



Original Research Article

Associations between patient-reported outcomes and radiation dose in patients treated with radiation therapy for primary brain tumours

L. Haldbo-Classen^{a,*}, A. Amidi^{a,b}, L.M. Wu^{b,c}, S. Lukacova^a, G. Oettingen^d,
Y. Lassen-Ramshad^e, R. Zachariae^{a,b}, J.F. Kallehauge^e, M. Høyer^e

^a Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

^b Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Sciences, Aarhus University, Denmark

^c Aarhus Institute of Advanced Studies, Aarhus University, Denmark

^d Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

^e Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Keywords:

Brain tumor

Radiation therapy

Patient-reported outcomes

Quality of life

Cognition

ABSTRACT

Aim: This study aimed to explore associations between radiation dose and patient-reported outcomes in patients with a primary non-glioblastoma brain tumour treated with radiation therapy (RT), with a focus on health-related quality-of-life (HRQoL) and self-reported cognitive function.

Methods: In this cross-sectional study, 78 patients who had received RT for a non-glioblastoma primary brain tumour, underwent neuropsychological testing and completed questionnaires on HRQoL, cognitive function, fatigue, depression, anxiety and perceived stress. The study explores the association between HRQoL scores, self-reported cognitive function and radiation doses to total brain, brainstem, hippocampus, thalamus, temporal lobes and frontal lobes. In addition, we examined correlations between neuropsychological test scores and self-reported cognitive function.

Results: The median time between RT and testing was 4.6 years (range 1–9 years). Patients who had received high mean radiation doses to the total brain had low HRQoL scores (Cohen's $d = 0.50$, $p = 0.04$), brainstem ($d = 0.65$, $p = 0.01$) and hippocampus ($d = 0.66$, $p = 0.01$). High mean doses to the total brain were also associated with low scores on self-reported cognitive functioning (Cohen's $d = 0.64$, $p = 0.02$), brainstem ($d = 0.55$, $p = 0.03$), hippocampus ($d = 0.76$, $p < 0.01$), temporal lobes ($d = 0.70$, $p < 0.01$) and thalamus ($d = 0.64$, $p = 0.01$). Self-reported cognitive function correlated well with neuropsychological test scores (correlation range 0.27–0.54).

Conclusions: High radiation doses to specific brain structures may be associated with impaired HRQoL and self-reported cognitive function with potentially negative implications to patients' daily lives. Patient-reported outcomes of treatment-related side-effects and their associations with radiation doses to the brain and its sub-structures may provide important information on radiation tolerance to the brain and sub-structures.

Introduction

Radiation therapy (RT) is an important treatment of primary brain tumours as it improves local control and survival in a broad range of tumour types [1,2,3]. Unfortunately, RT is associated with risk of long-term impairment of cognitive function and quality of life [4,5]. Non-glioblastoma brain tumour patients are often young and have a relatively long expected survival [6–8]. Assessment of health-related quality of life (HRQoL) and patient-reported outcomes (PRO) are therefore

crucial in follow-up after RT for a brain tumour [9–12]. In a previous publication we found that high radiation dose to the brain and its sub-structures was associated with poor scores on neuropsychological testing [13]. However results from neuropsychological testing may not correspond fully to the patients' perception of their own functions, and self-reported cognition can provide important complementary information about patients' overall functioning [14,15]. Self-reported cognitive impairments are often associated with poor overall HRQoL [15–18] and may further be associated with fatigue, depression, anxiety,

* Corresponding author.

E-mail address: lenhald@rm.dk (L. Haldbo-Classen).

¹ ORCID: 0000-0002-0175-5187.

<https://doi.org/10.1016/j.ctro.2021.09.006>

Received 22 April 2021; Received in revised form 18 September 2021; Accepted 20 September 2021

Available online 27 September 2021

2405-6308/© 2021 The Authors. Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under

the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and stress [9,19–21]. Data on patients' perception of commonly occurring treatment related side-effects and their associations with radiation doses to the brain and its sub-volumes may provide important information about the radiation tolerance of the brain and its sub-volumes. Such information could be translated into dose-volume constraints used in radiation therapy planning. However, so far, clinical evidence on dose-volume constraints to the brain is limited or inconsistent and often based on expert consensus rather than evidence [4,17,18,22,23].

