HHS Public Access

Author manuscript

Acta Oncol. Author manuscript; available in PMC 2020 May 01.

Published in final edited form as:

Acta Oncol. 2019 May ; 58(5): 745–752. doi:10.1080/0284186X.2018.1557786.

Long-term cognitive dysfunction after radiation therapy for primary brain tumors

Lene Haldbo-Classen[a], **Ali Amidi**[b], **Lisa M. Wu**[c], **Slavka Lukacova**[a], **Gorm von Oettingen**[d], **Hanne Gottrup**[e], **Robert Zachariae**[b], **Morten Høyer**[f]

[a]Department of Oncology, Aarhus University Hospital, Aarhus, Denmark;

[b]Department of Oncology and Department of Psychology and Behavioral Sciences, Unit for Psychooncology and Health Psychology, Aarhus University Hospital and Aarhus University, Aarhus, Denmark;

[c]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA;

[d]Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark;

[e]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark;

[f]Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Abstract

Background: The extent of radiation therapy (RT)-induced changes in cognitive function is unknown. RT with protons instead of photons spares the healthy brain tissue more and is believed to reduce the risk of cognitive dysfunction. There is modest knowledge on which parts of the brain we need to spare, to prevent cognitive dysfunction. To uncover which cognitive domains are most affected, we compared cognitive functioning in brain tumor patients treated with neurosurgery and RT with brain tumor patients treated with neurosurgery alone.

Methods: A cross-sectional study assessing cognitive function in 110 patients with a primary brain tumor grades I–III or medulloblastoma (grade IV) treated at Aarhus University Hospital (AUH), Denmark between 2006 and 2016. Two cohorts were established: a cohort of 81 brain tumor patients who had received neurosurgery followed by RT (RT+), and a cohort of 29 brain tumor patients who had only received neurosurgery (RT−). The patients underwent questionnaires and neuropsychological assessment with standardized tests.

Results: Mean age was 53.5 years with an average time since diagnosis of 7.3 years. Compared with normative data, lower average scores were observed for the entire group on domains concerning verbal learning and memory ($p < .001$), attention and working memory ($p < .001$), processing speed ($p < .001$), and executive functioning ($p < .001$). Compared to RT− patients, RT+ patients scored lower on domains concerning processing speed ($p = .04$) and executive function (p

CONTACT L. Haldbo-Classen lenhaldb@rm.dk Department of Oncology, Aarhus University Hospital, 8000 Aarhus C, Denmark.

Disclosure statement

No potential conflict of interest was reported by the authors.

= .05) and had higher impairment frequency on verbal fluency (p = .02) with 16% of patients exceeding 1.5 SD below normative data.

Conclusions: Our results indicate that treatment, including RT, for a primary brain tumor may have negative long-term impact on cognitive function, especially on processing speed and executive function.

Introduction

Radiation therapy (RT) plays an important role in the treatment of primary brain tumors, resulting in local control or prolonged progression-free survival for most patients with primary brain tumors [1,2]. RT may have a negative impact on cognitive functioning that can be deleterious to quality of life [1,3]. Cognitive dysfunction can be defined as impairment of one or more cognitive functions such as attention, memory, language and executive function [4]. The etiology of cognitive dysfunction in brain tumor patients is multifactorial and may be caused by the tumor itself, tumor-related epilepsy and treatment related factors such as neurosurgery, RT and chemotherapy [5]. Currently, knowledge about cognitive dysfunction following cranial radiation is limited and reported prevalence varies from 19% to 83% [3]. This variability could be explained by heterogeneity in cohort characteristics such as tumor-related variables (e.g., type, location, size) and patient demographics (e.g., age, educational level) [3]. Due to improvements in the treatment of brain tumors, prolonged survival and the relatively young age of patients at the time of diagnosis mean that other commonly occurring symptoms such as fatigue, sleep disturbance, depression, anxiety and stress have also drawn attention as they also impair quality of life [6–8].

In order to optimize current regimens and to take advantage of novel RT approaches for patients with brain tumors (e.g., intensity-modulated radiation therapy [IMRT] and proton therapy), a greater understanding of potential associations between RT and cognitive dysfunction is needed, including region-specific effects. Of particular importance is the hippocampus, which is an area of the brain related to learning and memory. Studies indicate that the hippocampus may be particularly sensitive to RT [1,9]. In recent years, RT of the hippocampus has drawn more attention due to its important function and because the use of novel RT techniques has made it possible to avoid or minimize hippocampal radiation [10,11]. Indeed, a study by Gondi et al. showed that the use of IMRT that avoided the hippocampus during whole brain RT was associated with preservation of memory and quality of life [12]. In addition, a positive dose–response relationship between hippocampal radiation dose and risk of cognitive decline has been observed [12]. However, the thresholds of the dose to the hippocampus and the cognitive effects are not clear [9,13]. In the present study, we aimed to compare long-term cognitive function in brain tumor patients who underwent neurosurgery and adjuvant RT to brain tumor patients who only underwent neurosurgery. We hypothesized that patients who had received RT would perform poorer on a test of verbal learning and memory as assessed by the Hopkins Verbal Learning Test revised (HVLT) [14] when compared to non-irradiated brain tumor patients, due to irradiation of hippocampal regions.

