metastasis of the cns[tw] OR metastases of the cns[tw] OR cns metasta*[tw] OR metastasis of central nervous system[tw] OR metastases of central nervous system[tw] OR metastasis of the central nervous system[tw] OR metastases of the central nervous system[tw] OR central nervous system metasta*[tw] OR intracranial metasta*[tw] OR cerebral metasta*[tw] OR intracerebral metasta*[tw] OR glial metastasis[tw] OR glial metastases[tw] OR neuroglial metasta*[tw] OR ((("Lymphoma"[Mesh] OR lymphom*[ti]) AND ("brain"[ti] OR "brains"[ti] OR "cns"[ti] OR central nervous system*[ti] OR intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR lymphoma of brain[tw] OR lymphomas of brain[tw] OR lymphoma of the brain[tw] OR lymphomas of the brain[tw] OR brain lymphoma*[tw] OR lymphoma of cns[tw] OR lymphomas of cns[tw] OR lymphoma of the cns[tw] OR lymphomas of the cns[tw] OR cns lymphoma*[tw] OR lymphoma of central nervous system[tw] OR lymphomas of central nervous system[tw] OR lymphoma of the central nervous system[tw] OR lymphomas of the central nervous system[tw] OR central nervous system lymphoma*[tw] OR intracranial lymphoma*[tw] OR cerebral lymphoma*[tw] OR intracerebral lymphoma*[tw] OR "glial lymphoma"[tw] OR "glial lymphomas"[tw] OR "neuroglial lymphoma"[tw] OR "neuroglial lymphomas"[tw]) AND ("Cognition Disorders"[Mesh] OR "Cognition"[Mesh] OR "Memory"[Mesh] OR "Memory Disorders"[Mesh] OR "Attention"[Mesh] OR sustained attention*[tw] OR divided attention*[tw] OR "Neuropsychological Tests"[Mesh] OR "Neuropsychology"[Mesh] OR neuropsych*[tw] OR neuro-psycho*[tw] OR neurobehav*[tw] OR neuro-behav*[tw] OR neurocognit*[tw] OR cognit*[tw] OR memory[tw] OR memories[tw] OR memoriz*[tw] OR memoris*[tw] OR mental[tw] OR mentaly[tw] OR mentally[tw] OR intelct*[tw] OR intellect*[tw] OR "Language"[Mesh] OR "language"[tw] OR arithmetic*[tw] OR executive function*[tw] OR executive attention function*[tw] OR executive dysfunction*[tw]) AND (randomized controlled trial[pt] OR random*[tiab] OR placebo*[tiab] OR controlled randomized trial*[tiab] OR controlled randomised trial*[tiab] OR controlled clinical trial*[tiab] OR controlled clinical stud*[tiab] OR (factorial*[ti] AND trial[ti]) OR crossover[tiab] OR cross over[tiab] OR cross-over[tiab] OR double blind*[-tiab] OR random*[ot] OR placebo*[ot] OR controlled randomized trial*[ot] OR controlled randomised trial*[ot] OR controlled clinical trial*[ot] OR controlled clinical stud*[ot] OR (factorial*[ot] AND trial[ot]) OR crossover[ot] OR double blind*[ot])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

MEDLINE (OVID version): 'Advanced Search'. (((exp Glioma/ OR glioma*.mp. OR neuroglioma*.mp. OR xanthoastrocytoma*.mp. OR xantoastrocytoma*.mp. OR astrocytoma*.mp. OR astro-cytoma*.mp. OR astroglioma*.mp. OR astro-glioma*.mp. OR oligoastrocytoma*.mp. OR oligoastro-cytoma*.mp. OR glioblastom*.mp. OR glio-blastom*.mp. OR oligodendroglioma*.mp. OR oligo-dendroglioma*.mp. OR oligoden-droglioma*.mp. OR oligodendroblastoma*.mp. OR ependymom*.mp. OR subependymom*.mp. OR gliosarcoma*.mp. OR glio-sarcoma*.mp. OR exp Meningioma/ OR meningioma*.mp. OR exp Craniopharyngioma/ OR craniopharyngioma*.mp. OR cranio-pharyngioma*.mp. OR brain

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EMBASE (OVID version): 'Advanced Search'. (((exp glioma/ OR glioma*.mp. OR neuroglioma*.mp. OR xanthoastrocytoma*.mp. OR xantoastrocytoma*.mp. OR exp astrocytoma/ OR astrocytoma*.mp. OR astro-cytoma*.mp. OR astroglioma*.mp. OR astro-glioma*.mp. OR oligoastrocytoma*.mp. OR oligoastro-cytoma*.mp. OR glioblastom*.mp. OR glio-blastom*.mp. OR oligodendrogloma*.mp. OR oligo-dendrogloma*.mp. OR oligoden-drogloma*.mp. OR oligodendroblastoma*.mp. OR oligo-dendro-blastoma*.mp. OR oligo-dendroblastoma*.mp. OR oligoden-droblastoma*.mp. OR oligodendro-blastoma*.mp. OR ependymom*.mp. OR subependymom*.mp. OR gliosarcoma*.mp. OR glio-sarcoma*.mp. OR exp meningioma/ OR meningioma*.mp. OR exp craniopharyngioma/ OR craniopharyngioma*.mp. OR cranio-pharyngioma*.mp. OR brain malign*.mp. OR malignant primary brain*.mp. OR primary malignant brain*.mp. OR malignant brain*.mp. OR glial tumour*.mp. OR glial tumor*.mp. OR glial neoplasm*.mp. OR glial cancer*.mp. OR glial carcinoma*.mp. OR glial malignan*.mp. OR neuroglial tumour*.mp. OR neuroglial tumor*.mp. OR neuroglial neoplasm*.mp. OR neuroglial cancer*.mp. OR neuroglial carcinoma*.mp. OR neuroglial malignanc*.mp.) OR (exp brain tumor/ OR ((tumour*.ti. OR tumor*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR ((tumour*.mp. OR tumor*.mp.) ADJ3 brain*.mp.) OR ((tumour*.mp. OR tumor*.mp.) ADJ3 cns.mp.) OR ((tumour*.mp. OR tumor*.mp.) ADJ3 central nervous system*.mp.) OR intracranial tumour*.mp. OR intracranial tumor*.mp. OR cerebral tumour*.mp. OR cerebral tumor*.mp. OR intracerebral tumour*.mp. OR intracerebral tumor*.mp. OR ((neoplasm*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR (neoplasm*.mp. ADJ3 brain*.mp.) OR (neoplasm*.mp. ADJ3 cns.mp.) OR (neoplasm*.mp. ADJ3 central nervous system*.mp.) OR intracranial neoplasm*.mp. OR cerebral neoplasm*.mp. OR intracerebral neoplasm*.mp. OR ((cancer*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR (cancer*.mp. ADJ3 brain*.mp.) OR (cancer*.mp. ADJ3 cns.mp.) OR (cancer*.mp. ADJ3 central nervous system*.mp.) OR intracranial cancer*.mp. OR cerebral cancer*.mp. OR intracerebral cancer*.mp. OR ((carcinoma*.ti.) AND ("brain".ti. OR "brains".ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR (carcinoma*.mp. ADJ3 brain*.mp.) OR cerebral carcinoma*.mp. OR intracerebral carcinoma*.mp. OR ((malignan*.ti.) AND (intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR cns malignan*.mp. OR central nervous system malignan*.mp. OR intracranial malignan*.mp. OR cerebral malignan*.mp. OR intracerebral malignan*.mp.) OR ((exp metastasis/ OR metasta*.ti. OR meta-sta*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR (metasta*.mp. ADJ3 brain*.mp.) OR (metasta*.mp. ADJ3 cns.mp.) OR (metasta*.mp. ADJ3 central nervous system*.mp.) OR intracranial metasta*.mp. OR cerebral metasta*.mp. OR intracerebral metasta*.mp. OR glial metasta*.mp. OR neuroglial metasta*.mp. OR exp brain lymphoma/ OR exp primary central nervous system lymphoma/ OR ((exp lymphoma/ OR lymphom*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR (lymphoma*.mp. ADJ3 brain*.mp.) OR (lymphoma*.mp. ADJ3 cns.mp.) OR (lymphoma*.mp. ADJ3 central nervous system*.mp.) OR intracranial lymphoma*.mp. OR cerebral lymphoma*.mp. OR intracerebral lymphoma*.mp. OR glial lymphoma*.mp. OR neuroglial lymphoma*.mp.) AND (exp cognitive defect/ OR exp cognition/ OR exp memory disorder/ OR sustained attention*.mp. OR divided attention*.mp. OR exp neuropsychological test/ OR exp neuropsychology/ OR neuropsych*.mp. OR neuro-psycho*.mp. OR neurobehav*.mp. OR neuro-behav*.mp. OR neuro-cognit*.mp. OR cognit*.mp. OR memory.mp. OR memories.mp. OR memoriz*.mp. OR memoris*.mp.

OR mental.mp. OR mentaly.mp. OR mentally.mp. OR intellect*.mp. OR intellect*.mp. OR exp "speech and language"/ OR "language".mp. OR arithmetic*.mp. OR executive function*.mp. OR executive attention function*.mp. OR executive dysfunction*.mp.) AND (exp randomized controlled trial/ OR random*.ab,ti. OR placebo*.ab,ti. OR controlled randomized trial*.ab,ti. OR controlled randomised trial*.ab,ti. OR controlled randomized stud*.ab,ti. OR controlled randomised stud*.ab,ti. OR controlled clinical trial*.ab,ti. OR controlled clinical stud*.ab,ti. OR (factorial*.ti. AND trial.ti.) OR crossover.ab,ti. OR cross over.ab,ti. OR cross-over.ab,ti. OR double blind*.ab,ti. OR random*.kw. OR placebo*.kw. OR controlled randomized trial*.kw. OR controlled randomised trial*.kw. OR controlled clinical trial*.kw. OR controlled clinical stud*.kw. OR (factorial*.kw. AND trial.kw.) OR crossover.kw. OR double blind*.kw.)) NOT (exp animal/ NOT human/)

PsychINFO (EBSCO version): ((DE "Glioma" OR "glioma*" OR "neuroglioma*" OR "xanthoastrocytoma*" OR "xantoastrocytoma*" OR "astrocytoma*" OR "astro-cytoma*" OR "astroglioma*" OR "astro-glioma*" OR "oligoastrocytoma*" OR "oligoastro-cytoma*" OR "glioblastom*" OR "glio-blastom*" OR "oligodendroglioma*" OR "oligo-dendroglioma*" OR "oligoden-droglioma*" OR "oligodendroblastoma*" OR "oligo-dendro-blastoma*" OR "oligo-dendroblastoma*" OR "oligoden-droblastoma*" OR "oligodendro-blastoma*" OR "ependymom*" OR "subependymom*" OR "gliosarcoma*" OR "glio-sarcoma*" OR "meningioma*" OR "craniopharyngioma*" OR "cranio-pharyngioma*" OR "brain malign*" OR "malignant primary brain*" OR "primary malignant brain*" OR "malignant brain*" OR "glial tumour*" OR "glial tumor*" OR "glial neoplasm*" OR "glial cancer*" OR "glial carcinoma*" OR "glial malignan*" OR "neuroglial tumour*" OR "neuroglial tumor*" OR "neuroglial neoplasm*" OR "neuroglial cancer*" OR "neuroglial carcinoma*" OR "neuroglial malignanc*") OR (DE "Brain Neoplasms" OR ((TI "tumour*" OR TI "tumor*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ((("tumour*" OR "tumor*") N2 "brain*") OR ((("tumour*" OR "tumor*") N2 "cns") OR ((("tumour*" OR "tumor*") N2 "central nervous system*") OR "intracranial tumour*" OR "intracranial tumor*" OR "cerebral tumour*" OR "cerebral tumor*" OR "intracerebral tumour*" OR "intracerebral tumor*" OR ((TI "neoplasm*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("neoplasm*" N2 "brain*") OR ("neoplasm*" N2 "cns") OR ("neoplasm*" N2 "central nervous system*") OR "intracranial neoplasm*" OR "cerebral neoplasm*" OR "intracerebral neoplasm*" OR ((TI "cancer*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("cancer*" N2 "brain*") OR ("cancer*" N2 "cns") OR ("cancer*" N2 "central nervous system*") OR "intracranial cancer*" OR "cerebral cancer*" OR "intracerebral cancer*" OR ((TI "carcinoma*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("carcinoma*" N2 "brain*") OR "cerebral carcinoma*" OR "intracerebral carcinoma*" OR ((TI "malignan*") AND (TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR "cns malignan*" OR "central nervous system malignan*" OR "intracranial malignan*" OR "cerebral malignan*" OR "intracerebral malignan*") OR ((TI "metasta*" OR TI "meta-sta*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("metasta*" N2 "brain*") OR ("metasta*" N2 "cns") OR ("metasta*" N2 "central nervous system*") OR "intracranial metasta*" OR "cerebral metasta*" OR "intracerebral metasta*" OR "glial metasta*" OR "neuroglial metasta*" OR ((TI "lymphom*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("lymphoma*" N2 "brain*") OR ("lymphoma*"

N2 "cns") OR ("lymphoma** N2 "central nervous system**") OR "intracranial lymphoma** OR "cerebral lymphoma** OR "intracerebral lymphoma** OR "glial lymphoma** OR "neuroglial lymphoma**") AND (DE "Cognitive Impairment" OR DE "Cognition" OR DE "Animal Cognition" OR DE "Mental Lexicon" OR DE "Social Cognition" OR DE "Memory" OR DE "Autobiographical Memory" OR DE "Early Memories" OR DE "Eidetic Imagery" OR DE "Episodic Memory" OR DE "Explicit Memory" OR DE "False Memory" OR DE "Implicit Memory" OR DE "Long Term Memory" OR DE "Memory Consolidation" OR DE "Memory Decay" OR DE "Memory Trace" OR DE "Prospective Memory" OR DE "Reminiscence" OR DE "Repressed Memory" OR DE "Retrospective Memory" OR DE "Short Term Memory" OR DE "Spatial Memory" OR DE "Spontaneous Recovery (Learning)" OR DE "Verbal Memory" OR DE "Visual Memory" OR DE "Iconic Memory" OR DE "Visuospatial Memory" OR DE "Semantic Memory" OR DE "Memory Disorders" OR DE "Amnesia" OR DE "Anterograde Amnesia" OR DE "Global Amnesia" OR DE "Retrograde Amnesia" OR DE "Attention" OR DE "Attentional Capture" OR DE "Divided Attention" OR DE "Monitoring" OR DE "Selective Attention" OR DE "Sustained Attention" OR DE "Vigilance" OR DE "Visual Attention" OR DE "Polysomnography" OR DE "Self Monitoring" OR DE "Source Monitoring" OR DE "Vigilance" OR DE "Attention Span" OR DE "Concentration" OR DE "Vigilance" OR "sustained attention** OR "divided attention** OR DE "Test Scores" OR DE "Cutting Scores" OR DE "Intelligence Quotient" OR DE "Standard Scores" OR DE "Neuropsychological Assessment" OR DE "Halstead Reitan Neuropsychological Battery" OR DE "Luria Nebraska Neuropsychological Battery" OR DE "Mini Mental State Examination" OR DE "Task Switching" OR DE "Wechsler Memory Scale" OR DE "Wisconsin Card Sorting Test" OR DE "Neuropsychology" OR neuropsycho** OR "neuro-psycho** OR "neurobehav** OR "neuro-behav** OR "neurocognit** OR "cognit** OR "memory" OR "memories" OR "memoriz** OR "memoris** OR "mental" OR "mentaly" OR "mentally" OR "intellect** OR "intellect** OR DE "Language" OR DE "Dialect" OR DE "Figurative Language" OR DE "Foreign Languages" OR DE "Form Classes (Language)" OR DE "Native Language" OR DE "Natural Language" OR DE "Phrases" OR DE "Profanity" OR DE "Rhetoric" OR DE "Sentences" OR DE "Sign Language" OR DE "Spelling" OR DE "Vocabulary" OR DE "Written Language" OR DE "Nonstandard English" OR DE "Metaphor" OR DE "Adjectives" OR DE "Adverbs" OR DE "Nouns" OR DE "Pronouns" OR DE "Verbs" OR DE "Anagrams" OR DE "Antonyms" OR DE "Homographs" OR DE "Homonyms" OR DE "Mental Lexicon" OR DE "Neologisms" OR DE "Sight Vocabulary" OR DE "Slang" OR DE "Synonyms" OR DE "Alphabets" OR DE "Initial Teaching Alphabet" OR DE "Letters (Alphabet)" OR DE "Handwriting" OR DE "Cursive Writing" OR DE "Handwriting Legibility" OR DE "Printing (Handwriting)" OR DE "Numbers (Numerals)" OR DE "Paragraphs" OR DE "Readability" OR DE "Consonants" OR DE "Vowels" OR "language" OR "arithmetic** OR "executive function** OR "executive attention function** OR "executive dysfunction*) AND (MR Treatment Outcome/Clinical Trial OR TI "random** OR AB "random** OR TI "placebo** OR AB "placebo** OR TI "controlled randomized trial** OR AB "controlled randomized trial** OR TI "controlled randomised trial** OR AB "controlled randomised trial** OR TI "controlled clinical trial** OR AB "controlled clinical trial** OR TI "controlled clinical stud** OR AB "controlled clinical stud** OR (TI "factorial** AND TI "trial") OR TI "crossover" OR AB "crossover" OR TI "double blind** OR AB "double blind** OR KW "random** OR KW "placebo** OR KW "controlled randomized trial** OR KW "controlled randomised trial** OR KW "controlled clinical trial** OR KW "controlled clinical stud** OR (KW "factorial** AND KW "trial") OR KW "crossover" OR KW "double blind**)