This cross-sectional study is a precursor for a national longitudinal study initiated by the Danish Neuro-Oncology Group with the aim of exploring radiation doses to various brain structures in patients with a primary non-glioblastoma brain tumour previously treated with RT and their associations with PROs; self-reported cognitive function, fatigue, depression, anxiety, stress, and overall HRQoL. The main focus is on associations between radiation dose and health related quality of life (HRQoL) and self-reported cognitive function. Some studies have found that the use of antiepileptic drugs to be associated with reduced self-reported cognitive function and HRQoL [20,24]. Thus, we also explored differences in PROs between patients with or without epilepsy and for patients who were still working versus patients who did not work due to their illness.

Material and methods

2.1. Study design and patients

The present paper is part of a larger study focusing on the relationships between radiation doses to the brain and its substructures and specific cognitive functions. The primary endpoint of the larger study was the association between outcomes on Hopkins Verbal Learning Test revised (HVLT-r) and radiation dose to the hippocampus. Previously, we reported data from the cognitive assessment and associations to radiation dose in this cross-sectional study [13]. In the present paper, we report the results for the PROs and associations with radiation dose.

The inclusion criteria were: primary non-glioblastoma brain tumour according to WHO 2016 guidelines [6]; RT between 2006 and 2016 at Aarhus University Hospital (AUH) or proton therapy abroad as part of a Danish referral program; progression-free since RT; age 18 years or older at time of diagnosis; Karnofsky performance status of 60–100; and capable of undergoing neuropsychological testing. Exclusion criteria were glioblastoma and inadequate Danish language proficiency. Patients completed questionnaires assessing PROs and a battery of standardized neuropsychological tests [13]. The neuropsychological tests were conducted by the same trained physician supervised by a senior researcher with expertise in neuropsychology in the period February 2017 to March 2018.

2.2. Radiation therapy

Details about RT have previously been reported [13]. In brief, participants received three-dimensional conformal RT (2006–2008; $n = 5$), or intensity-modulated RT (IMRT) and daily cone-beam computed tomography (after 2008; $n = 64$). RT was given with 1.8–2.0 Gy fractions to total doses of 45–60 Gy. Nine patients were referred to proton therapy at the Skandion Clinic, Uppsala, Sweden, Heidelberg Ion Beam Therapy Center, Germany or the MD Anderson Cancer Center, Houston, USA.

2.3. Radiation dose to brain structures

The following structures: brain (without brainstem and clinical target volume), brainstem, hippocampus, temporal lobe, frontal lobe and thalamus, were delineated on the computer tomography (CT) scan co-registered with a contrast enhanced 3D T1-weighted magnetic resonance imaging (MRI) scan [25,26]. All contouring was performed by one oncologist and reviewed by a neurosurgeon and a neuro-oncologist. Mean doses from these contours were converted to biologically

equivalent doses in 2 Gy fractions (EQD₂) assuming an α/β ratio of 3 Gy [27].

2.4. Patient-reported outcomes (PROs)

HRQoL was assessed with the European Organization for Research and Treatment of Cancer Quality-of-Life Instrument (EORTC QLQ-C30) [28]. The EORTC QLQ-C30 includes six functional scales, three symptom scales, and additional single-item scales, resulting in a total of 15 outcomes [28]. In the present study, we used the *HRQoL summary score* calculated as the mean of the combined 13 QLQ-C30 scale and item scores (excluding global quality of life and financial impact) [29,30]. When scoring the QLQ-C30, symptom scale scores are reversed so that all outcomes are in the same direction and raw scores are transformed to linear scales ranging from 0 to 100 with higher scores representing better HRQoL [28,29,30].

Self-reported cognitive functioning was measured with The Patient's Assessment of Own Functioning Inventory (PAOFI) [14], designed to evaluate patients' experiences of their functional capacity in everyday activities [31]. The PAOFI consists of four subscales that directly address cognitive functions: a Memory subscale, a Language and Communication subscale, a Motor/Sensory-Perceptual subscale and a Higher Level Cognitive and Intellectual Function (HLCF) subscale. A higher rating on any item indicated a lesser degree of impairment [32].