Methods

Study design and patients

In this cross-sectional study, we assessed cognitive functioning in 110 patients with a primary brain tumor grades I–III or medulloblastoma (grade IV) who underwent neurosurgery with or without adjuvant RT between 2006 and 2016 at Aarhus University Hospital (AUH), Denmark. Inclusion criteria were patients who: received a confirmed diagnosis of a primary brain tumor of grades I–III or medulloblastoma according to WHO 2016 guidelines [15]; were age 18 years or older; had a Karnofsky performance status of 60–100; were capable of undergoing cognitive testing; and were progression-free after RT (the irradiated group (RT+)) or since last operation (the non-irradiated group (RT−)). The exclusion criteria were: having a diagnosis of glioblastoma and non-Danish speaking.

All patients were recruited at the Departments of Oncology and Neurosurgery at AUH. Potential participants were identified through the electronic medical chart system and the national pathology database and invited by letter to participate in the study. Two cohorts were established: A cohort of 81 brain tumor patients who had received neurosurgery followed by RT (RT+), and a cohort of 29 brain tumor patients matched on age and educational level who only received neurosurgery (RT−). The recruitment ratio (RT+ vs. RT −) was 3:1.

RT consisted of 1.8–2.0 Gy per fraction with total doses ranging from 45 to 60 Gy. From 2006 to 2008, seven of the patients were treated with three-dimensional conformal RT (3D-CRT) and were set up by laser systems and skin marks supplied by portal imaging. After 2008, 65 of the patients received IMRT and were set up with daily cone beam computed tomography (CBCT). In most cases, static field IMRT technique was used. Nine patients in the RT+ group received proton therapy at the MD Anderson Cancer Center, Houston, Texas, Heidelberg Ion Beam Therapy Center, Germany or the Skandion Clinic, Uppsala, Sweden.

Cognitive testing

All participants underwent cognitive assessment with a battery of standardized cognitive tests covering the following cognitive domains: processing speed; attention and working memory; verbal learning and memory; verbal fluency; and executive functions. The average time from diagnosis to test time was 7.3 years. Standardized tests included the Trail Making Test Parts A and B (TMT A&B) [16]; HVLT [14]; Controlled Oral Word Association Test (COWAT) – Animals and letter S [17]; Coding and Digit Span subtests from the Wechsler Adult Intelligence Scale Version IV (WAIS-IV) [18]; Paced Auditory Serial Addition Test (PASAT)-3 seconds trial only [19]; and the Stroop Color and Word Test [20]. The included tests are described in Table 1.

Cognitive testing was conducted by the same trained physician (LHC) supervised by an expert neuropsychologist (AA). All patients were tested during 2016 or 2017, with an average time since diagnosis of 7.6 years for the RT+ patients and 6.3 years for the RT− patients. Testing took approximately 60 minutes. Additionally, participants answered a questionnaire, which took approximately 30 minutes. Self-reported memory, language, communication, motor/sensory-perceptual, and higher level cognitive and intellectual

function were assessed with the Patient Assessment of Own Functioning Inventory (PAOFI) [21], quality of life was assessed with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) [22], sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [23], fatigue was assessed with the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue Scale, version 4) [24], symptoms of depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) [25], and perceived stress was assessed by the Perceived Stress Scale (PSS) [26].

Statistics

Sample size was estimated with power analysis based on *total recall* of the HVLT [27]. Previously reported mean total recall in a non-irradiated group (mean T_{RT-}) was 28.7 (SD: 4.7). We considered a reduction of 3.0 as being clinically relevant [14] and with a 3:1 allocation of RT + to RT−, a power of 80% and a two-sided p of .05, the study required 78 RT + and 26 RT− patients. We included three extra in each group to compensate for potential drop outs.

For the purpose of group comparisons, all cognitive test outcomes were converted to *z*-scores using published normative data adjusted for age, and when available, education level. Test *z*-scores were then tested with a one-sample *t*-test to assess overall cognitive functioning. Subsequently, group comparisons (RT + vs. RT−) were tested using independent sample *t*-tests.

Substantial cognitive impairment at the individual level was determined using cutoff criteria published by the International Cancer and Cognition Task Force (ICCTF). ICCTF recommends reporting the frequency of cognitive impairment by identifying the number of patients with two or more test scores at or below 1.5 SDs from the normative mean [27]. Therefore, test-specific cognitive impairment was determined as a *z*-score exceeding −1.5, while overall cognitive impairment (OCI) was determined as having two different test *z*-scores exceeding −1.5. Between-group differences in test-specific and OCI frequencies were tested with Fisher's exact test.