CINAHL (EBSCO-version): Search mode: 'Boolean/Phrase'. ((MH "Glioma" OR "glioma** OR "neuroglioma** OR "xanthoastrocytoma** OR "xanthoastrocytoma** OR "astrocytoma** OR "astro-cytoma** OR "astroglioma** OR "astro-glioma** OR "oligoastrocytoma** OR "oligoastro-cytoma** OR "glioblastom** OR "glio-blastom** OR "oligodendroglioma** OR "oligo-dendroglioma** OR

"oligoden-droglioma*" OR "oligodendroblastoma*" OR "oligo-dendro-blastoma*" OR "oligo-dendro-blastoma*" OR "oligoden-droblastoma*" OR "oligodendro-blastoma*" OR "ependymom*" OR "subependymom*" OR "gliosarcoma*" OR "glio-sarcoma*" OR MH "Meningioma" OR "meningioma*" OR MH "Craniopharyngioma" OR "craniopharyngioma*" OR "cranio-pharyngioma*" OR "brain malign*" OR "malignant primary brain*" OR "primary malignant brain*" OR "malignant brain*" OR "glial tumour*" OR "glial tumor*" OR "glial neoplasm*" OR "glial cancer*" OR "glial carcinoma*" OR "glial malignan*" OR "neuroglial tumour*" OR "neuroglial tumor*" OR "neuroglial neoplasm*" OR "neuroglial cancer*" OR "neuroglial carcinoma*" OR "neuroglial malignanc*" OR (MH "Brain Neoplasms*" OR ((TI "tumour*" OR TI "tumor*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ((("tumour*" OR "tumor*") N2 "brain*") OR ((("tumour*" OR "tumor*") N2 "cns") OR ((("tumour*" OR "tumor*") N2 "central nervous system*") OR "intracranial tumour*" OR "intracranial tumor*" OR "cerebral tumour*" OR "cerebral tumor*" OR "intracerebral tumour*" OR "intracerebral tumor*" OR ((TI "neoplasm*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("neoplasm*" N2 "brain*") OR ("neoplasm*" N2 "cns") OR ("neoplasm*" N2 "central nervous system*") OR "intracranial neoplasm*" OR "cerebral neoplasm*" OR "intracerebral neoplasm*" OR ((TI "cancer*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("cancer*" N2 "brain*") OR ("cancer*" N2 "cns") OR ("cancer*" N2 "central nervous system*") OR "intracranial cancer*" OR "cerebral cancer*" OR "intracerebral cancer*" OR ((TI "carcinoma*") AND (TI "brain" OR TI "brains" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("carcinoma*" N2 "brain*") OR "cerebral carcinoma*" OR "intracerebral carcinoma*" OR ((TI "malignan*") AND (TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR "cns malignan*" OR "central nervous system malignan*" OR "intracranial malignan*" OR "cerebral malignan*" OR "intracerebral malignan*" OR (MH "Neoplasm Metastasis*" OR TI "metasta*" OR TI "meta-sta*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("metasta*" N2 "brain*") OR ("metasta*" N2 "cns") OR ("metasta*" N2 "central nervous system*") OR "intracranial metasta*" OR "cerebral metasta*" OR "intracerebral metasta*" OR "glial metasta*" OR "neuroglial metasta*" OR ((MH "Lymphoma*" OR TI "lymphom*") AND (TI "brain" OR TI "brains" OR TI "cns" OR TI "central nervous system*" OR TI "intracranial*" OR TI "cerebral*" OR TI "intracerebral*" OR TI "glial*" OR TI "neuroglia*")) OR ("lymphoma*" N2 "brain*") OR ("lymphoma*" N2 "cns") OR ("lymphoma*" N2 "central nervous system*") OR "intracranial lymphoma*" OR "cerebral lymphoma*" OR "intracerebral lymphoma*" OR "glial lymphoma*" OR "neuroglial lymphoma*" AND (MH "Cognition Disorders*" OR MH "Cognition*" OR MH "Memory*" OR MH "Memory Disorders*" OR MH "Attention" OR "sustained attention*" OR "divided attention*" OR MH "Neuropsychological Tests" OR MH "Neuropsychology" OR neuropsycho* OR "neuro-psycho*" OR "neurobehav*" OR "neuro-behav*" OR "neurocognit*" OR "cognit*" OR "memory" OR "memories" OR "memoriz*" OR "memoris*" OR "mental" OR "mentaly" OR "mentally" OR "intellect*" OR MH "Language*" OR "language" OR "arithmetic*" OR "executive function*" OR "executive attention function*" OR "executive dysfunction*") AND (PT "randomized controlled trial" OR TI "random*" OR AB "random*" OR TI "placebo*" OR AB "placebo*" OR TI "controlled randomized trial*" OR AB "controlled randomized trial*" OR TI "controlled randomised trial*" OR AB "controlled randomised trial*" OR TI "controlled randomized stud*" OR AB "controlled randomized stud*" OR TI "controlled randomised stud*" OR AB "controlled randomised stud*" OR TI "controlled clinical trial*" OR AB "controlled clinical trial*" OR TI "controlled clinical stud*" OR AB "controlled clinical stud*" OR

(TI "factorial*" AND TI "trial") OR TI "crossover" OR AB "crossover" OR TI "cross over" OR AB "cross over" OR TI "cross-over" OR AB "cross-over" OR TI "double blind*" OR AB "double blind*" OR MW "random*" OR MW "placebo*" OR MW "controlled randomized trial*" OR MW "controlled randomised trial*" OR MW "controlled randomized stud*" OR MW "controlled clinical trial*" OR MW "controlled clinical stud*" OR (MW "factorial*" AND MW "trial") OR MW "crossover" OR MW "double blind*")

Cochrane: 'Search' - 'Title, Abstract, Keywords'. Search Limits: 'Word variations will not be searched'.
 ((glioma* OR neuroglioma* OR xanthoastrocytoma* OR xantoastrocytoma* OR astrocytoma* OR astro NEXT cytoma* OR astroglioma* OR astro NEXT glioma* OR oligoastrocytoma* OR oligoastro NEXT cytoma* OR glioblastom* OR glio NEXT blastom* OR oligodendrogloma* OR oligo NEXT dendrogloma* OR oligoden NEXT drogloma* OR oligodendroblastoma* OR oligo NEXT dendro NEXT blastoma* OR oligo NEXT dendroblastoma* OR oligoden NEXT droblastoma* OR oligodendro NEXT blastoma* OR ependymom* OR subependymom* OR gliosarcoma* OR glio NEXT sarcoma* OR meningioma* OR craniopharyngioma* OR cranio NEXT pharyngioma* OR brain NEXT malign* OR malignant NEXT primary NEXT brain* OR primary NEXT malignant NEXT brain* OR malignant NEXT brain* OR glial NEXT tumour* OR glial NEXT tumor* OR glial NEXT neoplasm* OR glial NEXT cancer* OR glial NEXT carcinoma* OR glial NEXT malignan* OR neuroglial NEXT tumour* OR neuroglial NEXT tumor* OR neuroglial NEXT neoplasm* OR neuroglial NEXT cancer* OR neuroglial NEXT carcinoma* OR neuroglial NEXT malignanc*) OR (((tumour* OR tumor*) NEAR/3 brain*) OR ((tumour* OR tumor*) NEAR/3 cns) OR ((tumour* OR tumor*) NEAR/3 central NEXT nervous NEXT system*) OR intracranial NEXT tumour* OR intracranial NEXT tumor* OR cerebral NEXT tumour* OR cerebral NEXT tumor* OR intracerebral NEXT tumour* OR intracerebral NEXT tumor* OR (neoplasm* NEAR/3 brain*) OR (neoplasm* NEAR/3 cns) OR (neoplasm* NEAR/3 central NEXT nervous NEXT system*) OR intracranial NEXT neoplasm* OR cerebral NEXT neoplasm* OR intracerebral NEXT neoplasm* OR (cancer* NEAR/3 brain*) OR (cancer* NEAR/3 cns) OR (cancer* NEAR/3 central NEXT nervous NEXT system*) OR intracranial NEXT cancer* OR cerebral NEXT cancer* OR intracerebral NEXT cancer* OR (carcinoma* NEAR/3 brain*) OR cerebral NEXT carcinoma* OR intracerebral NEXT carcinoma* OR cns NEXT malignan* OR central NEXT nervous NEXT system NEXT malignan* OR intracranial NEXT malignan* OR cerebral NEXT malignan* OR intracerebral NEXT malignan*) OR (metasta* NEAR/3 brain*) OR (metasta* NEAR/3 cns) OR (metasta* NEAR/3 central NEXT nervous NEXT system*) OR intracranial NEXT metastas* OR cerebral NEXT metastas* OR intracerebral NEXT metastas* OR glial NEXT metastas* OR neuroglial NEXT metastas* OR (lymphoma* NEAR/3 brain*) OR (lymphoma* NEAR/3 cns) OR (lymphoma* NEAR/3 central NEXT nervous NEXT system*) OR intracranial NEXT lymphoma* OR cerebral NEXT lymphoma* OR intracerebral NEXT lymphoma* OR glial NEXT lymphoma* OR neuroglial NEXT lymphoma*) AND (sustained NEXT attention* OR divided NEXT attention* OR neuropsych* OR neuro NEXT psycho* OR neurobehav* OR neuro NEXT behav* OR neurocognit* OR cognit* OR memory OR memories OR memoriz* OR memoris* OR mental OR mentaly OR mentally OR intellect* OR intellect* OR "language" OR arithmetic* OR executive NEXT function* OR executive NEXT attention NEXT function* OR executive NEXT dysfunction*) AND (random* OR placebo* OR controlled NEXT randomized NEXT trial* OR controlled NEXT randomised NEXT trial* OR controlled NEXT randomized NEXT stud* OR controlled NEXT randomised NEXT stud* OR controlled NEXT clinical NEXT trial* OR controlled NEXT clinical NEXT stud* OR (factorial* AND trial) OR crossover OR cross NEXT over OR double blind*)

Table S1. Characteristics of relevant publications (N=77 based on 65 RCTs) (page 187-191)

Authors	Trial name	Patient histology and broad experimental treatment	Overall sample size	Cognitive measures	NCO endpoint	Number of criteria [^]	Number of test battery criteria [†]
Ahles et al. ¹	CALGB 8083	SCLC; chemo, RT and PCI	57	TMT-B	Secondary	7/16	n.a.
Ahles et al. ²	CALGB 8534	SCLC; warfarin, PCI	342	TMT-B	Secondary	11/16	4/6
Aoyama et al. ³	JROSG-99-1	BM; SRS ± WBRT	132	MMSE	Secondary	11/15	3/6
Armstrong et al. ⁴	RTOG 0525	GBM; TMZ	191	HVLT-R, TMT, COWA	Secondary	11/16	7/7
Arragada et al. ⁵		SCLC; PCI	300	MMSE, judgment, language, praxis	Secondary	7/15	n.a.
Berk et al. ⁶	RTOG 0119	BM; melatonin and RT	126	MMSE	Secondary	7/15	n.a.
Boele et al. ⁷		PBT (11 HGG, 14 LGG, 12 MG); modafinil	37	AVLT, MST, Stroop, LDST, CST, fluency	Secondary	9/15	n.a.
Brown et al.; Brown et al.; Daniels et al.; Laack et al. ⁸⁻¹¹	EORTC inter-group 86-72-51	LGG; RT	203; 20	MMSE; MMSE, WAIS-R, Stroop, AVLT, BVRT, TMT, COWA	Secondary	12/15	5/6
Brown et al. ¹²	RTOG 0614	BM; WBRT ± memantine	554	HVLT, TMT, COWA, MMSE	Primary	21/26	7/7
Brown et al. ¹³	NCT00377156	BM; SRT ± WBRT	213	HVLT-R, Grooved Pegboard, TMT, COWA	Primary	21/25	7/7
Brown et al. ¹⁴	NCCTG N107C/CEC3	BM; post surgery SRT ± WBRT	194	HVLT-R, Grooved Pegboard, TMT, COWA	Primary	21/26	7/7
Buckner et al. ¹⁵		HGG (49 AO, 18 AOA, 293 GBM); RT and BCNU ± INF	360	MMSE	Secondary	7/15	n.a.
Butler et al. ¹⁶		BT (33 primary, 35 BM); RT ± d-MPH	68	MMSE	Secondary	8/15	n.a.
Canney et al. ¹⁷		Mammaca; PCI	51	ACE-R	Secondary	5/15	n.a.
Chang et al.; Taychakhoonayudh et al. ^{18,19}		BM; SRS ± WBRT	58; 55	HVLT#, WAIS III digit span and digit symbol, TMT, COWA, Grooved Pegboard	Primary; secondary*	16/25	7/7
Chinot et al. ²⁰		GBM; RT+TMZ ± BEV	912	MMSE	Secondary	4/15	n.a.
Corn et al. ²¹	RTOG 0118	BM; WBRT ± thalimide	176	MMSE	Secondary	8/15	n.a.
Field et al. ²²	ACTRN 12610000915055	GBM; carboplatin + BEV	122	MMSE, CogState;	Secondary	2/15	n.a.
Fogarty et al. ²³	WBRTMeI	BM; WBRT	100	NCF (unclear which)	Secondary	4/16	n.a.

Authors	Trial name	Patient histology and broad experimental treatment	Overall sample size	Cognitive measures	NCO endpoint	Number of criteria [^]	Number of test battery criteria [†]
Gehring et al.; Gehring et al. ^{24,25}		Glioma (117 LGG, 23 HGG); rehabilitation	140	Stroop, digit span, LDST, MST, TEA, VVLT, CST, letter fluency, animal and profession fluency, BADS; Stroop, Digit span, LDST, VVLT	Primary; secondary	23/26	6/6
Gehring et al. ²⁶	NCT00418691	PBT (3 grade II, 9 grade III, 9 grade IV, 3 other); methylphenidate and modafinil	24	Digit span, digit symbol, TMT, HVLT, COWA, Grooved pegboard;	Primary	20/25	6/6
Gilbert et al. ²⁷	RTOG 0825	GBM; BEV	666	HVLT, TMT, COWA	Secondary	7/15	n.a.
Gondi et al.; Gore et al.; Sun et al. ²⁸⁻³⁰	RTOG 0212 and 0214; RTOG 0214	NSCLC and SCLC; PCI; NSCLC; PCI	621; 356	HVLT; MMSE, HVLT	Secondary	12/15	4/6
Gorlia et al.; Mirimanoff et al. ^{31,32}	EORTC/NCIC 26981-22981/CE.3	GBM; RT ± TMZ	573	MMSE	Secondary	8/15	n.a.
Gregor et al. ³³		SCLC; PCI	314	NART, PASAT, Rey, AVLT	Secondary	7/15	n.a.
Herrlinger et al. ³⁴	NOA-03	PCNSL; MTX, WBRT vs. PCV	37 (6)	MMSE, German Leistungsprüf-system-50+, WMS, Testbat-terie zur Auf-merksamkeit-sprüfung Bell's test, letter cancellation, drawing	Secondary	7/15	n.a.
Herrlinger et al. ³⁵	GLARIUS (NCT00967330)	GBM; BEV +IRI vs. TMZ	182	MMSE	Secondary	5/15	n.a.
Herrlinger et al. ³⁶	G-PCNSL-SG1	PCNSL; HD-MTX-based chemotherapy ± WBRT	31	MMSE	Secondary	9/15	n.a.
Keime-Guibert et al. ³⁷	NCT00430911	GBM; RT	85	MMSE, MDRS	Secondary	8/15	n.a.
Kepka et al. ³⁸	NCT01535209	BM; SRS vs. WBRT after surgery	59	MMSE+ neurological score	Co-primary	13/25	n.a.
Kirkpatrick et al. ³⁹	NCT01017497	BM; SRS	49	MMSE, TMT	Secondary	5/15	n.a.
Kirste et al. ⁴⁰		BT (11 GBM, 33 BM); boswellia serrata	44	MMSE	Secondary	7/15	n.a.
Knisely et al. ⁴¹		BM; RT ± thalidomide	183	MMSE;	Secondary	4/16	n.a.
Le Pechoux et al.; Wolfson et al. ^{42,43}	PCI99-01, EORTC 2200308004, RTOG 0212 and IFCT 99-01	SCLC; PCI	720; 264	HVLT, COWA, TMT;	Secondary; primary	12/25	n.a.