Fatigue was measured with The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) scale, version 4 [33]. Higher scores represent better functioning or less fatigue [33]. A FACIT-Fatigue score ≤ 30 indicates severe fatigue [34]. Symptoms of anxiety and depression were measured with The Hospital Anxiety and Depression Scale (HADS) [35]. The total scores of HADS was interpreted as follows: Score 0–7 = normal; score 8–10 = mild symptoms; score 11–14 moderate symptoms; and score ≥ 15 = severe symptoms [36]. Perceived Stress was measured with The Perceived Stress Scale (PSS), a stress assessment instrument containing about feelings and thoughts during the last month [37,38]. A total score 0–13 indicates low stress, 14–26 indicates moderate stress, and 27–40 indicates high stress [39].

2.5. Cognitive assessment

The patients underwent cognitive assessment with a battery of standardized neuropsychological tests covering the following domains: processing speed; attention and working memory; verbal learning and memory; verbal fluency; and executive functions [13]. Tests included the Trail Making Test - Parts A and B (TMT A & B) [40]; Hopkins Verbal Learning Test - Revised (HVLT-R) [41]; Controlled Oral Word Association Test (COWAT) – Animals and letter S [42]; Coding and Digit Span subtests from the Wechsler Adult Intelligence Scale - Version IV (WAIS-IV) [43]; Paced Auditory Serial Addition Test (PASAT) – 3-second trial only [44]; and the Stroop Colour and Word Test [45].

2.6. Statistical analyses

Sample size was originally estimated based on a study comparing cognitive function in irradiated and non-irradiated brain tumour patients and described in an earlier publication [21]. Statistical power analysis was based on total recall of the HVLT-R [21]. The present analysis include only the irradiated group. It was predefined which associations between PROs and brain structures should be examined. ClinicalTrials.gov number: ID NCT04118426

To identify patients who are particularly at risk for impaired HRQoL, we dichotomized outcomes on PRO. There are no standardised clinical cut-off scores for the EORTC QLQ-C30 or the PAOFI in brain tumour patients. We chose to dichotomize EORTC QLQ-C30 and the PAOFI scores as the 25% of patients with the poorest scores represented the "impaired group" and the remaining 75% with better scores represented the "unimpaired group". For the FACIT-Fatigue, patients were

dichotomized into fatigue (i.e., FACIT-Fatigue scores ≤ 30) ($n = 14$) and non-fatigue patients ($n = 64$) [34]. For the HADS Depression subscale, patients were dichotomized into patients with mild-severe symptoms (i.e., HADS Depression scores ≥ 8) ($n = 7$) and patients with no symptoms ($n = 69$) [36]. For the HADS Anxiety subscale, patients were dichotomized into patients with mild-severe symptoms (i.e., HADS Anxiety scores ≥ 8) ($n = 14$) and patients with no symptoms ($n = 64$) [36]. For the PSS, patients were dichotomized into patients with moderate stress (i.e., PSS scores ≥ 14) ($n = 27$) and patients with no stress ($n = 49$) [39]. To determine whether there were differences between the mean EQD₂ of delineated structures in the two dichotomized groups for each PRO, independent sample *t*-tests were conducted, and effect sizes were calculated (Cohen's *d*). Independent sample *t*-tests were conducted to determine possible differences in PROs between patients with and without epilepsy and between patients who were still working versus patients who did not work due to their illness.

Pearson correlations were used to explore correlations between: EORTC QLQ-C30 and PAOFI scores, with HADS Depression, HADS Anxiety, PSS and FACIT-Fatigue; and to examine whether tumour size, age, tumour grade, gender or time since RT correlated with scores on the EORTC QLQ-C30 and the PAOFI; and to examine correlations between cognitive test scores and PAOFI scores. Chi-square tests were used to explore potential differences between the two groups (impaired vs unimpaired) across tumour type and location.

Results

3.1. Sociodemographic and clinical characteristics

Eighty-one out of 121 eligible patients consented to participate. The 40 patients who declined did not differ from consenting patients with respect to age ($p < 0.01$), gender ($p = 0.05$) or tumour type ($p = 0.04$). Three patients were excluded from the current analysis, as two patients' treatment plans could not be obtained, and one patient had only received one fraction of RT. The median time since RT was 4.6 years and median age of patients at time of assessment was 53.5 years. Participant demographic and clinical characteristics are shown in Table 1.