Results

In both the RT + and the RT− group, 65% of the invited patients consented to participate. Twenty-six percent of the declining patients gave no reason for declining the invitation. Among the remaining declining patients, the primary reasons for declining were insufficient time or energy.

Sociodemographic, clinical and self-reported variables

The sociodemographic and clinical characteristics of the patients are presented in Table 2. RT+ patients were younger than RT− patients (mean 52.1 vs. 57.7 years, respectively) and time since diagnosis was longer in the RT+ group compared with RT− (mean 7.6 and 6.3 years, respectively). Patients in the RT− group were more likely to be married, have more children, be retired and have a higher income than RT+ patients. Self-reported performance status was slightly higher in the RT− group (mean 92.6 vs. 89.4). Overall, the level of depressive symptoms for the entire group was in the mild range (HADS, mean = 8.8), while

symptoms of anxiety were moderate in magnitude (HADS, mean =12.9). No statistically significant differences were observed between treatment groups in either of these symptoms. There was a slightly higher frequency of antiepileptic drug usage in the RT+ group whereas there was no difference in the use of antidepressants between the groups.

Tumor types in the RT− group included meningiomas, pituitary adenomas and gliomas. There was a greater variety of tumor types in the RT+ group including meningiomas, pituitary adenomas, gliomas, medulloblastomas and more rare tumors. In both groups, the majority of tumors were located supratentorially. Tumors were larger in RT+ patients compared with RT−patients (mean diameter 38 mm vs. 31 mm, respectively). In the RT− group, 80% had gross tumor resection (open surgery or transsphenoidal surgery). In the RT+ group, only 37% had gross tumor resection, but more had biopsies and partial tumor resections.

Overall, RT+ patients reported more difficulties with their memory, language and communication, motor/sensory perceptual and higher level cognitive and intellectual function. However, compared with RT−, these findings were only significant for language and communication difficulties (p= .05). Furthermore, the RT+ group reported poorer sleep quality (p= .04).

Cognitive functions

Cognitive outcomes and impairment frequencies for all participants are presented in Table 3. Compared with normative data, the entire group of patients had lower scores on HVLT-total, HVLT-delayed, PASAT, WAIS Coding, Stroop reading, Stroop interference and TMT-B.

Compared with RT−, RT+ scored lower on WAIS Coding and Stroop interference with indication of lower scores on COWAT-Animals. A higher impairment frequency was observed in RT+ (16%) on COWAT-Animals indicating that 16% of patients exceed 1.5 SD below normative data. There was a tendency for higher impairment frequencies in the RT+ group compared with the RT− group on TMT-A, TMT-B, HVLT total, HVLT delayed, Coding, COWAT letter S, STROOP reading and STROOP interference. However, these differences did not reach statistical significance.

Correlations between self-reported cognitive functioning and performance on cognitive tests for the entire group are presented in Table 4. Statistically significant correlations were found between several cognitive domains of the PAOFI and performance on cognitive tests.

Discussion

Our results revealed that both irradiated and non-irradiated brain tumor patients had significantly poorer long-term cognitive functioning compared with normative data. This was evident for the domains of verbal learning and memory, attention and working memory, processing speed, and executive functioning, where significantly lower average scores were observed for the entire group (RT+ and RT−).

Prior to the study, we hypothesized that RT+ patients would be more impaired in verbal learning and memory compared with non-irradiated patients due to irradiation of

hippocampal regions. We failed to confirm our hypothesis. RT+ patients did score lower on a test of verbal learning and memory, but the difference did not reach statistical significance. RT+ patients scored significantly lower on tests related to the domains of processing speed and executive function. RT+ patients also had lower scores on a test of semantic verbal fluency, but the difference did not reach statistical significance. Furthermore, there was a higher impairment frequency on the same test in the RT+ group with 16% of patients scoring 1.5 SD below normative data. It is possible that verbal fluency may be an area of vulnerability for RT+ patients as well.

Consistently, higher impairment frequencies were also observed in the RT+ patients compared with RT− patients on tests of processing speed, executive functioning, memory, phonemic verbal fluency and OCI. These findings, although not statistically significant, indicate a trend toward lower cognitive functioning in RT+ patients. The RT− group evidenced a higher impairment frequency on a test of attention and working memory, but this was likely confounded by the fact that eight patients in the RT+ group could not complete the test because it was too difficult and were thus excluded from the analysis.