Authors	Trial name	Patient histology and broad experimental treatment	Overall sample size	Cognitive measures	NCO endpoint	Number of criteria [^]	Number of test battery criteria [†]
Locke et al. ⁴⁴		PBT (17 glioma, 2 MG); rehabilitation	19	R-BANS	Secondary	5/15	n.a.
Magni et al. ⁴⁵		BT; anesthesia	120	SOMCT	Primary	10/23	n.a.
Magni et al. ⁴⁶		BT; anesthesia	120	SOMCT	Primary	10/23	n.a.
Martorano et al. ⁴⁷		BT; anesthesia	69	SOMCT, RLAS	Secondary	6/15	n.a.
Mehta et al. ⁴⁸	PCYC-0211	BM; WBRT ± motexafin	554	HVLT, COWA, TMT; scales for orientation etc.	Secondary	5/15	n.a.
Mehta et al.; Meyers et al.; Li et al. ⁴⁹⁻⁵¹	PCI-P120-9801	BM; WBRT ± motexafin data from 1 arm	401; 208	HVLT, COWA, TMT, Grooved Pegboard	Secondary	10/16	n.a.
Murray et al.; Regine et al. ^{52,53}	RTOG 91-04	BM; AF WBRT; BM; AF vs. AH WBRT	445	MMSE	Secondary	10/15	3/6
Necib et al. ⁵⁴	NCT00389883	BT (LGG 6, HGG 18, astrocytoma 4, MG 25, BM 7, other 6); anesthesia	69	MMS(E)	Secondary	4/15	n.a.
Omuro et al. ⁵⁵	ANOCEF-GOELAMS (NCT00503594)	CNS lymphoma; MTX+TMZ vs MTX+PCV	95	MMSE, MDRS, Grober verbal memory, TMT; Derouesne scale, Apathy scale, Cummings neuropsychiatric invent	Secondary	9/15	n.a.
Owensworth et al. ⁵⁶		PBT (7 LGG, 7 HGG, 15 GBM, 6 MG, 6 pituitary, 6 colloid cysts, 2 craniopharyngioma, 5 missing); psycho-social	50	HVLT, Digit span, Rey, TMT, fluency	Secondary	5/15	n.a.
Page et al. ⁵⁷		PBT (33 GBM, 7 MG, 14 other); armodafinil with RT	54	HVLT, Digit span, TMT, fluency	Secondary	10/15	6/6
Palmer et al. ⁵⁸		MG, schwannoma; surgery	100	MMSE	Secondary	2/15	n.a.
Peng et al. ⁵⁹	NCT00975910	PBT (21 LGG, 16 HGG, 35 MG, 8 other); lidocaine	94	MMSE, IMCT (memory & concentration)	Primary	18/25	3/6
Pesce et al. ⁶⁰	SAKK 70/03	BM; WBRT + TMZ vs. gefitinib	59	MMSE, TMT	Secondary	5/15	n.a.
Pottgen et al. ⁶¹		NSCLC; PCI	106 (11)	TMT, WMS, Digit span, Benton, Leistungspruf system nach Horn, Corsi, TAP (attention)	Secondary	6/15	n.a.
Prabhu et al. ⁶²	RTOG 98-02	LGG; RT ± PCV	251	MMSE	Secondary	13/16	3/6

Authors	Trial name	Patient histology and broad experimental treatment	Overall sample size	Cognitive measures	NCO endpoint	Number of criteria [^]	Number of test battery criteria [†]
Prados et al. ⁶³		HGG; carboplatin ± RMP-7	122	Digit span, Digit symbol, HVLT, COWA, TMT, Grooved pegboard	Secondary	3/15	n.a.
Rapp et al. ⁶⁴	NCT00369785	BT (20 grade II, 38 grade III, 23 GBM, 22 MG, 6 pilocytic, 21 other, 53 BM, 15 PCI); donepezil	198	HVLT, Rey, TMT, COWA, Digit span, Grooved pegboard	Primary	17/25	6/6
Reijneveld et al. ⁶⁵	EORTC 22033-26033	LGG; TMZ vs. RT	477	MMSE	Secondary	13/16	4/7
Roos et al. ⁶⁶	TROG 98.05	BM: (radio)surgery ± WBRT	19	MMSE	Secondary	3/15	n.a.
Souhami et al. ⁶⁷	RTOG 93-05	BM; RT with BCNU ± SRS	203	MMSE	Secondary	6/15	n.a.
Stupp et al. ⁶⁸	CENTRIC EORTC 26071-22072	GBM; cilengitide	545	MMSE	Secondary	2/15	n.a.
Stupp et al. ⁶⁹	NCT00916409	GBM; TMZ ± TTF	695	MMSE	Secondary	2/15	n.a.
Talke et al. ⁷⁰		Supratentorial intracranial surgery; anesthesia	60	Digital symbol substitution, P-deletion; orienting	Secondary	3/15	n.a.
Taylor et al. ⁷¹	NCCTG (2 trials)	HGG; (159 grade III, 542 grade IV); RT+BCNU vs. RT+PCNU; RT+BCNU and IFN vs. RT+ BCNU	701	MMSE	Secondary	12/16	3/6
Trojanowski et al. ⁷²		Glioma (49 grade II, 67 grade III, 82 grade IV); RT ± CCNU	198	Measures for sensory recognition, praxis, drawing, speech, reading, writing, memory, calculation, thinking	Secondary	4/15	n.a.
Wang et al. ⁷³	RTOG 9402	Anaplastic oligodendroglioma; RT ± PCV	289	MMSE	Secondary	12/16	4/7
Wefel et al. ⁷⁴	BRAIN (NCT00345163)	GBM; BEV ± CPT-11	167	HVLT, TMT, COWA	Secondary	12/16	6/6
Weller et al. ⁷⁵	DIRECTOR (NCT00941460)	GBM; different TMZ regimens	105	MMSE	Secondary	2/15	n.a.
Yang et al. ⁷⁶		BT (10 MG, 5 GBM, 2 astrocytoma, 6 BM, 15 other); virtual reality	38	MMSE, CNT (including concentration, word-color test, digit span, verbal and visual learning), TMT	Primary	11/25	n.a.

Authors	Trial name	Patient histology and broad experimental treatment	Overall sample size	Cognitive measures	NCO endpoint	Number of criteria [^]	Number of test battery criteria [†]
Zucchella et al. ⁷⁷		PBT (7 LGG, 25 HGG, 16 MG, 5 other); reha-bilitation	58	MMSE, Digit span, Corsi, RAVLT, Raven, TMT, FAB, Attentive matrices, Rey, COWA; aphasia	Primary	14/25	n.a.

[^]Total number of criteria for primary NCO outcome: 27, for secondary NCO outcome: 16. Not all criteria were applicable in all RCTs; [†] Only applicable in 'high-quality' studies. Total number of criteria: 7. Not all criteria were applicable in all RCTs. For studies with NCO as secondary outcomes, the level of the used test battery was judged adequate when all criteria were fulfilled. For studies with NCO as primary outcome, also longer than the advised 30-40 minutes assessment was judged acceptable⁷⁸; * In case NCO was both a primary and secondary endpoint in different publications, it was included as primary endpoint; # studies describing overlapping trials; * data about only one treatment arm; GBM glioblastoma multiforme; HGG high-grade glioma; LGG low-grade glioma; MG meningioma; NSCLC non-small cell lung carcinoma; SCLC small cell lung carcinoma; TMZ temozolomide; PCV procarbazine, lomustine, and vincristine; BCNU carmustine; PCNU 1-(2-chloroethyl)-3(2,6 dioxo-lpiperidyl)-l-nitrosourea; BEV bevacizumab; RT radiotherapy; WBRT whole brain radiotherapy; SRS stereotactic radiosurgery; PCI prophylactic cranial irradiation; OS Overall survival; PFS progression free survival; MMSE mini-mental state examination; HVL(-R) Hopkins verbal learning test (-revised); TM: trail making test; COWA controlled word association test; AVL auditory verbal learning test; LDST letter digit substitution test; CST concept shifting test; WAIS Wechsler adult intelligence scale; BVRT Benton visual retention test; ACE-R Addenbrooke's cognitive examination -revised; MDRS Mattis dementia rating scale; MST memory scanning test; TEA test of everyday attention; VVLT visual verbal learning test; BADS behavioral assessment of the dysexecutive syndrome; NAR: national adult reading test; PASAT paced auditory serial addition test; R-BANS repeatable battery for the assessment of neuropsychological status; SOMCT short orientation memory concentration test; RLAS Rancho los amigos scale; CNT computerized neuropsychological test

References

1. Ahles TA, Silberfarb PM, Rundle AC, et al. Quality of life in patients with limited small-cell carcinoma of the lung receiving chemotherapy with or without radiation therapy, for cancer and leukemia group B. *Psychother Psychosom*. 1994;62(3-4):193-199.
2. Ahles TA, Silberfarb PM, Herndon J, et al. Psychologic and neuropsychologic functioning of patients with limited small-cell lung cancer treated with chemotherapy and radiation therapy with or without warfarin: a study by the Cancer and Leukemia Group B. *J Clin Oncol*. 1998;16(5):1954-1960.
3. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2007;68(5):1388-1395.
4. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. *J Clin Oncol*. 2013;31(32):4076-4084.
5. Arriagada R, Le CT, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst*. 1995;87(3):183-190.
6. Berk L, Berkey B, Rich T, et al. Randomized phase II trial of high-dose melatonin and radiation therapy for RPA class 2 patients with brain metastases (RTOG 0119). *Int J Radiat Oncol Biol Phys*. 2007;68(3):852-857.
7. Boele FW, Douw L, de GM, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro Oncol*. 2013;15(10):1420-1428.
8. Brown PD, Buckner JC, O'Fallon JR, et al. Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the folstein mini-mental state examination. *J Clin Oncol*. 2003;21(13):2519-2524.
9. Brown PD, Buckner JC, O'Fallon JR, et al. Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2004;59(1):117-125.
10. Daniels TB, Brown PD, Felten SJ, et al. Validation of EORTC prognostic factors for adults with low-grade glioma: a report using intergroup 86-72-51. *Int J Radiat Oncol Biol Phys*. 2011;81(1):218-224.
11. Laack NN, Brown PD, Ivnik RJ, et al. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys*. 2005;63(4):1175-1183.
12. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429-1437.
13. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA*. 2016;316(4):401-409.
14. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1049-1060.
15. Buckner JC, Schomberg PJ, McGinnis WL, et al. A phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma. *Cancer*. 2001;92(2):420-433.
16. Butler JM, Jr, Case LD, Atkins J, et al. A phase III, double-blind, placebo-controlled prospective randomized clinical trial of

- d-threo-methylphenidate HCl in brain tumor patients receiving radiation therapy. *Int J Radiat Oncol Biol Phys.* 2007;69(5):1496-1501.
17. Canney P, Murray E, Dixon-Hughes J, Lewsley LA, Paul J. A Prospective Randomised Phase III Clinical Trial Testing the Role of Prophylactic Cranial Radiotherapy in Patients Treated with Trastuzumab for Metastatic Breast Cancer - Anglo Celtic VII. *Clin Oncol (RCollRadiol).* 2015;27(8):460-464.
 18. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037-1044.
 19. Taychakhoonavudh S, Franzini L, Lal LS, et al. Comparison of time trade-off utility with neurocognitive function, performance status, and quality of life measures in patients with metastatic brain disease. *J Radiat Oncol.* 2014;3(2):215-221.
 20. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370(8):709-722.
 21. Corn BW, Moughan J, Knisely JP, et al. Prospective evaluation of quality of life and neurocognitive effects in patients with multiple brain metastases receiving whole-brain radiotherapy with or without thalidomide on Radiation Therapy Oncology Group (RTOG) trial 0118. *Int J Radiat Oncol Biol Phys.* 2008;71(1):71-78.
 22. Field KM, Simes J, Nowak AK, et al. Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. *Neuro Oncol.* 2015;17(11):1504-1513.
 23. Fogarty GB, Hong A, Dolven-Jacobsen K, et al. First interim analysis of a randomised trial of whole brain radiotherapy in melanoma brain metastases confirms high data quality. *BMC Res Notes.* 2015;8:192.
 24. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol.* 2009;27(22):3712-3722.
 25. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoorn MM. Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. [Erratum appears in *J Int Neuropsychol Soc.* 2011 Mar;17(2):384]. *J Internat Neuropsychol Soc.* 2011;17(2):256-266.
 26. Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol.* 2012;107(1):165-174.
 27. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370(8):699-708.
 28. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214.[Erratum appears in *J Clin Oncol.* 2011 Aug 10;29(23):3204]. *J Clin Oncol.* 2011;29(3):272-278.
 29. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J Clin Oncol.* 2011;29(3):279-286.
 30. Gondi V, Paulus R, Bruner DW, et al. Decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation for lung cancer: pooled secondary analysis of Radiation Therapy Oncology Group randomized trials 0212 and 0214. *Int J Radiat Oncol Biol Phys.* 2013;86(4):656-664.
 31. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol.* 2008;9(1):29-38.
 32. Mirimanoff RO, Gorlia T, Mason W, et al.

- Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol*. 2006;24(16):2563-2569.
33. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer*. 1997;33(11):1752-1758.
 34. Herrlinger U, Kuker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. *Ann Neurol*. 2005;57(6):843-847.
 35. Herrlinger U, Schafer N, Steinbach JP, et al. Bevacizumab Plus Irinotecan Versus Temozolomide in Newly Diagnosed O6-Methylguanine-DNA Methyltransferase Nonmethylated Glioblastoma: The Randomized GLARIUS Trial. *J Clin Oncol*. 2016;34(14):1611-1619.
 36. Herrlinger U, Schafer N, Fimmers R, et al. Early whole brain radiotherapy in primary CNS lymphoma: negative impact on quality of life in the randomized G-PCNSL-SG1 trial. *J Cancer Res Clin Oncol*. 2017.
 37. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. *N Engl J Med*. 2007;356(15):1527-1535.
 38. Kepka L, Tyc-Szczepaniak D, Bujko K, et al. Stereotactic radiotherapy of the tumor bed compared to whole brain radiotherapy after surgery of single brain metastasis: Results from a randomized trial. *Radiother Oncol*. 2016;121(2):217-224.
 39. Kirkpatrick JP, Wang Z, Sampson JH, et al. Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: results of a randomized trial. *Int J Radiat Oncol Biol Phys*. 2015;91(1):100-108.
 40. Kirste S, Treier M, Wehrle SJ, et al. Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. *Cancer*. 2011;117(16):3788-3795.
 41. Knisely JP, Berkey B, Chakravarti A, et al. A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). *Int J Radiat Oncol Biol Phys*. 2008;71(1):79-86.
 42. Le Pechoux, Laplanche A, Faivre-Finn C, et al. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). *Ann Oncol*. 2011;22(5):1154-1163.
 43. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81(1):77-84.
 44. Locke DE, Cerhan JH, Wu W, et al. Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumors: a pilot study. *J Support Oncol*. 2008;6(8):383-391.
 45. Magni G, Baisi F, La RI, et al. No difference in emergence time and early cognitive function between sevoflurane-fentanyl and propofol-remifentanyl in patients undergoing craniotomy for supratentorial intracranial surgery. *J Neurosurg Anesthesiol*. 2005;17(3):134-138.
 46. Magni G, Rosa IL, Melillo G, Savio A, Rosa G. A comparison between sevoflurane and desflurane anesthesia in patients undergoing craniotomy for supratentorial intracranial surgery. *Anesth Analg*. 2009;109(2):567-571.
 47. Martorano PP, Aloj F, Baietta S, et al. Sufentanil-propofol vs remifentanyl-propofol during total intravenous anesthesia for neurosurgery. A multicentre study. *Minerva Anestesiologica*. 2008;74(6):233-243.