3.2. Pros and radiation dose

For the EORTC QLQ-C30 and PAOFI, cut-off scores were 79 for EORTC QLQ-C30; 41.5 for PAOFI Memory; 40.5 for PAOFI Language; and 39.5 for PAOFI HLCF. Chi-square tests revealed no significant differences between the two groups (impaired vs unimpaired) across tumour type and location (Supplementary Table 1).

Patients with poor scores on the EORTC QLQ-C30 had received significantly higher mean EQD₂ to the total brain ($p = 0.04$), brainstem ($p = 0.01$) and hippocampus ($p = 0.01$), compared to the remaining patients. Similar differences in radiation dose could not be found for the thalamus, the temporal or frontal lobes. Poor scores on the PAOFI Memory subscale were associated with higher EQD₂ doses to the total brain ($p < 0.01$), hippocampus ($p = 0.01$), temporal lobes ($p = 0.02$), frontal lobes ($p = 0.03$) and thalamus ($p = 0.01$); poor scores on the PAOFI HLCF subscale were associated with higher EQD₂ doses to the total brain ($p = 0.02$), brainstem ($p = 0.03$), hippocampus ($p < 0.01$), temporal lobes ($p < 0.01$), and thalamus ($p = 0.01$); whereas no association with dose was found for PAOFI Language scores (Fig. 1 and Supplementary Table 2). Patients in the high fatigue group had received higher doses to the brainstem ($p = 0.02$), hippocampus ($p = 0.02$), temporal lobes ($p = 0.02$) and thalamus ($p = 0.01$).

3.3. Pros and associated parameters

Statistically significant correlations were found between HADS Depression ($p < 0.01$), HADS Anxiety ($p < 0.01$), PSS ($p < 0.01$), FACIT-Fatigue ($p < 0.01$), and scores of the EORTC QLQ-C30, PAOFI Memory,

Table 1

Sociodemographic and clinical characteristics of participants.

Number of participants	78 (100%)
Age, median (range) in years	53.5 (20–79)
Gender, N (%)	
Male	47 (60%)
Female	31 (40%)
Education in years, median (range)	14 (7–20)
Employment, N (%)	
Working	36 (46%)
Not working due to their illness	22 (28%)
Retired	20 (26%)
Karnofsky Performance Score mean (range)	90 (70–100)
Tumour type, N (%)	
Meningioma	21 (27%)
Pituitary adenoma	17 (22%)
Glioma grade II	18 (23 %)
Glioma grade III	12 (15%)
Medulloblastoma, NOS	7 (9%)
Other rare brain tumours	3 (4%)
Surgery, N (%)	
None	3 (4%)
Biopsy	11 (14%)
Partial tumour resection	30 (39%)
Gross tumour resection	34 (43%)
Radiation	
60.0 Gy/30	20 (26%)
56.0 Gy/28	1 (1%)
54.0 Gy/30	28 (36%)
50.4 Gy/28	4 (5%)
50.0 Gy/25	1 (1%)
45.0 Gy/25	22 (28%)
44.0 Gy/24	2 (3%)
Number of surgeries N (%)	
None	3 (4%)
1	45 (58%)
1+	30 (38%)
Location, N (%)	
Frontal lobe left	9 (12%)
Frontal lobe right	8 (10%)
Temporal lobe left	6 (8%)
Temporal lobe right	2 (2%)
Parietal lobe left	4 (5%)
Parietal lobe right	2 (3%)
Fossa posteria	7 (9%)
Thalamus	2 (2%)
Midline	4 (5%)
Base of skull	34 (44%)
Antiepileptic drug, N (%)	
Yes	21 (27%)
No	57 (73%)
Antidepressants, N (%)	
Yes	9 (12%)
No	69 (88%)
Chemotherapy, N (%)	
None	59 (76%)
Procarbazine, Lomustine and Vincristine	7 (9%)
Temozolomide	2 (2%)
Other	10 (13%)
Years since diagnosis, median (range)	6.6 (1–27)
Years since radiation therapy, median (range)	4.6 (1–9)
EORTC QLQ-C30, mean (SD)	85.49 (13.22)
PAOFI, mean (SD)	
Memory	46.17 (8.87)
Language and communication	44.18 (6.82)
Motor and sensory	27.11 (3.35)
Higher Level of Cognitive Function	44.54 (8.79)
HADS, mean (SD)	
Depression	2.86 (3.41)
Anxiety	4.21 (3.65)
PSS, mean (SD)	11.47 (7.19)
FACIT-Fatigue, mean (SD)	40.55 (9.48)