On self-reported cognitive functioning, RT+ patients reported significantly more language and communication difficulties. There was a tendency for greater reports of impairment to memory, motor/sensory-perceptual functioning, and to higher level cognitive and intellectual functions in RT+ patients. Importantly, there were associations between self-reported cognitive functioning and objective cognitive test scores. In other studies, self-reported measures of cognition have tended to show weak correlations with objective cognitive tests [8]. Often, however, measures of self-reported cognition have tended to be general and rarely assessed specific domains [28]. An advantage of the PAOFI, which was used in the present study, is that it allows for the assessment of specific domains of cognitive functioning. We found associations between self-reported and objectively assessed cognitive functions on verbal learning and memory, attention and working memory, processing speed, verbal fluency and executive function. The magnitude of the associations ranged from small to medium with higher levels of self-reported cognitive impairment being associated with lower performance on the cognitive tests. This indicates some agreement between test results and the patients' own perceptions of their cognitive function when using the PAOFI.

Although a comparison of our findings with other studies in brain tumor patients is important, it is complicated to do so due to the heterogeneity in neuropsychological tests and criteria for defining cognitive dysfunction that have been used [29,30]. A review of 17 articles by Loon et al. on assessment methods of cognitive functioning showed that a total of 46 different tests were used. Furthermore, they found variability in the definition of cognitive function such that the reported prevalence ranged from 19% to 83% [30]. This heterogeneity makes it challenging to contrast and compare results across studies. Furthermore, it is important to remember that cognitive dysfunction in brain tumor patients is multifactorial. It may be caused by the tumor itself, tumor-related epilepsy, and other adjuvant treatments [5]. It is not possible to directly assign cognitive dysfunction to one specific factor. Klein et al. found that irradiated low grade glioma patients did less well in some cognitive tests compared with non-irradiated low grade glioma patients [8]. Cognitive impairment was mainly present in patients receiving a high dose fraction exceeding 2 Gy per

fraction [8]. None of the included patients in our study received dose fraction exceeding 2 Gy and yet we found slightly poorer cognitive function in RT+ patients compared with RT− patients, which is in contrast to Klein's study. Douw et al. conducted a follow-up on Klein et al.'s study and found an association between RT and cognitive deterioration, regardless of fraction dose at long-term follow up (mean 12 years) with the domain of attention most affected [31]. Other studies have found no significant differences in cognitive functioning after RT [2,32,33]. However, all but one of them [33] had small sample sizes (ranging from 11 to 41), and may have lacked statistical power to detect any differences. Our results suggest that both the tumor itself and RT may have a negative impact on cognitive functioning.

With respect to psychosocial outcomes, the RT+ group had significantly poorer sleep quality than the RT− group. We had expected more fatigue and higher levels of depression, stress and anxiety in the RT+ group compared to the RT− group, but no differences were observed on self-reported outcomes on fatigue, depression, stress or anxiety between the two groups. Neither was there any difference on quality of life. In Denmark, 7% of the population are on antidepressant drugs [34]. In our study population, it was slightly higher; 11% in the RT+ group and 10% in the RT− group suggesting a higher prevalence of depression in brain tumor patients.

This study has a number of important strengths. We used cognitive tests recommended by EORTC and ICCTF exploring a broad spectrum of cognitive domains. Our patient cohort was relatively large and all patients underwent the same tests and questionnaires in the same settings and all were tested by the same examiner (LHC) supervised by an experienced neuropsychologist (AA). Furthermore, non-irradiated brain tumor patients served as a control, in order to make the two groups (RT+ and RT−) as similar as possible.

However, there are also limitations that need to be considered when interpreting the findings. First, the cross-sectional design necessarily limits the interpretation of study results. We have no pretreatment assessment of cognitive function and therefore are unaware of the patients' cognitive functioning before they were diagnosed, before neurosurgery and before RT. Second, we cannot clearly distinguish whether impaired cognitive function is caused by the tumor, neurosurgery or RT as the majority of patients in the present study had a tumor located in the frontal and temporal lobes – areas responsible for executive functions, attention, processing speed and memory – that were also the exact areas where the majority of RT+ patients received the highest radiation dose. The cognitive impairments noted were also found in the entire study sample. Third, it may have been underpowered to demonstrate cognitive dysfunction in all relevant domains, or alternatively, the selected tests may not have been sensitive enough to detect such differences between groups. Finally, the study included a matched nonirradiated cohort of brain tumor patients for comparison. Unfortunately, the matched groups were not completely comparable. In the RT− group, the tumors are primarily grades I–II while in the RT+, most tumors are grades I–III and medulloblastoma. The potential impact of these inherent differences is difficult to assess.