48. Mehta MP, Shapiro WR, Phan SC, et al. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: results of a phase III trial. *Int J Radiat Oncol Biol Phys.* 2009;73(4):1069-1076.
49. Mehta MP, Rodrigus P, Terhaard CH, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol.* 2003;21(13):2529-2536.
50. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol.* 2004;22(1):157-165.
51. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol.* 2007;25(10):1260-1266.
52. Murray KJ, Scott C, Zachariah B, et al. Importance of the mini-mental status examination in the treatment of patients with brain metastases: a report from the Radiation Therapy Oncology Group protocol 91-04. *Int J Radiat Oncol Biol Phys.* 2000;48(1):59-64.
53. Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs. accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group Study 91-04. *Int J Radiat Oncol Biol Phys.* 2001;51(3):711-717.
54. Necib S, Tubach F, Peuch C, et al. Recovery from anesthesia after craniotomy for supratentorial tumors: comparison of propofol-remifentanyl and sevoflurane-sufentanyl (the PROMIFLUNIL trial). *J Neurosurg Anesthesiol.* 2014;26(1):37-44.
55. Omuro A, Chinot O, Taillandier L, et al. Methotrexate and temozolomide versus methotrexate, procarbazine, vincristine, and cytarabine for primary CNS lymphoma in an elderly population: an intergroup ANOCEF-GOELAMS randomised phase 2 trial. *Lancet Haematol.* 2015;2(6):e251-e259.
56. Ownsworth T, Chambers S, Damborg E, Casey L, Walker DG, Shum DH. Evaluation of the making sense of brain tumor program: a randomized controlled trial of a home-based psychosocial intervention. *Psychooncology.* 2015;24(5):540-547.
57. Page BR, Shaw EG, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. *Neuro Oncol.* 2015.
58. Palmer JD, Francis JL, Pickard JD, Iannotti F. The efficacy and safety of aprotinin for hemostasis during intracranial surgery. *J Neurosurg.* 2003;98(6):1208-1216.
59. Peng Y, Zhang W, Zhou X, Ji Y, Kass IS, Han R. Lidocaine Did Not Reduce Neuropsychological-Cognitive Decline in Patients 6 Months After Supratentorial Tumor Surgery: A Randomized, Controlled Trial. *J Neurosurg Anesthesiol.* 2016;28(1):6-13.
60. Pesce GA, Klingbiel D, Ribi K, et al. Outcome, quality of life and cognitive function of patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy combined with gefitinib or temozolomide. A randomised phase II trial of the Swiss Group for Clinical Cancer Research (SAKK 70/03). *Eur J Cancer.* 2012;48(3):377-384.
61. Pottgen C, Eberhardt W, Grannass A, et al. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. *J Clin Oncol.* 2007;25(31):4987-4992.
62. Prabhu RS, Won M, Shaw EG, et al. Effect of the addition of chemotherapy to radiotherapy on cognitive function in patients with low-grade glioma: secondary analysis of RTOG 98-02. *J Clin Oncol.* 2014;32(6):535-541.
63. Prados MD, Schold Sc Jr SC, Fine HA, et al. A randomized, double-blind, placebo-controlled, phase 2 study of RMP-7

- in combination with carboplatin administered intravenously for the treatment of recurrent malignant glioma. *Neuro Oncol.* 2003;5(2):96-103.
64. Rapp SR, Case LD, Peiffer A, et al. Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial. *J Clin Oncol.* 2015;33(15):1653-1659.
 65. Reijneveld JC, Taphoorn MJ, Coens C, et al. Health-related quality of life in patients with high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol.* 2016;17(11):1533-1542.
 66. Roos DE, Wirth A, Burmeister BH, et al. Whole brain irradiation following surgery or radiosurgery for solitary brain metastases: mature results of a prematurely closed randomized Trans-Tasman Radiation Oncology Group trial (TROG 98.05). *Radiother Oncol.* 2006;80(3):318-322.
 67. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys.* 2004;60(3):853-860.
 68. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): A multicentre, randomised, open-label, phase 3 trial. *The Lancet Oncology.* 2014;15(10):1100-1108.
 69. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-Treating fields plus temozolomide vs temozolomide alone for glioblastoma a randomized clinical trial. *JAMA - Journal of the American Medical Association.* 2015;314(23):2535-2543.
 70. Talke P, Caldwell JE, Brown R, Dodson B, Howley J, Richardson CA. A comparison of three anesthetic techniques in patients undergoing craniotomy for supratentorial intracranial surgery. *Anesthesia & Analgesia.* 2002;95(2):430-435.
 71. Taylor BV, Buckner JC, Cascino TL, et al. Effects of radiation and chemotherapy on cognitive function in patients with high-grade glioma. *J Clin Oncol.* 1998;16(6):2195-2201.
 72. Trojanowski T, Peszynski J, Turowski K, et al. Quality of survival of patients with brain gliomas treated with postoperative CCNU and radiation therapy. *J Neurosurg.* 1989;70(1):18-23.
 73. Wang M, Cairncross G, Shaw E, et al. Cognition and quality of life after chemotherapy plus radiotherapy (RT) vs. RT for pure and mixed anaplastic oligodendrogliomas: radiation therapy oncology group trial 9402. *Int J Radiat Oncol Biol Phys.* 2010;77(3):662-669.
 74. Wefel JS, Cloughesy T, Zazzali JL, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. *Neuro Oncol.* 2011;13(6):660-668.
 75. Weller M, Tabatabai G, Kastner B, et al. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive Glioblastoma: The DIRECTOR Trial. *Clinical Cancer Research.* 2015;21(9):2057-2064.
 76. Yang S, Chun MH, Son YR. Effect of virtual reality on cognitive dysfunction in patients with brain tumor. *Ann Rehabil Med.* 2014;38(6):726-733.
 77. Zucchella C, Capone A, Codella V, et al. Cognitive rehabilitation for early post-surgery inpatients affected by primary brain tumor: a randomized, controlled trial. *J Neurooncol.* 2013;114(1):93-100.
 78. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol.* 2012;108(2):309-318.

Part V

General discussion
and future directions

9

Summary, general discussion and future directions



The aim of this thesis was to expand our knowledge about the level of neurocognitive functioning (NCF) and of health-related quality of life (HRQoL) of brain tumor patients with primary and secondary brain tumors during the disease course, that can be used to optimize treatment and individual patient care. In this section we present a summary and discussion of the main findings of the articles in this thesis, together with a discussion of methodological limitations and future directions.

Summary and discussion of main findings

The impact of the tumor on NCF

We found a high percentage of patients suffering from neurocognitive impairments caused by the tumor itself, regardless of the type of tumor. That is, in our samples of high-grade glioma patients ($n = 62$; **chapter 2**), low- and high-grade glioma patients ($n = 72$; **chapter 6**) and brain metastases ($n = 97$; **chapter 3**), the presence of a brain tumor was associated with cognitive impairments. Indeed, before anti-tumor treatment, 79% of the glioma patients and 53% of brain metastatic patients suffered from clinically relevant neurocognitive impairments in at least one domain. The lower frequency of brain metastases patients with cognitive impairments may be explained by the fact that the median tumor volume was smaller in this group, and that brain metastases in general do not infiltrate into surrounding healthy brain tissue, in contrast to gliomas.¹ The percentage of impairments in glioma patients prior to surgery was similar as compared to earlier studies.²⁻⁴ However, for brain metastatic patients, the frequency of impairments was lower compared to earlier data,^{5,6} possibly due to differences in the composition of patient groups, tests used, and cut-off scores used to define a deficit.

In line with other studies,^{5,7,8} we found that verbal memory and attention had the lowest scores and were the most frequently impaired neurocognitive functions preceding treatment in all brain tumor patients (**chapter 2, 3, 4 and 6**). In addition, impairments in working memory and executive functioning were often seen in glioma patients (**chapter 2 and 6**), suggesting that primary brain tumors affect mainly neurocognitive functions in which multiple brain regions, forming large networks, are involved. This hypothesis is supported by our findings in the study on the association between neurocognitive impairment and tumor location, where we demonstrated that a large frontoparietal network in the left hemisphere was related to the observed attention and executive functioning impairments (**chapter 6**). Finally, we also observed a relatively frequent impairment in visuoconstructive abilities in brain metastatic patients (**chapter 3**), which may negatively impact spatial orientation in daily life. This neurocognitive function has only sporadically been studied in brain tumor patients, with different results: Boone et al. found 19% of glioma patients impaired in visuoconstruction,⁹ while Wefel et al. found 4-16% of high-grade glioma patients impaired in this domain.³

Various aspects of the tumor can influence NCF. In the present thesis, we specifically studied the impact of tumor location, tumor burden (expressed in both tumor volume and number of brain lesions), and tumor grade or growth rate (based on the comparison between low-grade and high-grade glioma).

Tumor location

We found that gliomas in the left hemisphere were associated with more frequent neurocognitive impairments (**chapter 6**) and poorer verbal memory, working memory and attention (**chapter 2**) than tumors in the right hemisphere. The finding that especially patients with left-sided tumors are vulnerable to neurocognitive impairments is in line with earlier studies,¹⁰⁻¹² and could be partially explained by the fact that we used mainly verbally assessed neurocognitive tests. Somewhat surprisingly, and in contradiction to other studies,¹³⁻¹⁵ we did not observe neurocognitive impairments to be associated with right hemispheric regions. That is, attentional and working memory impairments prior to surgery were almost exclusively associated with left hemispheric tumor locations. Again, this might be due to the absence of spatial attention tasks in our protocol, while these are mainly used in other studies on the attention network.^{13,16}

Tumor volume

In our high-grade glioma sample, large left hemispheric tumor patients had poorer executive functioning compared to patients with small tumors in that hemisphere (**chapter 2**). Larger tumor volume, but not the number of brain metastases, was also associated with worse NCF (i.e. information processing speed) in our brain metastatic group (**chapter 3**). These results are in line with earlier research.^{5,17,18} Moreover, intracranial tumor progression, i.e. an increase in tumor volume, was associated with worsening of executive functioning and motor function in brain metastatic patients. Although active systemic disease was found to have no significant impact on NCF at baseline, we were unfortunately not able to evaluate the impact of extracranial tumor progression during the follow-up period. Therefore, we could not study a possible impact of systemic chemotherapy on cognition, while there is evidence from breast cancer patients that this could impact NCF.^{19,20} A limitation of our studies is that we only examined the tumor volume itself and not the volume of surrounding edema, while this latter might negatively impact NCF in an additional way due to its space occupying properties.

Tumor grade/growth rate

The question whether tumor grade is associated with severity of neurocognitive impairments has been studied for a long time. In 1984, Hom and Reitan found that patients with slowly growing glioma had fewer neurocognitive impairments than patients with fast growing tumors.²¹ However, these authors did not correct for the older age of the patients with fast growing tumors. When corrected for age, others did not find neurocognitive differences between low- and high-grade glioma,²² which is in line with our results in the low- and high-grade sample (**chapter 6**). However, this issue is still under debate, as several others did observe more severe or more

frequent neurocognitive impairments in patients with high-grade, and therefore more fast growing tumors, compared to low-grade tumors.²³⁻²⁵ More recently, it has been suggested that specific genetic markers might better represent tumor growth rate, and consequently neurocognitive impairments, than traditional tumor grading based on histopathology only. For example, isocitrate dehydrogenase 1 wild type (IDH1-WT) tumors are more proliferative and aggressive than IDH1-mutant (IDH1-M) tumors.³ It was found that patients with IDH1-WT tumors indeed suffered from more frequent impairments and lower scores in memory, processing speed, visuoconstruction, language and executive functioning, compared to patients with IDH1-M tumors, irrespective of lesion size. One could hypothesize that a higher growth rate might result in less efficient brain networks and less time for brain plasticity to compensate for functional loss.^{3,26} However, in an earlier study using magnetoencephalography to construct functional networks in low- and high-grade glioma patients, low grade glioma patients had altered networks which were correlated with cognitive impairments, while functional networks of high-grade glioma patients did not differ from healthy controls.²⁷ Future research must shed light on the question whether functional networks and genetic mutations are indeed related to differences in NCF in glioma patients, and whether networks and mutations are related to each other.

The impact of the tumor on HRQoL

In our sample of anaplastic oligodendroglioma survivors, pre-treatment HRQoL data was evaluated in an earlier study.²⁸ The authors found considerable deterioration in HRQoL compared to the healthy population.²⁸ Similarly, we found that brain metastatic patients had impaired HRQoL scores prior to treatment, i.e. statistically and clinically relevant lower HRQoL scores in preselected scales compared to normative data (**chapter 3**). Similar results were observed by other authors in brain metastatic patients prior to treatment.^{18,29,30} At the individual patient level, a vast majority of 89% of patients showed clinically relevant and statistically significant lower scores in at least one of the six explored EORTC QLQ-C30 scales when compared to the general population, of which physical functioning was most frequently affected (57%) (**chapter 4**). Overall, these results indicate that brain metastatic patients are already impaired at onset, most likely caused by both systemic and intracranial tumor.

The impact of anti-tumor treatment on NCF

In this thesis, the effects of different anti-tumor treatments (surgery, stereotactic radiotherapy and combined radiotherapy and chemotherapy) on NCF have also been examined.

Surgery

In **chapter 2** and **7**, low- and high-grade glioma patients were neurocognitively tested before and after surgery, and pre- and postoperative results were compared. The results of these studies provide information about the immediate and medium long-term morbidity of surgery. On group level, a lower percentage of patients suffered from neurocognitive impairments after surgery when compared to their pre-surgical performance (59% versus 79%, respectively). Of the 39 patients with high-grade glioma, 49% showed improvement, while 23% declined after a median of 5 weeks after surgery (**chapter 2**). Changes in cognitive performance at follow-up relative to the pre-operative level of NCF were not related to tumor characteristics or extent of resection. In a sample with predominantly low-grade glioma patients ($n = 59$, **chapter 7**), cognitive decline was more often observed than cognitive improvement (42% versus 17%, respectively) 12 months after surgery. It should be noted though, that some patients received additional anti-tumor treatment during follow-up. The difference between the two studies may be explained by differences in follow-up interval, because with a mean follow-up interval of one year possible practice effects are reduced, and other treatments such as radiotherapy may also have contributed to a decline. Other factors that may have contributed to these differences are variations in extent of resection or tumor location, which were both measured in a more refined way in the predominantly low-grade glioma study. Indeed, especially patients with right hemispheric tumors, mainly located in the frontal region and corpus callosum, were found to be vulnerable to neurocognitive decline after surgery when compared to patients with left sided tumors (**chapter 7**). It may be that particularly in right sided brain tumor patients, damage to essential neural networks occurred due to the resection, which may have caused neurocognitive decline. That is, not (only) the location of the tumor, but also the functional organization of neurocognitive functions in brain networks, might be an important factor in causing neurocognitive impairments. Another explanation, from a methodological point of view, might be that patients with left-sided tumors were already more impaired prior to surgery, leaving less room for deterioration after surgery compared to the pre-operative cognitively intact patients with right sided tumors.

Stereotactic radiotherapy

We also evaluated the short-term effect of stereotactic radiotherapy (SRT) on NCF in patients with brain metastases, which was found to have no clinically relevant impact (**chapter 3**). In a cohort of 97 brain metastases patients, baseline NCF was worse compared to healthy controls but remained stable during the six months after SRT. This was found on both group and individual patient level (**chapter 4**), and is in line with other studies on SRT in brain metastatic patients, in which no clear cognitive changes have been observed in the early months after treatment³¹⁻³³.

Possible explanations for this stable NCF might be the highly focused treatment of SRT, thereby not affecting surrounding healthy brain tissue, the overall relatively small tumor volumes which were treated with SRT, and, probably most important, the short follow-up intervals. That is, radiotherapy might impair NCF mainly at the long-term, as was found for radiotherapy regimes as used in low grade glioma patients 6 and 12 years after treatment^{34,35}. Nonetheless, this is far less relevant for the majority of brain metastases patients, as survival in this patient group is often much shorter than in low grade glioma patients.