N: number of patients. NOS: not otherwise specified. SD: standard deviation. EORTC QLQ-C30: Health Related Quality of life. PAOFI: Patient's Assessment of Own Functioning Inventory, with the Memory, Language and Higher Level of Cognitive Function (HLCF) subscales. HADS: The Hospital Anxiety and Depression Scale. PSS: The Perceived Stress Scale. FACIT-Fatigue: with Functional Assessment of Chronic Illness Therapy.

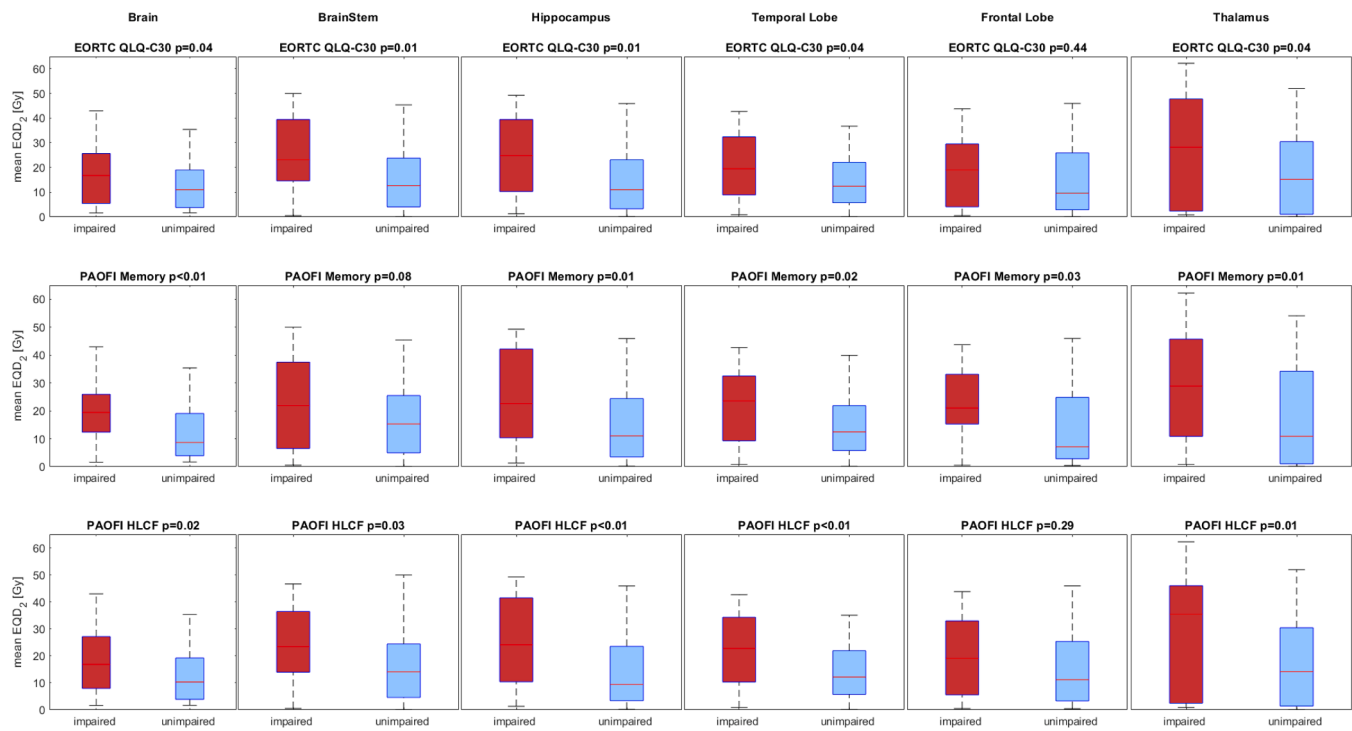


Fig. 1. EQD₂ of brain structures and outcomes on EORTC QLQ-C30, PAOFI Memory and PAOFI HLCF in impaired and unimpaired patients. EQD₂; biological equivalent doses in 2 Gy fractions. EORTC QLQ-C30: Health Related Quality of life. PAOFI: Patient's Assessment of Own Functioning Inventory with the Memory and Higher Level of Cognitive Function (HLCF) subscales. * T-test, two-tailed p value < 0.05. Note: For the EORTC QLQ-C30 and the PAOFI, scores were dichotomized into "impaired group" (the 25% of patients with the poorest scores) and the "unimpaired group" (the remaining 75% with better scores). For complete dataset, see Supplementary Table 2.