Despite the aforementioned limitations, the present study is one of the largest of its kind and with a comprehensive battery of cognitive tests covering a broad spectrum of cognitive

domains. Our findings not only establish the feasibility of assessing cognition and psychosocial outcomes in brain tumor patients, but also provide us with an important first step in better understanding potential risks associated with RT. Specifically, the present study shows a clear pattern of cognitive impairment for the entire group compared to normative data. A less clear pattern is found when exploring if RT+ patients are more impaired than RT− patients. We did not find a hypothesized difference between groups in verbal learning and memory, but did detect areas of vulnerability in the RT+ group in processing speed, verbal fluency and executive function. Further research is needed using a prospective design with repeated assessment in a well-powered sample to corroborate our findings and to learn about the effects of radiation dose and tumor characteristics of relevant brain areas on cognition as well.

Conclusions

Results of the present study indicate that treatment, including RT, for primary brain tumors may have a negative impact on cognitive functioning even years after treatment. Although there were indications of domains being more impaired in RT+ patients than RT− patients, more research is needed to further investigate RT treatment-related effects on cognitive functioning. The present study may be used to generate specific hypotheses for future studies.

Funding

The Research Ethics Committee of Central Denmark Region approved this study (no. 1-10-72-367-15).

References

[1]. Saad S, Wang TJC. Neurocognitive deficits after radiation therapy for brain malignancies. Am J Clin Oncol. 2015;38:634–640. [PubMed: 25503433]

[2]. Hahn CA, Zhou S-M, Raynor R, et al. Dose-dependent effects of radiation therapy on cerebral blood flow, metabolism, and neuro-cognitive dysfunction. Int J Radiat Oncol Biol Phys. 2009 DOI:10.1016/j.ijrobp.2008.05.061

[3]. van Kessel E, Baumfalk AE, van Zandvoort MJE, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. J Neurooncol. 2017 DOI:10.1007/s11060-017-2503-z

[4]. Ali FS, Hussain MR, Gutiérrez C, et al. Cognitive disability in adult patients with brain tumors. Cancer Treat Rev. 2018 DOI:10.1016/j.ctrv.2018.02.007

[5]. Pinkham MB, Bertrand KC, Olson S, et al. Clinical study hippocampal-sparing radiotherapy: the new standard of care for World Health Organization grade II and III gliomas? 2014 DOI:10.1016/j.jocn.2013.04.005

[6]. Hendrix P, Hans E, Griessenauer CJ, et al. Neurocognitive function surrounding the resection of frontal WHO grade I meningiomas: a prospective matched-control study. World Neurosurg. 2017 DOI:10.1016/j.wneu.2016.10.095

[7]. McAleer MF, Brown PD. Neurocognitive function following therapy for low-grade gliomas. Semin Radiat Oncol. 2015 DOI:10.1016/j.semradonc.2015.02.005

[8]. 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 DOI:10.1016/S0140-6736(02)11398-5

[9]. Gondi V, Hermann BP, Mehta MP, et al. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol. 2013;85:348–354.

[10]. Tsai P-F, Yang C-C, Chuang C-C, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol. 2015;10 DOI:10.1186/s13014-015-0562-x [PubMed: 25572571]

[11]. Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. Radiother Oncol. 2010;97:370–376. [PubMed: 20970214]

[12]. 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. JCO. 2014;32: 3810–3816.

[13]. Jaspers J 14 - The hippocampal NTCP model could not be validated within the EORTC-22033 low-grade glioma trial. 2018; 20–21.

[14]. Benedict RHB, Schretlen D, Groninger L, et al. Hopkins verbal learning test? Revised: normative data and analysis of inter-form and test–retest reliability. Clin Neuropsychol (Neuropsychol, Dev Cogn Sect D). 1998 DOI:10.1076/clin.12.1.43.1726

[15]. 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;131:803–820. [PubMed: 27157931]

[16]. Reitan R Validity of the trail making test as an indicator of organic brain damage. Percept Mot Skills. 1958 DOI:10.2466/PMS.8.7.271-276

[17]. Thurstone LL. Primary mental abilities. Science. 1948;108:2813.

[18]. Wechsler D Wechsler adult intelligence scale – fourth edition (WAIS-IV). San Antonio; 2008.

[19]. Wiens AN, Fuller KH, Crossen JR. Paced auditory serial addition test: adult norms and moderator variables. J Clin Exp Neuropsychol. 1997 DOI:10.1080/01688639708403737

[20]. Stroop JR. Stroop color word test. J Exp Physiol. 1935 DOI:10.1007/978-0-387-79948-3

[21]. Chelune GJ, Heaton RK, Lehman RAW. Neuropsychological and personality correlates of patients' complaints of disability. 1986 DOI:10.1007/978-1-4613-2211-5_4

[22]. 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 DOI:10.1093/jnci/85.5.365

[23]. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 DOI:10.1016/0165-1781(89)90047-4

[24]. Tennant KF, Takacs SE, Gau J-T, et al. A preliminary study of symptomatic fatigue in rural older adults. Aging Clin Exp Res. 2012 DOI:10.3275/8054