Radiotherapy and chemotherapy

In **chapter 5** we were able to study long-term effects of treatment on NCF in 32 patients with anaplastic glioma. This study did not show any difference in NCF between patients who received radiotherapy compared to combined treatment of radiotherapy with adjuvant chemotherapy. However, the range of neurocognitive performance was large in this sample, with 26% of patients not having any neurocognitive problems, versus 30% suffering from severe neurocognitive impairments in various domains. Unfortunately, this sample was too small to identify predictors of neurocognitive impairment. Most likely tumor recurrence accounted for more severe impairments. Another explanation might be differences in the genetic profile of the tumors, which were not determined in this population. Previously, it has been shown that IDH1-WT patients have more neurocognitive impairments than patients with IDH1-M tumors.³ Data on NCF in long-term anaplastic glioma survivors are scarce. In a previous study, results indicated stable MMSE scores in progression-free anaplastic glioma survivors, while progressive disease was associated with a decline in MMSE scores³⁶. The fact that these authors did not find such high variety in NCF in (progression-free) long-term survivors, might be due to the use of the insensitive MMSE.

The impact of anti-tumor treatment on HRQoL

Stereotactic radiotherapy

Not only neurocognitive performance in patients with one to three brain metastases after SRT was relatively stable, at group level also HRQoL remained stable in the six months after treatment, except for a decline in physical functioning and fatigue (**chapter 3**). Two earlier studies in patients with brain metastases showed mixed results regarding changes in HRQoL within three months after radiotherapy compared to baseline, with both improvements and deterioration in several HRQoL scales, including global health status, physical functioning, fatigue, motor dysfunction and communication deficits.^{18,30} However, in both studies only a minority of patients received SRT alone and results from subgroup analysis are not available.

In contrast to the stable HRQoL scores at group level, our study also showed that

there were large differences on the individual patient level (**chapter 4**). First, on a scale/item level, both improvements and deterioration over time were observed. If a similar number of patients deteriorated and improved, the scores balance, resulting in 'stable' scores as observed in the analysis on group level. On a patient level, however, it was observed that most patients experience both clinical meaningful decline and improvement in their HRQoL. The reason we found differences on the scale/item level can be explained by the fact that in the group analysis mean scores are used, while at the individual patient level we looked at the percentage of patients who deteriorated, remained stable or improved in different scales/items. Moreover, when looking at the patient level, all scales are analyzed together, as a patient may experience all symptoms. This type of analysis therefore provides additional information on the impact of treatment on different HRQoL aspects for an individual patient, and emphasizes that the concept of HRQoL is indeed multidimensional. Our method of including only those scales and items in primary analyses which are considered most important for brain tumor patients, only reflects the group level and does not address which scales or items are important for the individual patient. An approach to better study (changes in) the individual defined HRQoL, might be to create a weighted sum score, in which the most important aspects of HRQoL for an individual patient contribute to a higher degree of the 'overall' HRQoL score than less important aspects.

Different aspects of the tumor were found to be associated with changes in HRQoL over time. That is, larger tumor volumes resulted in lower mean scores of physical and self-perceived cognitive functioning over the six month follow-up period. Intracranial progression of brain metastases was only associated with a significant and clinically relevant deterioration of motor dysfunction. At the individual level, no associations between intracranial progression or systemic activity and change in HRQoL scales were observed. Similarly, in a previous study on brain metastases, no association between intracranial recurrence and worsening of HRQoL was found.²⁹ The robust association between intracranial progression and HRQoL decline seen in glioma patients³⁷ might be less clear in brain metastases patients because many of the newly detected lesions on MRI are asymptomatic.

Radiotherapy and chemotherapy

Long-term effects of anti-tumor treatment on HRQoL was assessed in our sample of anaplastic glioma survivors (**chapter 5**). In this study, we found HRQoL at a mean of 12 years after diagnosis to be relatively stable in progression-free patients compared to their 2.5 years post-treatment evaluation, and not different between patients treated with radiotherapy alone or radiotherapy combined with chemotherapy. Although this finding may be the result of the analytical approach, i.e. on group level only, it is also likely that other factors do contribute to a decline in HRQoL. Indeed, in patients with tumor progression, we observed lower HRQoL. This finding is in line

with earlier studies,^{37,38} in which the occurrence of progression was found to be the main reason for a deterioration in HRQoL.

We also examined the association between NCF and HRQoL in our study on long-term anaplastic glioma survivors (**chapter 5**). Worse NCF was weakly to moderately correlated with self-reported lower physical functioning, social functioning and future uncertainties, but not with global health status or other HRQoL scales and items. Previously, a strong correlation between NCF and HRQoL, including physical, mental and disease-specific aspects, was found in low-grade glioma patients, although both NCF and HRQoL were relatively mildly affected.³⁹ In another glioma sample, it was found that verbal learning predicted general well-being scores and disease-specific symptoms, processing speed predicted social well-being scores, and executive functioning predicted functional well-being scores, assessed by the FACT-General and Brain module.⁴⁰ Also correlations between NCF and HRQoL have been observed in a heterogeneous sample of brain tumor patients.⁴¹ Explanations why we did not find such strong associations are the small sample size, and because in our sample a part of the patient group did show such severe neurocognitive impairments that these patients might have not been able to adequately fill in the self-report HRQoL questionnaires. Besides that, perhaps NCF does directly influence aspects of HRQoL, such as social functioning and more complex or instrumental activities of daily living, but does not directly affect other aspects of HRQoL, such as impairments in physical functioning or basic activities of daily living. This hypothesis is partly supported by the results of an RCT on the effect of a cognitive rehabilitation program on NCF and HRQoL: although rehabilitation had a positive effect on objective cognitive functioning after six months, only subjective mental fatigue improved too, while overall HRQoL did not.⁴²

The impact of neurocognitive outcomes on clinical decision-making

As most brain tumor patients cannot be cured, treatment focusses on prolonging survival in the best possible condition. For this, NCF is an important outcome measure, reflecting the capabilities to function independently in daily life. Neurocognitive outcomes can therefore be used in evaluating the net clinical benefit of a specific treatment, balancing survival against impact of treatment on patients' functioning. To determine the net clinical benefit of a treatment on group level in a clinical trial, it is necessary to have all available (neurocognitive) information, reported in a clear and complete way. In our systematic review (**chapter 8**), we found that of the 65 RCTs performed in patients with brain tumors and including information on NCF, only 20 (31%) satisfied a sufficient number of criteria to be classified as 'high-quality' level of reporting of neurocognitive outcome evidence. Not surprisingly, the level of reporting was more often classified as 'high-quality' in RCTs using neurocognitive outcomes as primary endpoint (57%) than in studies using neurocognitive outcomes

as secondary endpoint (23%), since there is more space available for reporting on neurocognitive outcomes in a manuscript not focusing on other outcomes. Moreover, most of these high-quality reporting studies did contribute to clinical decision-making, by providing information on the limited impact of a favorable treatment in terms of survival on NCF, or on a favorable impact on NCF of one of two treatments with comparable survival.

It is a major limitation though, that most studies are limited in providing NCF information for clinical decision making, as the majority (69%) of RCTs did not meet the criteria for high-quality reporting and 40% of studies only included cognitive screening instruments. To incorporate results on NCF in clinical decision-making, more extensive test batteries and better reporting of the outcomes are necessary. It is promising though that more recent trials did make use of more comprehensive test batteries, satisfying criteria as measuring the relevant neurocognitive functions, use of tests sensitive to change, and availability of parallel test versions.⁴³⁻⁴⁵

Discussion of methodological limitations

Testing NCF and HRQoL in brain tumor patients is accompanied by different methodological challenges, related to the patient group, the study design and the type of assessments.

Limitations related to the patient group

Having a brain tumor is a serious illness with poor prognosis. Some patients have a poor condition or are affected by severe neurological or cognitive impairments and could therefore not be included in our research. As a result, a bias could exist towards the inclusion of a highly selected patient group, which have better NCF. This will lead to an underestimation of the actual neurocognitive impairment in this patient population. The same is true for drop-out and missing data during the study period: after primary treatment or throughout the disease course some patients deteriorated neurologically and/or cognitively in such a way that they were not able to participate in the post-treatment or follow-up assessments. In some patients, this resulted in missing data (missing scores because tests or questionnaires could not be (completely) administered at the prespecified time point) or even in drop-out (the patient was no longer assessed). Again, this might have resulted in an underestimation of neurocognitive decline after treatment. Various statistical methods exist to deal with missing data,⁴⁶ all which have advantages and disadvantages. In our study on SRT patients we used linear mixed models to impute missing values based on the pattern/mean of obtained values. By using this model, changes over time can be analysed in a sophisticated way, but it requires more computations to meet the necessary

requirements.⁴⁷ In the studies with only pre- and post-operative assessment and in the studies in which we studied the individual patient level, imputation is not preferred, thereby accepting a possible selection bias.

Limitation related to study design

In this thesis we only used observational study designs, both cross-sectional (chapter 5 and 6) and longitudinal (chapter 2, 3, 4, and 7), but no randomized controlled designs. In a cross-sectional study design, correlational, but no causal, relationships between NCF and treatment or brain tumor related characteristics could be examined, and no changes over time could be assessed. Although this is possible in longitudinal designs, it would be more informative to study NCF and HRQoL in a randomized controlled design. For example, evaluating (change in) NCF in brain metastatic patients treated with WBRT vs SRT could result in finding causal relationships and thereby more robust information on NCF. However, because of ethical considerations, this type of RCT cannot be performed in all situations.

Limitations related to type of assessment

Although informative and content covering, neurocognitive testing and HRQoL assessment result in many (subtest/scale) scores. When analyzing these scores separately, many statistical tests are required, resulting in a higher chance of type I error (rejection of a true null-hypothesis). To reduce this chance, and because of clarity, we chose to combine scores for different neurocognitive subtests into domains. However, this method might result in missing relevant outcomes, and multiple testing was not eliminated completely. Depending on the study question, a more detailed analysis of all specific subtest scores, or a combination of subtest scores, might be preferable. That is, when studying the impact of a treatment on specific aspects of a neurocognitive function, the use of detailed subtest scores may be preferred, while in a study on the impact of tumor or treatment on NCF in general, combination of test scores seems preferred. For the EORTC QLQ-C30 questionnaire, the categorization into functioning and symptom scales, covering multiple questions (range 2-5), is well-known. However, together with the symptom scales and single items, a total of 13 scales/items are available for analysis. With the inclusion of the QLQ-BN20, an additional 11 scales/items could be analyzed. Again, to reduce type I error, several scales were selected for primary analysis. We chose to include scales most relevant to brain tumor patients, also based on earlier results,²⁹ and decided to analyze the other scales only in an explorative way.

Another problem with combining neurocognitive outcomes, is that no consensus exists on how each test or subtest should be best grouped into a particular domain. For example, verbal memory tests are not only linked to memory, but also to information processing speed and attention, and for substitution tests not only information

processing speed but also attention and memory are required.⁴⁸ Although we made a categorization also used by others,^{34,49,50} combining subtest scores in a different way might lead to different outcomes.

A related issue to the use of neurocognitive tests and HRQoL questionnaires is defining change over time. Statistically significant changes were studied in chapter 3, which provided information about differences in the patient's scores in comparison to scores of the general population. However, a statistically significant difference does not provide information if this is also a clinically meaningful difference. Similarly, a change over time can be statistically significant, but not clinically meaningful, i.e. "change that results in meaningful reduction of symptoms or improvement in functioning".⁵¹ It is under debate what kind of change in test scores is necessary to obtain such a clinical meaningful change. In this thesis, we followed standard clinical neuropsychology practices, by defining a clinically relevant change as ≥ 1.5 standard deviation for NCF,⁴⁹ and ≥ 10 points for scales/items of HRQoL questionnaires.⁵² Another way of measuring NCF over time is the use of a reliable change index (RCI), which has indeed been used in a number of brain tumor trials.^{53,54}

Finally, we did not assess factors such as fatigue and depression in a systematic way, while these do frequently occur in brain tumor patients.^{55,56} As these factors can confound the relationship between tumor or treatment on the one hand and NCF on the other, it would be of interest to take fatigue and mood disorders into account. However, assessing these issues with patient-reported outcomes leads to an even higher burden for the patients, which might result in higher drop-out rates. We decided to decrease the burden as much as possible and to focus on NCF, thereby taking these limitations for granted.

Practical implications

The results of this thesis lead to some practical recommendations for further research and clinical care. That is, proper assessment, reporting and interpretation of results of neurocognitive tests and HRQoL assessment is of importance. In clinical trials evaluating new treatments, a standard neurocognitive test protocol with objective tests is preferred, covering all relevant cognitive functions for this patient group. This holds especially true for patients with low- and high-grade glioma with relatively good survival. In GBM patients, with poor survival, repeated standard neurocognitive testing might be more complicated as the costs (e.g. burden) might outweigh the benefits, and should therefore only be incorporated in case of specific research questions. Although a neurocognitive test protocol might be more difficult to incorporate in trials when compared to screening instruments, the outcomes are more valuable for use in clinical decision-making as they provide more detailed

information. Recently a short standardized protocol is incorporated in clinical trials with NCF as secondary outcome,^{44,45,57-59} however, not all cognitive domains relevant for brain tumor patients are included. That is, we, and others, found attention^{2,60} and working memory^{61,62} to be impaired in a substantial part of patients and these are not assessed in the standard protocol.⁴⁴ To date, no consensus exists which test(s) could be added to better study all important neurocognitive functions. One proposal for the use of standardized test batteries is to complement a concise test protocol, which encompasses a minimal set of tests necessary to evaluate relevant cognitive domains, with various standardized sets of neuropsychological tests when more detailed aspects of NCF are investigated. Also, consensus should be reached regarding the way test scores should be combined into neurocognitive domain scores. To accomplish this, these topics could be discussed in international neuro oncology groups such as the RANO. Finally, better reporting of neurocognitive outcomes is necessary, because only then this information can be adequately interpreted and incorporated by clinicians in brain tumor care.

In clinical practice it is required to balance the desirable information obtained by neuropsychological tests against the burden for patients. To minimize this burden, again it would be valuable to minimize the standard test protocol as much as possible, and to extend this in a standardized way in individual patients when specific neurocognitive complaints or impairments are suspected. Especially patients vulnerable for neurocognitive impairments and lower HRQoL, such as patients with large tumor volume, tumors located in the left hemisphere or surgically treated tumors in the right hemisphere as found in our studies, should be regularly evaluated during their disease trajectory to offer optimal care. The same can be recommended for relatively young patients or patients with long survival, as even mild neurocognitive impairments might negatively impact their functioning at work and in social roles.

Future directions

The studies described in this thesis have contributed to a better understanding of NCF and HRQoL in patients with different types of brain tumors, both at the short- and long-term. The tumor itself has a large impact on NCF, while treatment with surgery, radiotherapy and chemotherapy does not seem to result in additional neurocognitive deterioration at the short-term at group level. However, subgroups of patients, such as patients with right-sided (frontal) tumors and patients at long-term follow-up, seem vulnerable to post-treatment neurocognitive decline. HRQoL is affected by the tumor itself, while treatment also has a negative impact on several HRQoL domains on group level. At the individual patient, most patients experience both a deterioration and improvement in the different HRQoL domains. Moreover, an

association between worse NCF and lower HRQoL was found.

The ultimate goal of treatment of brain tumor patients is to improve or maintain patients' functioning and wellbeing while prolonging survival. To reach this goal, we should improve our knowledge at different levels. First, better understanding of the pathophysiology of brain tumors and its treatment is warranted. That is, knowing better which tumor-related aspects (volume, grading, molecular aspects and genetic mutations) play an important role in cognitive impairments may help in identifying strategies to prevent or treat these impairments. To shed more light on this, a new follow-up assessment of the patients with anaplastic oligodendroglioma survivors included in this thesis, has recently been initiated. With information at even longer follow-up, together with more specific tumor characteristics (e.g. genetic factors) obtained by improved techniques, it might be possible to better understand the different tumor aspects related to NCF. But also considering other genetic factors⁶³ or patients' characteristics which are known to impact neurocognitive functioning, such as diabetes, could be relevant to determine the risk of a patient to develop neurocognitive impairments. Better understanding of the impact of a specific treatment on the pathophysiology of a tumor might also be helpful to prevent neurocognitive impairments. For example, in recent years the suggestion has been made to spare the hippocampus when giving (whole brain) radiotherapy. By doing this, memory functions and HRQoL of brain metastatic patients were found to be preserved at six months follow-up compared to historical controls.⁶⁴ On the other hand, NCF, which encompasses more than memory, might be more widespread in larger brain networks. Sparing only the hippocampus does not result in sparing of these networks and other neurocognitive functions.