[25]. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 DOI:10.1111/j.1600-0447.1983.tb09716.x

[26]. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983 DOI:10.2307/2136404

[27]. Wefel JS, Vardy J, Ahles T, et al. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011;12: 703–708. [PubMed: 21354373]

[28]. Hutchinson AD, Hosking JR, Kichenadasse G, et al. Complications of treatment objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. Cancer Treat Rev. 2012;38:926–934. [PubMed: 22658913]

[29]. Gehring K, Sitskoorn MM, Aaronson NK, et al. Interventions for cognitive deficits in adults with brain tumours. Lancet Neurol. 2008 DOI:10.1016/S1474-4422(08)70111-X

[30]. Loon E, Heijenbrok-Kal M, Loon W, et al. Assessment methods and prevalence of cognitive dysfunction in patients with low-grade glioma: a systematic review. J Rehabil Med. 2015;47: 481–488. [PubMed: 25994416]

[31]. Douw L, Klein M, Fagel SSAA, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. 2009;8 DOI:10.1016/S1474

[32]. Taphoorn MJ, Schiphorst AK, Snoek FJ, et al. Cognitive functions and quality of life in patients with low-grade gliomas: the impact of radiotherapy. Ann Neurol. 1994 DOI:10.1002/ana.410360111

[33]. Brummelman P, Sattler MGA, Meiners LC, et al. Cognitive performance after postoperative pituitary radiotherapy: a dosimetric study of the hippocampus and the prefrontal cortex. Eur J Endocrinol. 2012 DOI:10.1530/EJE-11-07496

[34]. Fortsat fald antidepressiv medicin 2016 – Sundhedsdatastyrelsen. Available from: https://sundhedsdatastyrelsen.dk/da/nyheder/2017/medicinforbrug-indblik-antidepressiver_04072017

Table 1.

Standardized neuropsychological tests included in the test battery.

Cognitive domain	Neuropsychological test	Outcome(s)	Description
Processing speed	Trail-Making Test Part A	Completion time in seconds	A paper-and-pencil test of visuomotor ability requiring the participant to draw a line between numbers, in sequence, randomly displayed on a page.
	WAIS-IV (Wechsler Adult Intelligence Scale Version IV) - Coding	Number correct	A paper-and-pencil test requiring the participant to copy symbols that correspond with numbers according to a key.
	Stroop word reading	Number of words	Number of simple words (green, red, blue) you can read in 45 seconds.
	Stroop color reading	Number of correct colors	Number of colored crosses (XXXXs) you can read in 45 seconds.
Attention and working memory	Paced Auditory Serial Addition Test (PASAT)	Number of correct responses	Participants are presented with single digit numbers at a fixed pace and instructed to add each pair of consecutive numbers continuously.
	WAIS-IV digit span	Number of correct responses	Participants recall strings of random digits presented auditorily. Trials include forward, backward and ordered recall.
Verbal learning and memory	Hopkins Verbal Learning Test - revised (HVLT)	Number of correct words recalled	Participants recall a list of 12 words presented to them over 3 trials. The total number of words recalled over the 3 trials represents total learning.
	HVLT delay	Number of correct words recalled	Participants recall as many words from the list of 12 words after a 30 minute delay.
Verbal fluency	Controlled Oral Word Association (COWAT) Letter S	Total number of words produced	Participants produce as many words as possible beginning with the letters S during a 1-minute period, respectively.
	COWAT, Animal	Total number of words produced	Participants name as many animals as possible during a 1-minute period.
Executive function	Trail-Making Test Part B	Completion time in seconds	A paper-and-pencil test that requires the participant to draw a line and alternately connect numbers and letters, in sequence, randomly displayed on a page.
	Stroop interference test	Number of correct responses	Participants are presented with words printed in a different color ink and have to name the color of the ink rather than reading the words.

Table 2.

Sociodemographic and clinical characteristics of participants.

Groups	RT+	RT−	*p* Value
N	81	29	
Age, mean (SD)	52.1 (15.7)	57.7 (14.6)	.10
Gender, *N* (%)			
Male	49 (60)	12 (41)	.08
Female	32 (40)	17 (59)	
Education in years, mean (SD)	14.4 (3.19)	14.2 (2.21)	.72
Marital status, *N* (%)			
Married	56 (69)	25 (86)	.05
Single	22 (27)	3 (10)	
Widow	3 (4)	1 (4)	
Children, *N* (%)			
0	18 (22)	3 (10)	.11
1+	63 (78)	26 (89)	
Income in Euro (€), *N* (%)			
0–26.869	30 (37)	7 (24)	.03
26.869–53.738	35 (44)	10 (35)	
53.738–80.608	9 (11)	10 (35)	
80.608>	6 (8)	2 (6)	
Work, *N* (%)			
No	18 (22)	4 (14)	.05
Full time (37 hours)	19 (24)	9 (31)	
Part time (less than 37 hours)	19 (24)	3 (10)	
Retired	22 (27)	13 (45)	
Studying	3 (3)	0 (0)	
Karnofsky Performance Score mean (SD)	89.4 (10.03)	92.6 (9.84)	.03
Smoking, *N* (%)			
Yes	11 (14)	1 (3)	.02
No	70 (86)	28 (97)	

Groups	RT+	RT−	*p* Value
Physical exercise (hours per week), *N* (%)			
1–7	61 (75)	20 (69)	>.05
7+	20 (25)	9 (31)	
Tumor type, *N* (%)			
Meningioma	22 (27%)	19 (65%)	.02
Pituitary adenoma	18 (22%)	8 (28%)	
Glioma grade II	16 (20%)	2 (7%)	
Glioma grade III	12 (15%)		
Medulloblastoma, NOS	7 (9%)		
Other rare brain tumors	6 (8%)		
Tumor size in mm at time of diagnosis, mean (SD)			
Longest diameter	38 (14.76)	31 (16.18)	.04
Diameter measured perpendicular to the longest diameter	28 (11.70)	24 (12.18)	.09
Surgery, *N* (%)			
None	11 (13)	0	.02
Biopsy (craniotomy)	4 (5)	1 (3)	
Biopsy (stereotactic)	7 (9)	0 (0)	
Partial tumor resection	29 (36)	5 (17)	
Gross tumor resection	18 (22)	15 (52)	
Transsphenoidal tumor resection	12 (15)	8 (28)	
Number of surgery, *N* (%)			
None	3 (4)	0	
1	66 (81)	26 (90)	
1+	12 (15)	3 (10)	
Location, *N* (%)			
Supratentorial	72 (89)	27 (93)	.01
Infratentorial	9 (11)	2 (7)	
Antiepileptic drug, *N* (%)			
Yes	20 (25)	5 (17)	.42
No	61 (75)	24 (83)	
Antidepressants, *N* (%)			

Groups	RT+	RT−	*p* Value
Yes	9 (11)	3 (10)	.91
No	72 (89)	26 (90)	
Chemotherapy, *N*(%)			
None	61 (75)	29 (100)	<.01
PCV	7 (9)		
Temozolomide	2 (2)		
Other	11 (14)		
RT type, *N*(%)			
Photons	72 (89)	0	<.01
Protons	9 (11)	0	
Radiation dose (1.8–2.0 Gy/fraction), *N*(%)			
44–45 Gy	26 (32)		<.01
50–54 Gy	32 (40)		
55–60 Gy	22 (27)		
Other	1 (1)		
None		29 (100)	
Time since diagnosis to cognitive evaluation in years, mean (SD)	7.62 (5.51)	6.33 (5.07)	.29
PAOFI			
Memory	45.07 (11.26)	48.17 (7.38)	.17
Language and communication	42.94 (9.66)	46.69 (5.73)	.05
Motor/sensory perceptual	26.48 (5.35)	27.867(3.12)	.18
Higher level cognitive functioning cognitive and intellectual function	43.46 (10.99)	46.83 (6.57)	.12
PSQI	5.25 (3.21)	4.10 (2.16)	.04
FACIT-F	40.38 (9.49)	43.38 (8.94)	.14
PSS	11.35 (7.16)	9.90 (7.43)	.36
HADS-anxiety	12.86 (2.41)	13.10 (2.24)	.64
HADS-depression	8.69 (1.62)	8.90 (1.18)	.53
EORTC QLQ-C30 - summary score	85.90 (14.07)	89.91 (2.03)	.18

PAOFI: Patient Assessment of Own Functioning Inventory; PSQI: Pittsburgh Sleep Quality Index; FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue Scale Version 4; PSS: Perceived Stress Scale; HADS: Hospital Anxiety and Depression Scale; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer QLQ-C30 (version 3). For PSQI, higher score indicates poorer sleep quality. For all other scales, higher scores indicate less symptom severity.

Table 3.

Mean score and standard deviations (SD) of neurocognitive test outcomes of all participants and substantial impairment frequency by cognitive domain ($z < -1.5$).