Second, neurocognitive impairments and impaired HRQoL may be prevented by optimizing treatment techniques or developing new techniques. Recently, proton therapy, a form of radiotherapy in which radiation is more focused on the tumor tissue resulting in lower radiation to surrounding healthy tissue, is now being studied.¹² Although Sherman et al. (2016) included only a small sample, they found that five years after proton therapy, NCF was preserved. In addition, targeted therapy has gained interest in the treatment of glioma and brain metastases, as this might lead to more individualized and focused treatment compared to chemotherapy, thereby preventing possible damage to white matter structures and hippocampus at the long-term.⁶⁵⁻⁶⁸ However, currently no data on neurocognitive outcomes after targeted therapy for brain tumors are available.

Third, in case of neurocognitive impairments or impaired HRQoL, treatment should be available to manage or improve these impairments. This can be accomplished by discussing HRQoL outcomes with the patient in clinical care, and providing treatment focused on the patient's main HRQoL impairments, e.g. physiotherapy in case of physical complaints, or a graded activity program to handle fatigue. For

neurocognitive impairments, tailored advice provided by a neuropsychologist, or by participating in cognitive rehabilitation programmes.⁴² To date however, only a few programs have been studied, and although results were promising, these are not yet implemented in clinical care. In order to provide patients adequate tailored psychological care and cognitive rehabilitation, a neuropsychologist should be part of the multidisciplinary tumor board. Although use of medication to improve neurocognitive impairments was hopeful, different drugs have found not to result in better (neurocognitive) functioning.⁶⁹⁻⁷¹ Finally, it is necessary to get more insight in the complex interactions between neurocognitive functioning, fatigue, mood disorders and HRQoL. With this information, specific psychological and/or cognitive interventions aimed at improving these different aspects can be better developed and incorporated into more tailored care.

References

1. Holly KS, Barker BJ, Murcia D, et al. High-grade Gliomas Exhibit Higher Peritumoral Fractional Anisotropy and Lower Mean Diffusivity than Intracranial Metastases. *Front Surg*. 2017;4:18.
2. van Loenen IS, Rijnen SJM, Bruijn J, Rutten GM, Gehring K, Sitskoorn MM. Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma. *World Neurosurg*. 2018; 117:e172-e179.
3. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro Oncol*. 2016;18(12):1656-1663.
4. Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol*. 2010;97(1):89-94.
5. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery*. 2007;60(2):277-283; discussion 283-274.
6. Gerstenecker A, Nabors LB, Meneses K, et al. Cognition in patients with newly diagnosed brain metastasis: profiles and implications. *J Neurooncol*. 2014;120(1):179-185.
7. Satoer D, Vork J, Visch-Brink E, Smits M, Dirven C, Vincent A. Cognitive functioning early after surgery of gliomas in eloquent areas. *J Neurosurg*. 2012;117(5):831-838.
8. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol*. 2011;103(3):541-549.
9. Boone M, Roussel M, Chauffert B, Le Gars D, Godefroy O. Prevalence and profile of cognitive impairment in adult glioma: a sensitivity analysis. *J Neurooncol*. 2016;129(1):123-130.
10. Wu AS, Witgert ME, Lang FF, et al. Neurocognitive function before and after surgery for insular gliomas. *J Neurosurg*. 2011;115(6):1115-1125.
11. Yoshii Y, Tominaga D, Sugimoto K, et al. Cognitive function of patients with brain tumor in pre- and postoperative stage. *Surg Neurol*. 2008;69(1):51-61.
12. Sherman JC, Colvin MK, Mancuso SM, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. *J Neurooncol*. 2016;126(1):157-164.
13. Petersen SE, Posner MI. The attention system of the human brain: 20 years after. *Annu Rev Neurosci*. 2012;35:73-89.
14. Raz A. Anatomy of attentional networks. *Anat Rec B New Anat*. 2004;281(1):21-36.
15. Corbetta M, Ramsey L, Callejas A, et al. Common behavioral clusters and subcortical anatomy in stroke. *Neuron*. 2015;85(5):927-941.
16. Murakami T, Hama S, Yamashita H, et al. Neuroanatomic pathway associated with attentional deficits after stroke. *Brain Res*. 2014;1544:25-32.
17. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys*. 2007;68(5):1388-1395.
18. Caissie A, Nguyen J, Chen E, et al. Quality of life in patients with brain metastases using the EORTC QLQ-BN20+2 and QLQ-C15-PAL. *Int J Radiat Oncol Biol Phys*. 2012;83(4):1238-1245.
19. Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FS. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *J Natl Cancer Inst*. 2006;98(23):1742-1745.
20. Collins B, MacKenzie J, Tasca GA, Scherling C, Smith A. Cognitive effects of chemotherapy in breast cancer patients: a

- dose-response study. *Psychooncology*. 2013;22(7):1517-1527.
21. Hom J, Reitan RM. Neuropsychological correlates of rapidly vs. slowly growing intrinsic cerebral neoplasms. *J Clin Neuropsychol*. 1984;6(3):309-324.
 22. Kayl AE, Meyers CA. Does brain tumor histology influence cognitive function? *Neuro Oncol*. 2003;5(4):255-260.
 23. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol*. 2017;134(1):9-18.
 24. Miotto EC, Junior AS, Silva CC, et al. Cognitive impairments in patients with low grade gliomas and high grade gliomas. *Arq Neuropsiquiatr*. 2011;69(4):596-601.
 25. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro Oncol*. 2015;17(4):580-587.
 26. Kesler SR, Noll K, Cahill DP, Rao G, Wefel JS. The effect of IDH1 mutation on the structural connectome in malignant astrocytoma. *J Neurooncol*. 2017;131(3):565-574.
 27. van Dellen E, Douw L, Hillebrand A, et al. MEG network differences between low- and high-grade glioma related to epilepsy and cognition. *PLoS One*. 2012;7(11):e50122.
 28. Taphoorn MJ, van den Bent MJ, Mauer ME, et al. Health-related quality of life in patients treated for anaplastic oligodendroglioma with adjuvant chemotherapy: results of a European Organisation for Research and Treatment of Cancer randomized clinical trial. *J Clin Oncol*. 2007;25(36):5723-5730.
 29. Soffietti R, Kocher M, Abacioglu UM, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013;31(1):65-72.
 30. Steinmann D, Paelecke-Habermann Y, Geinitz H, et al. Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. *BMC Cancer*. 2012;12:283.
 31. Onodera S, Aoyama H, Tha KK, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. *J Neurooncol*. 2014;120(2):311-319.
 32. Minniti G, Esposito V, Clarke E, et al. Stereotactic radiosurgery in elderly patients with brain metastases. *J Neurooncol*. 2013;111(3):319-325.
 33. Kirkpatrick JP, Wang Z, Sampson JH, et al. Defining the optimal planning target volume in image-guided stereotactic radiosurgery of brain metastases: results of a randomized trial. *Int J Radiat Oncol Biol Phys*. 2015;91(1):100-108.
 34. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol*. 2009;8(9):810-818.
 35. Klein M, Heimans JJ, Aaronson NK, et al. Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet*. 2002;360(9343):1361-1368.
 36. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol*. 2013;31(3):337-343.
 37. Bosma I, Reijneveld JC, Douw L, et al. Health-related quality of life of long-term high-grade glioma survivors. *Neuro Oncol*. 2009;11(1):51-58.
 38. Taphoorn MJ, Henriksson R, Bottomley A, et al. Health-Related Quality of Life in a Randomized Phase III Study of Bevacizumab, Temozolomide, and Radiotherapy in Newly Diagnosed Glioblastoma. *J Clin Oncol*. 2015;33(19):2166-2175.

39. Boele FW, Zant M, Heine EC, et al. The association between cognitive functioning and health-related quality of life in low-grade glioma patients. *Neurooncol Pract.* 2014;1(2):40-46.
40. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psychooncology.* 2017;26(5):617-624.
41. Ownsworth T, Dwan T, Chambers S, Walker DG, Shum DH. The moderating effect of estimated pre-morbid IQ on the relationship between neuropsychological status and subjective well-being after brain tumour. *J Psychosom Res.* 2014;76(3):257-260.
42. Gehring K, Sitskoorn MM, Gundy CM, et al. Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. *J Clin Oncol.* 2009;27(22):3712-3722.
43. Klein M, Duffau H, De Witt Hamer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. *J Neurooncol.* 2012;108(2):309-318.
44. Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol.* 2013;14(10):e407-e416.
45. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol.* 2011;12(7):703-708.
46. Eekhout I, de Boer RM, Twisk JW, de Vet HC, Heymans MW. Missing data: a systematic review of how they are reported and handled. *Epidemiology.* 2012;23(5):729-732.
47. Molenberghs G, Verbeke G. A review on linear mixed models for longitudinal data, possibly subject to dropout. *Statistical Modelling.* 2001;1:235-269.
48. Wechsler D. *Wechsler Adult Intelligence Scale III, [Dutch revision. Technical Manual].* Lisse2000.
49. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment.* Vol 4. New York: Oxford University Press; 2004.
50. Meyers CA, Cantor SB. Neuropsychological assessment and treatment of patients with malignant brain tumors. In: Prigatano GP, Pliskin NH, eds. *Clinical neuropsychology and cost outcome research, a beginning.* New York: Psychology Press, Inc.; 2003:159-173.
51. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol.* 2003;56(5):395-407.
52. Osoba D, Aaronson NK, Muller M, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. *Qual Life Res.* 1996;5(1):139-150.
53. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. *Neuro Oncol.* 2003;5(2):89-95.
54. Wefel JS, Cloughesy T, Zazzali JL, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. *Neuro Oncol.* 2011;13(6):660-668.
55. Struik K, Klein M, Heimans JJ, et al. Fatigue in low-grade glioma. *J Neurooncol.* 2009;92(1):73-78.
56. Rooney AG, Carson A, Grant R. Depression in cerebral glioma patients: a systematic review of observational studies. *J Natl Cancer Inst.* 2011;103(1):61-76.
57. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* 2011;12(6):583-593.
58. Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. *Neuro Oncol.* 2011;13(3):353-361.
59. Klein M, De Witt Hamer PC. Neurocognitive outcome and resective brain tumor surgery in adults. In: Duffau H, ed. *Brain mapping:*

- from neural basis of cognition to surgical applications. Vol 1. New York; 2011.
60. Ruge MI, Ilmberger J, Tonn JC, Kreth FW. Health-related quality of life and cognitive functioning in adult patients with supratentorial WHO grade II glioma: status prior to therapy. *J Neurooncol.* 2011;103(1):129-136.
 61. Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. *J Neurooncol.* 2007;81(3):305-313.
 62. Mu YG, Huang LJ, Li SY, et al. Working memory and the identification of facial expression in patients with left frontal glioma. *Neuro Oncol.* 2012;14 Suppl 4:iv81-89.
 63. Liu Y, Zhou R, Sulman EP, et al. Genetic Modulation of Neurocognitive Function in Glioma Patients. *Clin Cancer Res.* 2015;21(14):3340-3346.
 64. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol.* 2014;32(34):3810-3816.
 65. Nolen SC, Lee B, Shantharam S, et al. The effects of sequential treatments on hippocampal volumes in malignant glioma patients. *J Neurooncol.* 2016;129(3):433-441.
 66. de Blank PM, Berman JI, Fisher MJ. Systemic Chemotherapy and White Matter Integrity in Tracts Associated with Cognition Among Children With Neurofibromatosis Type 1. *Pediatr Blood Cancer.* 2016;63(5):818-824.
 67. Lin L, Cai J, Jiang C. Recent Advances in Targeted Therapy for Glioma. *Curr Med Chem.* 2017;24(13):1365-1381.
 68. Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. *Ann Oncol.* 2016;27(12):2288-2294.
 69. Gehring K, Patwardhan SY, Collins R, et al. A randomized trial on the efficacy of methylphenidate and modafinil for improving cognitive functioning and symptoms in patients with a primary brain tumor. *J Neurooncol.* 2012;107(1):165-174.
 70. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* 2013;15(10):1429-1437.
 71. Boele FW, Douw L, de GM, et al. The effect of modafinil on fatigue, cognitive functioning, and mood in primary brain tumor patients: a multicenter randomized controlled trial. *Neuro Oncol.* 2013;15(10):1420-1428.

Appendix

Samenvatting

Samenvatting en discussie van de belangrijkste bevindingen

Het doel van dit proefschrift was om de kennis over het niveau van neurocognitief functioneren en van gezondheidsgerelateerde kwaliteit van leven (hierna voor de leesbaarheid 'kwaliteit van leven' genoemd) van patiënten met een primaire of secundaire hersentumor tijdens de ziekte te vergroten, en zo de behandeling en individuele patiëntzorg te verbeteren. In dit deel geven we een samenvatting en discussie van de belangrijkste bevindingen beschreven in dit proefschrift.

Invloed van de tumor op neurocognitief functioneren

Een belangrijke bevinding was dat een hoog percentage van patiënten neurocognitieve stoornissen had veroorzaakt door de tumor zelf, ongeacht het soort tumor. In onze studies met hooggradig glioompatiënten (n = 62; **hoofdstuk 2**) laag- en hooggradig glioompatiënten (n = 72; **hoofdstuk 6**) en patiënten met hersenmetastasen (n = 97; **hoofdstuk 3**), was de aanwezigheid van een hersentumor geassocieerd met cognitieve stoornissen. Al voor de start van de antitumorbehandeling had 79% van de patiënten met een glioom, en 53% van de patiënten met hersenmetastasen, last van klinisch relevante neurocognitieve stoornissen in tenminste één domein. Het lagere percentage neurocognitieve stoornissen bij patiënten met hersenmetastasen zou verklaard kunnen worden door het feit dat het mediane tumorvolume kleiner was in deze groep, en doordat hersenmetastasen, in tegenstelling tot gliomen, over het algemeen niet infiltreren in het omringende gezonde hersenweefsel. Het percentage cognitieve stoornissen bij glioompatiënten voorafgaand aan de operatie was vergelijkbaar met eerdere onderzoeken. Bij patiënten met hersenmetastasen was het percentage neurocognitieve stoornissen echter lager dan in eerdere studies, mogelijk als gevolg van verschillen in de samenstelling van de patiëntgroepen, de gebruikte tests en de gehanteerde afkappunten om een cognitieve stoornis te definiëren.

In overeenstemming met andere studies vonden wij dat de laagste scores werden

behaald op de domeinen verbaal geheugen en aandacht, en dat deze neurocognitieve functies het vaakst waren aangedaan voorafgaand aan de behandeling bij alle hersentumorpatiënten (**hoofdstuk 2, 3, 4 en 6**). Daarnaast hadden glioompatiënten vaak stoornissen in het werkgeheugen en executief functioneren (**hoofdstuk 2 en 6**), wat suggereert dat primaire hersentumoren voornamelijk neurocognitieve functies beïnvloeden waarbij meerdere hersengebieden betrokken zijn die grote netwerken vormen. Deze hypothese wordt ondersteund door onze bevindingen in de studie naar de associatie tussen neurocognitieve stoornissen en tumorlocatie, waar we aantoonen dat een groot frontoparietaal netwerk in de linker hemisfeer gerelateerd was aan de geobserveerde stoornissen in aandacht en executief functioneren (**hoofdstuk 6**). Tot slot vonden we bij patiënten met een tot drie hersenmetastasen ook relatief vaak een stoornis in visuoconstructieve vaardigheden (**hoofdstuk 3**), wat een negatieve invloed kan hebben op de ruimtelijke oriëntatie in het dagelijks leven. Deze neurocognitieve functie is eerder slechts sporadisch onderzocht in hersentumorpatiënten, met wisselende uitkomsten: zo is gevonden dat 19% van de glioompatiënten beperkt waren in visuoconstructie, terwijl anderen vonden dat 4-16% van de hooggradig glioompatiënten in dit domein een stoornis hadden.

Verschillende aspecten van de tumor kunnen het neurocognitief functioneren beïnvloeden. In dit proefschrift hebben we specifiek de invloed van de tumorlocatie, de tumorlast (zowel uitgedrukt in tumorvolume als in het aantal hersenlaesies), en de tumorgradering of groeisnelheid (gebaseerd op de vergelijking tussen laaggradige en hooggradige gliomen) onderzocht.