Cognitive domain	Cognitive test	Mean, (SD)[a] All patients	*p* Value	Mean (SD)[a] RT+	Mean (SD)[a] RT−	*p* Value[b]	NCI, *N* (%) *z* < 1.5 RT+	NCI, *N* (%) *z* < 1.5 RT−	*p* Value[c]
Processing speed	TMT-A	−0.13 (1.33)	.31	−0.18 (1.38)	0.03 (1.18)	.47	8 (10%)	2 (7%)	1.00
	WAIS-IV Coding	−0.23 (0.98)	.01*	−0.35 (0.98)	0.09 (0.91)	.04*	7 (9%)	0 (0%)	0.11
	Stroop reading (word and color)	−1.19 (1.06)	.00*	−1.29 (1.08)	−0.91 (0.97)	.10	26 (36%)	6 (21%)	0.10
Attention and working memory	PASAT (3 seconds only)	−0.83 (1.16)	.00*	−0.87 (1.15)	−0.73 (1.22)	.61	24 (33%)	11 (39%)	0.35
	WAIS-IV digit span	−0.18 (0.88)	.83	−0.04 (0.82)	0.03 (1.02)	.71	2 (3%)	2 (7%)	0.28
Verbal learning and memory	HVLT-total	−0.63 (1.19)	.00*	−0.69 (1.21)	−0.44 (1.12)	.33	25 (31%)	5 (17%)	0.12
	HVLT delayed	−1.02 (1.35)	.00*	−1.01 (1.40)	−1.04 (1.20)	.93	31 (38%)	11 (38%)	0.58
Verbal fluency	COWAT (animals)	−0.16 (1.20)	.16	−0.26 (1.30)	0.12 (0.82)	.07	13 (16%)	0 (0%)	0.01*
	COWAT (letter S)	0.03 (1.14)	.80	−0.30 (1.17)	0.20 (1.08)	.34	9 (11%)	2 (7%)	0.41
Executive function	TMT-B	−0.26 (1.37)	.05*	−0.34 (1.47)	−0.03 (1.05)	.29	10 (12%)	3 (10%)	1.00
	Stroop interference test	−0.44 (1.01)	.00*	−0.55 (1.02)	−0.13 (0.94)	.05*	12 (15%)	1 (3%)	0.09
Global Composite Score		−0.40 (0.71)	.00*	−0.43 (0.70)	−0.29 (0.74)	.38	28 (42%)	8 (29%)	0.16

HVLT-r: Hopkins Verbal Learning Test – revised; PASAT: Paced Auditory Serial Addition Test, 3 seconds only. WAIS-IV digit span; TMT-A: Trail-Making Test Part A. WAIS-IV – Coding. Stroop reading (word and color); COWAT: Controlled Oral Word Association Task; HVLT: Hopkins Verbal Learning Test – revised; NCI: neurocognitive impairment; PASAT: Paced Auditory Serial Addition Test; TMT-A: Trail-Making Test Part A; TMT-B: Trail-Making Test Part B; WAIS-IV: Wechsler Adult Intelligence Scale Version IV.

[a] Negative scores indicate poorer test performance.

[b] Between-group *t*-test.

[c] Fisher's exact test.

* Significant findings by a two-tailed *p* value.

Table 4.

Pearson's correlation tests between self-reported cognitive functioning and performance on neuropsychological tests for the entire group.

		Neurocognitive tests											
		TMT-A	**TMT-B**	**HVLT total**	**HVLT delayed**	**PASAT**	**COWAT animal**	**COWAT letter S**	**WAIS coding**	**WAIS digit span**	**Stroop reading**	**Stroop interference**	**GCS**
Self-reported cognitive functioning	PAOFI Memory	0.27	0.24	0.13	0.10	0.00	0.25	0.15	0.28	0.17	0.15	0.19	0.09
	p Value	0.04*	0.01*	0.18	0.29	0.99	0.01*	0.12	0.00*	0.08	0.13	0.05*	0.36
	PAOFI Language and communication	0.32	0.39	0.26	0.19	0.19	0.29	0.23	0.30	0.29	0.24	0.21	0.30
	p Value	0.00*	0.00*	0.01*	0.04*	0.06	0.00*	0.01*	0.00*	0.00*	0.01*	0.03*	0.00*
	PAOFI Motor/Sensory-Perceptual	0.18	0.12	0.12	0.02	0.06	0.12	0.02	0.17	0.10	0.08	0.10	0.10
	p Value	0.06	0.23	0.23	0.87	0.58	0.22	0.81	0.07	0.31	0.43	0.29	0.32
	PAOFI HLCF	0.39	0.29	0.24	0.21	0.09	0.32	0.18	0.33	0.29	0.20	0.14	0.21
	p Value	0.00*	0.00*	0.01*	0.03*	0.36	0.00*	0.06	0.01*	0.00*	0.04*	0.14	0.04*

TMT-A: Trail-Making Test Part A; TMT-B: Trail-Making Test Part B; HVLT: Hopkins Verbal Learning Test - revised; PASAT: Paced Auditory Serial Addition Test, 3 seconds only; COWAT: Controlled Oral Word Association Task; GCS: Global Composite Score; WAIS-IV: Wechsler Adult Intelligence Scale Version IV; PAOFI: Patient Assessment of Own Functioning Inventory: HLCF: Higher Level of Cognitive Functioning.

*Statistically significant correlations (two-tailed).