Tumorlocatie

We hebben gevonden dat gliomen in de linker hemisfeer vaker geassocieerd zijn met neurocognitieve stoornissen (**hoofdstuk 6**), zoals slechter verbaal geheugen, werkgeheugen en aandacht (**hoofdstuk 2**), dan tumoren in de rechter hemisfeer. De bevinding dat vooral patiënten met een linkszijdige tumor kwetsbaar zijn voor neurocognitieve stoornissen komt overeen met de resultaten van eerdere studies, en kan deels verklaard worden doordat we voornamelijk neurocognitieve tests hebben gebruikt die verbaal moeten worden afgenomen. Enigszins verrassend, en in tegenstelling tot andere onderzoeken, vonden we niet dat neurocognitieve stoornissen geassocieerd waren met gebieden in de rechter hemisfeer. Aandacht- en werkgeheugenstoornissen voor de operatie waren namelijk bijna uitsluitend geassocieerd met tumorlocaties in de linker hemisfeer. Wederom kan dit komen doordat in ons protocol geen spatiële aandachtstaken waren opgenomen, terwijl die vooral gebruikt worden in andere studies naar het aandachtnetwerk.

Tumorvolume

In onze steekproef van hooggradig glioompatiënten hadden patiënten met een grote tumor in de linker hemisfeer een slechter executief functioneren vergeleken met patiënten met een kleine tumor in deze hemisfeer (**hoofdstuk 2**). Een groter tumorvolume, maar niet het aantal hersenmetastasen, was ook geassocieerd met slechter neurocognitief functioneren (op het gebied van informatieverwerkingsnelheid) van patiënten met hersenmetastasen (**hoofdstuk 3**). Deze resultaten komen overeen met eerder onderzoek. Bovendien was intracraniele tumorprogressie, oftewel een toename in tumorvolume, geassocieerd met een verslechtering van het executief functioneren en van de motorische functie van patiënten met hersenmetastasen. Hoewel actieve systemische ziekte geen significante invloed had op het neurocognitief functioneren bij aanvang ('baseline') van onze studie, konden we helaas niet de invloed van extracraniele tumorprogressie tijdens de follow-up evalueren. Hierdoor konden we de mogelijke invloed van systemische chemotherapie op cognitie niet bestuderen, terwijl er bewijs is bij patiënten met borstkanker dat dit het neurocognitief functioneren negatief kan beïnvloeden. Een beperking van onze studies is dat we alleen tumorvolume zelf, en niet het volume van omgevend oedeem, hebben onderzocht, terwijl dit laatste het neurocognitief functioneren additioneel kan beïnvloeden als gevolg van ruimte-inname.

Tumorgradering/ groeisnelheid

De associatie tussen tumorgradering en de ernst van neurocognitieve stoornissen wordt al lange tijd onderzocht. Onderzoekers vonden dat patiënten met langzaam groeiende gliomen minder neurocognitieve stoornissen hadden dan patiënten met snelgroeiende tumoren. Deze onderzoekers corrigeerden echter niet voor de oudere leeftijd van de patiënten met snelgroeiende tumoren. Wanneer gecorrigeerd werd voor leeftijd, werden geen verschillen gevonden in neurocognitie tussen patiënten met een laaggradig en patiënten met een hooggradig glioom, wat overeenkomt met onze resultaten in de laag- en hooggradig glioompatiëntgroep (**hoofdstuk 6**). Deze kwestie staat echter nog altijd ter discussie, omdat een aantal andere onderzoekers vaker en ernstiger neurocognitieve stoornissen vonden bij patiënten met een hooggradig glioom, d.w.z. een snelgroeiende tumor, vergeleken met patiënten met een laaggradig glioom. Recent is gesuggereerd dat specifieke genetische markers de groeisnelheid van de tumor beter representeren, en daarmee neurocognitieve stoornissen, dan traditionele tumorgradering die uitsluitend gebaseerd is op de histopathologie. Zo zijn 'isocitraat dehydrogenase 1 wildtype' (IDH1-WT)-tumoren meer proliferatief en agressiever dan 'IDH1-mutante' (IDH1-M)-tumoren. Er is gevonden dat patiënten met IDH1-WT-tumoren inderdaad vaker cognitieve stoornissen hadden, en lagere scores op gebied van geheugen, verwerkingsnelheid, visuoconstructie, taal en executief functioneren, vergeleken met patiënten met

IDH1-M-tumoren. Men kan veronderstellen dat een hogere groeisnelheid resulteert in minder efficiënte hersennetwerken en minder tijd voor hersenplasticiteit om te compenseren voor functioneel verlies. Echter, in een studie waarin gebruik is gemaakt van magneto-encefalografie om functionele netwerken in laag- en hooggradig glioompatiënten te construeren, hadden patiënten met een laaggradig glioom veranderde netwerken die gecorreleerd waren met cognitieve stoornissen, terwijl de functionele netwerken van patiënten met een hooggradig glioom niet verschilden van gezonde controles. Toekomstig onderzoek moet meer inzicht geven in de vraag of functionele netwerken en genetische mutaties inderdaad gerelateerd zijn aan verschillen in het neurocognitief functioneren in glioompatiënten, en of netwerken en mutaties aan elkaar gerelateerd zijn.

Invloed van de tumor op kwaliteit van leven

In onze groep lange overlevers met een anaplastisch oligodendroglioom is de kwaliteit van leven voorafgaand aan de behandeling in een eerder onderzoek onderzocht. Deze onderzoekers vonden dat patiënten een aanzienlijk slechtere kwaliteit van leven hadden dan de gezonde populatie. Vergelijkbaar hiermee vonden wij dat patiënten met hersenmetastasen ook een lagere kwaliteit van leven hadden voorafgaand aan de behandeling (**hoofdstuk 3**). Dat wil zeggen dat er sprake was van statistisch en klinisch relevante lagere scores op geselecteerde kwaliteit van leven-schalen vergeleken met een normgroep. Andere onderzoekers vonden ook dat patiënten met hersenmetastasen voorafgaand aan de behandeling een slechtere kwaliteit van leven hadden. Op het individuele patiëntniveau had een grote meerderheid (89%) van onze patiënten klinisch relevante, en statistisch significante, lagere scores op tenminste één van de zes onderzochte kwaliteit van leven-schalen in vergelijking met de algemene populatie, waarbij fysiek functioneren het vaakst was aangedaan (57%) (**hoofdstuk 4**). Over het algemeen wijzen deze resultaten erop dat patiënten met hersenmetastasen al bij aanvang van de ziekte aangedaan zijn, waarschijnlijk veroorzaakt door zowel de systemische als intracraniele tumoren.

Invloed van anti-tumorbehandeling op neurocognitief functioneren

In dit proefschrift zijn ook de effecten van verschillende anti-tumorbehandelingen (operatie, stereotactische radiotherapie en gecombineerde radiotherapie en chemotherapie) op het neurocognitief functioneren onderzocht.

Operatie

In **hoofdstuk 2** en **7** werden laag- en hooggradig glioompatiënten voor en na de operatie op hun neurocognitief functioneren onderzocht, en deze pre- en postoperatieve resultaten werden vergeleken. De resultaten van deze studies

geven informatie over de morbiditeit van een operatie op de korte en middellange termijn. Op groepsniveau had na de operatie een lager percentage patiënten last van neurocognitieve stoornissen vergeleken met hun preoperatieve prestaties (respectievelijk 59% en 79%; **hoofdstuk 2**). Van de 39 patiënten met een hooggradig glioom verbeterde 49%, terwijl 23% verslechterde na een mediaan van 5 weken na de operatie (**hoofdstuk 2**). Veranderingen in cognitieve prestaties gedurende follow-up vergeleken met het preoperatieve niveau waren niet gerelateerd aan tumorkenmerken of de mate van resectie. In onze studie waarin voornamelijk laaggradig glioompatiënten werden geïncludeerd (n = 59, **hoofdstuk 7**), werd 12 maanden na de operatie vaker een cognitieve achteruitgang dan verbetering gezien (respectievelijk 42% en 17%). Opgemerkt dient te worden dat sommige patiënten additionele antitumorbehandeling kregen tijdens de follow-up. Het verschil tussen beide studies kan verklaard worden door verschillen in de duur van de follow-up, want met een gemiddelde follow-up van één jaar worden eventuele leereffecten gereduceerd, en andere behandelingen zoals radiotherapie kunnen ook hebben bijgedragen aan een achteruitgang in het neurocognitief functioneren. Andere factoren die mogelijk hebben bijgedragen aan deze verschillen zijn variaties in de mate van resectie of in de tumorlocatie. Beide aspecten zijn op een verfijndere manier gemeten in onze studie met voornamelijk laaggradig glioompatiënten dan in de studie met hooggradig glioompatiënten. Patiënten met tumoren in de rechter hemisfeer, voornamelijk gelokaliseerd in de frontale regio en het corpus callosum, bleken kwetsbaarder voor neurocognitieve achteruitgang na de operatie dan patiënten met tumoren in de linker hemisfeer (**hoofdstuk 7**). Het is mogelijk dat vooral bij patiënten met rechtszijdige tumoren schade aan essentiële neurale netwerken is opgetreden door de resectie, wat een neurocognitieve achteruitgang kan hebben veroorzaakt. Dit wijst erop dat niet (alleen) de locatie van de tumor, maar ook de functionele organisatie van neurocognitieve functies in hersennetwerken, een belangrijke factor kan zijn in het veroorzaken van neurocognitieve stoornissen. Een andere, methodologische, verklaring kan zijn dat patiënten met linkszijdige tumoren reeds voor de operatie meer aangedaan waren, waardoor er minder ruimte was om verder achteruit te gaan na de operatie, vergeleken met de preoperatief cognitief intacte patiënten met rechtszijdige tumoren.

Stereotactische radiotherapie

We hebben ook het kortetermijneffect van stereotactische radiotherapie (SRT) op het neurocognitief functioneren van patiënten met hersenmetastasen onderzocht. SRT bleek geen klinisch relevante invloed op het neurocognitief functioneren te hebben (**hoofdstuk 3**). In dit cohort van 97 patiënten was het neurocognitief functioneren op baseline slechter vergeleken met gezonde controles, maar bleef tijdens de zes maanden na SRT stabiel. Dit werd zowel op groepsniveau als op

individueel patiëntniveau gevonden (**hoofdstuk 4**), en komt overeen met andere studies naar SRT in patiënten met hersenmetastasen, waarin geen duidelijke cognitieve veranderingen zijn gevonden in de eerste maanden na behandeling. Mogelijke verklaringen voor dit stabiele neurocognitief functioneren kunnen zijn dat SRT een zeer gerichte behandeling is, waardoor omringend gezond hersenweefsel niet wordt aangetast, er overwegend relatief kleine tumorvolumes werden behandeld met SRT, en, vermoedelijk het belangrijkste, de duur van de follow-up kort was. Mogelijk heeft radiotherapie voornamelijk op de lange termijn nadelige effecten op het neurocognitief functioneren, zoals is gevonden bij patiënten met een laaggradig glioom zes en 12 jaar na de behandeling met radiotherapie. Dit is echter veel minder relevant voor de meerderheid van patiënten met hersenmetastasen, omdat de overleving in deze groep vaak veel korter is dan in patiënten met laaggradig gliomen.

Radiotherapie en chemotherapie

In **hoofdstuk 5** konden we de langetermijneffecten van behandeling op het neurocognitief functioneren in 32 patiënten met een anaplastisch glioom bestuderen. Deze studie liet geen verschil in cognitie zien tussen patiënten die radiotherapie kregen en patiënten die een gecombineerde behandeling met radiotherapie en aanvullende chemotherapie kregen. De variatie in neurocognitieve prestaties was echter groot in deze groep, waarbij 26% van de patiënten geen neurocognitieve beperkingen hadden, terwijl 30% aan ernstige neurocognitieve stoornissen in verscheidende domeinen leed. Helaas was deze groep te klein om voorspellers van neurocognitieve stoornissen te identificeren. Waarschijnlijk was tumorrecidief verantwoordelijk voor ernstiger stoornissen. Een andere verklaring kan zijn dat er verschillen bestonden in het genetische profiel van de tumoren, dat in deze populatie niet bepaald was. Eerder is gevonden dat IDH-WT-patiënten meer neurocognitieve stoornissen hebben dan patiënten met IDH-M-tumoren. Er zijn weinig data over het neurocognitief functioneren op de lange termijn van patiënten met een anaplastisch glioom. In een eerder onderzoek wezen de resultaten op een stabiele score op het screeningsinstrument 'Mini Mental Status Examination' (MMSE) in langetermijnoverlevers met een progressievrij anaplastisch glioom, terwijl progressieve ziekte geassocieerd was met een daling in de MMSE-score. Dat deze onderzoekers geen grote variatie in neurocognitief functioneren vonden in (progressievrije) langetermijnoverlevers, kan komen doordat de MMSE een ongevoelig instrument is om veranderingen in cognitie te meten.

Invloed van antitumorbehandeling op kwaliteit van leven

Stereotactische radiotherapie

Niet alleen was de neurocognitieve prestatie van patiënten met een tot drie hersenmetastasen na SRT relatief stabiel, op groepsniveau was de kwaliteit van leven ook stabiel in de zes maanden na behandeling, behalve dat er een achteruitgang

in fysiek functioneren en vermoeidheid werd gezien (**hoofdstuk 3**). Twee eerdere studies bij patiënten met hersenmetastasen lieten wisselende resultaten zien met betrekking tot veranderingen in kwaliteit van leven in de eerste drie maanden na radiotherapie vergeleken met baseline, met zowel verbetering als verslechtering in verschillende kwaliteit van leven-schalen, inclusief globale gezondheidsstatus, fysiek functioneren, vermoeidheid, motorische problemen en communicatieproblemen. Echter, in beide studies kreeg slechts een minderheid van de patiënten uitsluitend SRT, en zijn er geen separate resultaten beschikbaar van deze subgroep.

In tegenstelling tot de stabiele scores in kwaliteit van leven op groepsniveau, liet onze studie zien dat er grote verschillen waren op individueel patiëntniveau (**hoofdstuk 4**). Ten eerste werden zowel verbeteringen als verslechteringen over de tijd gezien in verschillende schalen en items. Als een vergelijkbaar aantal patiënten verbetert en verslechtert, worden de scores uitgemiddeld en is het resultaat een 'stabiele' score, zoals ook de analyse op groepsniveau liet zien. Op patiëntniveau werd echter gevonden dat de meeste patiënten zowel een klinisch relevante achteruitgang als een verbetering ervoeren in hun kwaliteit van leven. De reden dat we verschillen vonden op de verschillende schalen en items kan verklaard worden door het feit dat in de analyse op groepsniveau gemiddelde scores zijn gebruikt, terwijl we op individueel niveau hebben gekeken naar het percentage patiënten dat achteruitging, stabiel bleef of verbeterde op de verschillende schalen/items. Bovendien werden op patiëntniveau alle schalen tegelijk geanalyseerd, omdat een patiënt alle symptomen kan ervaren. Deze manier van analyse geeft daardoor additionele informatie over de invloed van behandeling op verschillende aspecten van de kwaliteit van leven voor een individuele patiënt, en benadrukt dat het concept kwaliteit van leven inderdaad multidimensioneel is. Onze keuze om alleen die schalen in de primaire analyse te includeren die beschouwd worden als het belangrijkste voor hersentumorpatiënten, geeft alleen het belang op groepsniveau weer en houdt geen rekening met welke schalen of items belangrijk zijn voor de individuele patiënt. Een manier om (veranderingen in) de kwaliteit van leven op individueel niveau beter te onderzoeken zou kunnen zijn om een gewogen somscore te berekenen, waarin de belangrijkste aspecten van kwaliteit van leven voor een individuele patiënt meer bijdragen aan de 'totale' kwaliteit van leven-score dan minder belangrijke aspecten.

Verschiedende aspecten van de tumor bleken geassocieerd te zijn met veranderingen in kwaliteit van leven in de loop van de tijd. Zo resulteerden grotere tumorvolumes in lagere gemiddelde scores wat betreft fysiek functioneren en subjectief ervaren cognitief functioneren gedurende de zes maanden follow-up na behandeling. Intracraniële progressie van de hersenmetastasen was alleen geassocieerd met een significante en klinisch relevante achteruitgang in motorische problemen. Op individueel niveau werden geen associaties gezien tussen intracraniële progressie of systemische activiteit, en verandering in kwaliteit van leven. Ook in een eerder onderzoek

werd geen verband gevonden tussen een intracranieel recidief van hersenmetastasen en een verslechtering in kwaliteit van leven. De robuuste associatie tussen intracranieële progressie en een achteruitgang in kwaliteit van leven zoals gezien wordt bij glioompatiënten, is wellicht minder duidelijk bij patiënten met hersenmetastasen omdat veel van de nieuwe leases die op de MRI gezien worden asymptomatisch zijn.

Radiotherapie en chemotherapie

De langetermijneffecten van antitumorbehandeling (in dit geval radiotherapie en chemotherapie) op kwaliteit van leven werd beoordeeld in onze studie met patiënten die reeds lang bekend waren met een anaplastisch glioom (**hoofdstuk 5**). In dit onderzoek vonden we dat de kwaliteit van leven van progressievrije patiënten relatief stabiel bleef gemiddeld 12 jaar na diagnose, vergeleken met hun scores 2,5 jaar na de behandeling, en dat deze scores niet verschilden tussen patiënten die behandeld waren met uitsluitend radiotherapie of met radiotherapie gecombineerd met chemotherapie. Hoewel deze bevinding het resultaat kan zijn van de analytische benadering, d.w.z. alleen op groepsniveau, is het ook waarschijnlijk dat andere factoren bijdragen aan een achteruitgang in kwaliteit van leven. Zo vonden we een lagere kwaliteit van leven bij patiënten met tumorprogressie. Deze bevinding komt overeen met de resultaten van eerder onderzoek, waarin tumorprogressie de belangrijkste reden was voor een achteruitgang in de kwaliteit van leven.

We hebben ook de associatie tussen het neurocognitief functioneren en de kwaliteit van leven onderzocht in de groep langetermijnoverlevers met een anaplastisch glioom (**hoofdstuk 5**). Slechter neurocognitief functioneren was zwak tot matig gecorreleerd met een lager zelf-gerapporteerd fysiek functioneren, sociaal functioneren en onzekerheid over de toekomst, maar niet met globale gezondheidsstatus of andere kwaliteit van leven-schalen of -items. Eerder was een sterke associatie gevonden tussen het neurocognitief functioneren en kwaliteit van leven, inclusief fysieke, mentale en ziekte-specifieke aspecten, bij patiënten met laaggradig gliomen, hoewel zowel het neurocognitief functioneren als de kwaliteit van leven relatief beperkt waren aangedaan. Andere onderzoekers vonden dat het domein verbaal leren de algemene welzijnsscore en ziekte-specifieke symptomen voorspelde bij glioompatiënten, dat het domein verwerkingssnelheid het sociale welzijn van patiënten voorspelde, en het executief functioneren het functionele welzijn. Ook zijn er correlaties gevonden tussen het neurocognitief functioneren en de kwaliteit van leven in een heterogene groep hersentumorphatiënten. Verklaringen waarom wij geen sterke associaties vonden zijn de kleine onderzoeksgroep, en omdat in onze studie een deel van de patiënten zulke ernstige neurocognitieve stoornissen had dat deze patiënten mogelijk niet in staat waren om zelf de kwaliteit van leven-vragenlijsten adequaat in te vullen. Daarnaast kan het zijn dat het neurocognitief functioneren misschien direct invloed heeft op bepaalde aspecten van kwaliteit van leven, zoals het sociaal

functioneren en complexere (zogenaamde instrumentele) activiteiten van het dagelijks leven, maar andere aspecten niet direct beïnvloedt, zoals het fysiek functioneren of simpele (zogenaamde basis) activiteiten in het dagelijks leven. Deze hypothese wordt deels ondersteund door de resultaten van een eerder uitgevoerd gerandomiseerd onderzoek naar het effect van een cognitief revalidatieprogramma op het neurocognitief functioneren en de kwaliteit van leven: hoewel revalidatie een positief effect had op het objectief cognitief functioneren na zes maanden, was alleen subjectieve mentale vermoeidheid ook verbeterd, maar de globale kwaliteit van leven niet.

Invloed van neurocognitieve uitkomsten op klinische besluitvorming

Omdat de meeste hersentumorpatiënten niet kunnen worden genezen, richt de behandeling zich op het verlengen van de overleving in de best mogelijke conditie. Daarom is het neurocognitief functioneren een belangrijke uitkomstmaat, die de vaardigheden om onafhankelijk te functioneren in het dagelijks leven weergeeft. Neurocognitieve uitkomsten kunnen daarom worden gebruikt om het zogenaamde 'netto klinische voordeel' van een bepaalde behandeling te evalueren, waarbij een langere overleving afgewogen wordt tegen de mogelijke negatieve invloed van de behandeling op het functioneren van de patiënt. Om het netto klinische voordeel van een behandeling op groepsniveau in een klinische trial te bepalen, is het noodzakelijk om alle beschikbare (neurocognitieve) informatie te hebben, die op een duidelijke en volledige manier is gerapporteerd. In onze systematische review (**hoofdstuk 8**) vonden we dat van de 65 gerandomiseerde trials die zijn uitgevoerd bij patiënten met hersentumoren, en die informatie bevatten over het neurocognitief functioneren, slechts 20 (31%) voldeden aan voldoende criteria om te worden geclassificeerd als een 'hoogwaardig' rapportageniveau. Het is niet verrassend dat het niveau van rapporteren vaker geclassificeerd werd als hoogwaardig in trials die neurocognitieve uitkomsten als primair eindpunt gebruikten (57%) dan in trials die neurocognitieve uitkomsten als secundaire eindpunten gebruikten (23%), omdat er meer ruimte beschikbaar is voor het rapporteren van neurocognitieve uitkomsten in een manuscript dat zich niet op andere uitkomstmaten richt. Bovendien bleek dat de meeste van deze 'hoogwaardige' geclassificeerde studies bijdroegen aan de klinische besluitvorming, door informatie te verschaffen over de geringe invloed van een behandeling op het neurocognitief functioneren terwijl deze behandeling wel resulteerde in een betere overleving, of over een gunstige uitkomst op het neurocognitief functioneren van één van de twee onderzochte behandelingen met vergelijkbare overleving.

Het is echter een groot probleem dat de meeste studies niet in staat zijn om goede informatie te verschaffen omtrent het neurocognitief functioneren voor de klinische besluitvorming, aangezien de meerderheid (69%) van de gerandomiseerde trials niet aan de criteria voldeed voor hoogwaardige rapportage, en in 40% van de studies uitsluitend screeningsinstrumenten werden gebruikt om cognitie te meten. Om

resultaten over het neurocognitief functioneren te kunnen integreren in de klinische besluitvorming zijn uitgebreidere testbatterijen dan screeningsinstrumenten, en een betere rapportage van de uitkomsten, noodzakelijk. Het is echter wel veelbelovend dat de recentere trials gebruik maakten van meer veelomvattende testbatterijen, en daarmee voldeden aan criteria zoals het meten van de relevante neurocognitieve functies, het gebruik van tests die gevoelig zijn voor veranderingen, en het gebruik van tests waarvan parallelversies beschikbaar zijn.

List of publications

- Habets EJJ***, Hendriks EJ*, Taphoorn MJB, Douw L, Zwinderman AH, Vandertop WP, Barkhof F, De Witt Hamer PC, Klein M. Association between tumor location and neurocognitive functioning using tumor localization maps. *J Neurooncol*. 2019 Sep;144(3): 573-582. doi:10.1007/s11060-019-03259-z. *Equal contribution
- Habets EJJ**, Taphoorn MJB, Klein M, Vissers T, Dirven L. The level of reporting of neurocognitive outcomes in randomised controlled trials of brain tumour patients: A systematic review. *Eur J Cancer*. 2018 Sep;100:104-125. doi: 10.1016/j.ejca.2018.05.014.
- Van der Meulen M, Dirven L, **Habets EJJ**, van den Bent MJ, Taphoorn MJB, Bromberg JEC. Cognitive functioning and health-related quality of life in patients with newly diagnosed primary CNS lymphoma: a systematic review. *Lancet Oncol*. 2018 Aug;19(8):e407-e418. doi: 10.1016/S1470-2045(18)30356-5.
- Petersen MA, Aaronson NK, Arraras JL, Chie WC, Conroy T, Costantini A, Dirven L, Fayers P, Gamper EM, Giesinger JM, **Habets EJJ**, Hammerlid E, Helbostad J, Hjermstad MJ, Holzner B, Johnson C, Kemmler G, King MT, Kaasa S, Loge JH, Reijneveld JC, Singer S, Taphoorn MJB, Thamsborg LH, Tomaszewski KA, Velikova G, Verdonck-de Leeuw IM, Young T, Groenvold M; European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Group. The EORTC CAT Core-The computer adaptive version of the EORTC QLQ-C30 questionnaire. *Eur J Cancer*. 2018 Sep;100:8-16. doi: 10.1016/j.ejca.2018.04.016.
- Van der Meer PB*, **Habets EJJ***, Wiggendaad RG, Verbeek-de Kanter A, Lycklama À Nijeholt GJ, Zwinkels H, Klein M, Dirven L, Taphoorn MJB. Individual changes in neurocognitive functioning and health-related quality of life in patients with brain oligometastases treated with stereotactic radiotherapy. *J Neurooncol*. 2018 Sep;139(2):359-368. doi: 10.1007/s11060-018-2868-7. *Equal contribution
- Hendriks EJ*, **Habets EJJ***, Taphoorn MJB, Douw L, Zwinderman AH, Vandertop WP, Barkhof F, Klein M, De Witt Hamer PC. Linking late cognitive outcome with glioma surgery location using resection cavity maps. *Hum Brain Mapp*. 2018 May;39(5):2064-2074. doi: 10.1002/hbm.23986. *Equal contribution

- Dirven L, Taphoorn MJB, Groenvold M, **Habets EJJ**, Aaronson NK, Conroy T, Reijneveld JC, Young T, Petersen MA, on behalf of the EORTC Quality of Life Group. Development of an item bank for computerized adaptive testing of self-reported cognitive difficulty in cancer patients. *Neuro-Oncology Practice*. 2017 Sep;4(3):189-196.
- Habets EJ**, Dirven L, Wiggendaad RG, Verbeek-de Kanter A, Lycklama À Nijeholt GJ, Zwinkels H, Klein M, Taphoorn MJ. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. *Neuro Oncol*. 2016 Mar;18(3):435-44. doi: 10.1093/neuonc/nov186.
- Schilder C, **Habets E**, Rundervoort R. Neuropsychologische gevolgen bij een patiënte met de ziekte van Fahr: De rol van de basale ganglia bij het cognitief functioneren. *Tijdschrift voor Neuropsychologie* 2016 Mrt;11(1):78-89.
- Zwinkels H, Dirven L, Vissers T, **Habets EJJ**, Vos MJ, Reijneveld JC, van den Bent MJ, Taphoorn MJB. Prevalence of changes in personality and behavior in adult glioma patients: a systematic review. *Neuro-Oncology Practice*. 2016;3(4): 222-231. <https://doi.org/10.1093/nop/npv040>
- Habets EJ**, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir (Wien)*. 2014 Aug;156(8):1451-9. doi: 10.1007/s00701-014-2115-8.
- Habets EJ**, Taphoorn MJ, Nederend S, Klein M, Delgadillo D, Hoang-Xuan K, Bottomley A, Allgeier A, Seute T, Gijtenbeek AM, de Gans J, Enting RH, Tijssen CC, van den Bent MJ, Reijneveld JC. Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. *J Neurooncol*. 2014 Jan;116(1):161-8. doi: 10.1007/s11060-013-1278-0.
- Winkens I, Van Heugten CM, Wade DT, **Habets EJ**, Fasotti L. Efficacy of time pressure management in stroke patients with slowed information processing: a randomized controlled trial. *Arch Phys Med Rehabil*. 2009 Oct;90(10):1672-9. doi: 10.1016/j.apmr.2009.04.016.

Award

Adult Quality of Life Research Award, Society for NeuroOncology, 2014

Dankwoord

Mijn dank gaat als eerste uit naar alle patiënten die hebben deelgenomen aan de verschillende studies beschreven in dit proefschrift. Ik heb respect voor hun inzet voor ons onderzoek in een periode waarin zij geconfronteerd werden met een hersentumor.

Graag bedank ik mijn promotores prof. dr. Martin J.B. Taphoorn, prof. dr. Martin Klein en copromotor dr. Linda Dirven.

Beste Martin, ik ben je dankbaar voor de kans die je mij met dit onderzoeksproject hebt geboden en het vertrouwen dat jij vanaf het begin in me hebt gehad. Je geduld en prettige commentaar op mijn eerdere stukken, je vermogen om onderzoekers samen te brengen, en de manier waarop jij het kwaliteit van leven-onderzoek combineert met de zorg voor de patiënt, bewonder ik zeer.

Beste Martin, jouw kennis van de neuropsychologie is essentieel geweest voor de uitvoering van de studies in dit proefschrift. Het was altijd de moeite waard om voor besprekingen naar het Amsterdam UMC te reizen, want ik kwam er met veel nieuwe (onderzoeks)ideeën van terug.

Beste Linda, dank voor je grote betrokkenheid bij de totstandkoming van dit proefschrift. Dankzij jouw scherpe vragen, methodologische kennis en voortvarendheid heb je mij tot het einde weten te motiveren.

Daarnaast wil ik alle collega's die betrokken zijn geweest bij de beschreven studies bedanken. Hanneke, mede dankzij jou voelde ik me vanaf de eerste dag thuis in het HMC. Dank voor je steun, de gesprekken over onze beider projecten, en de gezelligheid tijdens congressen. Fred Kloet, Rob Walchenbach, Ruud Wiggeraad, Antoinette Verbeek, Geert Lycklama à Nijeholt, Pim van der Meer en Thomas Vissers, dank voor de prettige samenwerking rondom een aantal van de studies. Collega's van het Amsterdam UMC, in het bijzonder Eef Hendriks, Philip De Witt Hamer, Linda Douw

en Jaap Reijneveld, het was mooi om met jullie een brug te slaan tussen verschillende onderzoeksgebieden.

Collega's van de medische psychologie, dank voor jullie interesse in mijn onderzoek, en voor de fijne samenwerking op het gebied van de patiëntzorg.

Veel dank aan mijn vrienden voor de steun, gezelligheid en welkome afleiding. In het bijzonder Esther B. en Daphne voor jullie leuke spontane ideeën. Miriam, Esther I., Denise, Laura, Marcia en Debbie, bedankt voor alle gezellige etentjes door het land. Hopelijk volgen er nog veel weekendjes met aanhang en kinderen. Jorine, Faustine en Sabine, al bijna mijn hele leven voelt het prettig vertrouwd om bij jullie te zijn.

In het bijzonder dank ik mijn familie en schoonfamilie. Judith, Rachel en Joël, we zijn alle vier heel verschillend maar dat maakt het des te leuker wanneer we elkaar zien. Met Nezir, Michel en Nickie, en de kinderen, zijn de familieweekenden een prettige afleiding en goed voor fijne gesprekken.

Lieve papa en mama, dank voor de ruimte die jullie mij altijd hebben gegeven om mijn eigen keuzes te maken, en voor alles wat jullie nu nog voor ons doen. Naast heel veel meer, hebben jullie mij geleerd me te blijven verwonderen over de wereld om me heen. Tonnie, Math, Rémi en Steven, bedankt dat jullie, ondanks de afstand, betrokken zijn om te zorgen dat het thuis ook goed loopt.

Lieve Thomas en Wouter, jullie brengen zoveel vrolijkheid, we gaan samen nog veel leuke avonturen beleven! Liefste Philip, dankjewel voor je steun, aanmoediging, gevoel voor humor, openheid, zorgzaamheid en liefde; met jou is mijn wereld een stuk mooier!



Curriculum vitae

Esther Habets was born on June 22nd, 1983 in Vianen. After graduating from the Goois Lyceum in Bussum, Esther studied psychology at Maastricht University. In 2005 she obtained her doctoral degree in biological psychology, after which she started a Master's program in Clinical Neuropsychology at Utrecht University. She completed a clinical internship at the Department of Neuropsychology of the University Medical Center Utrecht, and a master thesis on tactile perception.

In 2007, she started working as a neuropsychologist at the Department of Neurology of the Haaglanden Medical Center (HMC; at that time named the Medical Center Haaglanden), at a 'Zorgvernieuwingsproject' (health care renewal project) under supervision of prof. dr. Martin J.B. Taphoorn. The aim was to improve care for brain tumor patients, including integration of neurocognitive assessments and counseling of patients in clinical care. In 2010, Esther started working as a neuropsychologist at the Department of Medical Psychology at the HMC. In the following years, she combined clinical patient care with research, including the work described in this thesis. In 2015 she started with the post-master education of 'Gezondheidszorgpsycholoog' (health-care psychologist) at the RINO institute Utrecht, which she completed in 2017. In April 2019, she started with the specialization training for Clinical Neuropsychologist at the RINO Utrecht.

Esther lives with her partner Philip Kerbusch and together they have two children.