PAOFI Language and PAOFI HLCF subscales (Table 2). Epilepsy was not associated with differential outcomes on the EORTC QLQ-C30 and the PAOFI subscales. Patients who did not work due to their brain tumour scored significantly lower on the EORTC QLQ-C30 ($p < 0.01$) and on the PAOFI Memory ($p < 0.01$), Language ($p < 0.01$) and HLCF subscales ($p < 0.01$) compared with patients who continued to work at some level (Table 3). Tumour size was correlated with scores from the PAOFI

Table 2
Correlation between EORTC QLQ-C30 and PAOFI subscales, and HADS Depression, HADS Anxiety, PSS and FACIT Fatigue.

PROs Pearsons correlation	EORTC QLQ-C30	PAOFI Memory	PAOFI Language	PAOFI Motor	PAOFI HLCF
HADS depression	−0.51*	−0.54*	−0.54*	−0.20	−0.56*
p value	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)	($p = 0.09$)	($p < 0.01$)
HADS anxiety	−0.49*	−0.39*	−0.38*	−0.16	−0.47*
p value	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)	($p = 0.16$)	($p < 0.01$)
PSS	−0.56*	−0.55*	−0.60*	−0.18	−0.63*
p value	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)	($p = 0.12$)	($p < 0.01$)
FACIT- Fatigue	0.80*	0.55*	0.58*	0.37*	0.66*
p value	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)	($p < 0.01$)

PROs: Patient-reported outcomes. EORTC QLQ-C30: EORTC Health Related Quality of life questionnaire. PAOFI: Patient's Assessment of Own Functioning Inventory, with the Memory, Language and Higher Level of Cognitive Function (HLCF) subscales. HADS depression and anxiety. The Hospital Anxiety and Depression Scale. PSS; The Perceived Stress Scale, FACIT-Fatigue, with Functional Assessment of Chronic Illness Therapy. *Pearson test, two-tailed p value < 0.05.

Table 3

PRO score between patients with or without epilepsy and with and without work (independent sample t -test).

	PROs	N = yes	N = no	Mean score (SD) Yes	Mean score (SD) No	p value	Effect size
Epilepsy	EORTC QLQ-C30	21	57	85 (15.53)	86 (12.42)	0.86	0.07
	PAOFI Memory	21	55	44 (8.79)	47 (8.83)	0.18	0.34
	PAOFI Language	21	55	44 (7.34)	44 (6.67)	0.67	0.00
	PAOFI HLCF	21	55	44 (6.99)	45 (9.44)	0.95	0.12
	Working status	36	22	89 (10.21)	75 (14.43)	<0.01*	1.12
Working status	EORTC QLQ-C30	35	21	50 (5.99)	40 (9.88)	<0.01*	1.22
	PAOFI Memory	35	21	46 (5.47)	40 (6.48)	<0.01*	1.00
	PAOFI Language	35	21	47 (6.40)	40 (9.57)	<0.01*	0.86
	PAOFI HLCF	35	21	47 (6.40)	40 (9.57)	<0.01*	0.86

Working status means working (full or part time) or not working due to their illness. EORTC QLQ-C30: Health Related Quality of life. PAOFI: Patient's Assessment of Own Functioning Inventory, with the Memory, Language and Higher Level of Cognitive Function (HLCF) subscales. Effect size of 0.2 is considered "small" effect size, of 0.5 represent a "medium" effect size and 0.8 a "large" effect size. * T-test, two-tailed p value < 0.05.

Memory ($p = 0.02$) and PAOFI Language ($p = 0.01$) subscales, but no other correlations with PROs were found for tumour size, age, tumour grade, gender and time since diagnosis (Supplementary Table 3).

3.4. Pros and cognitive test results

We previously found a correlation between self-reported cognitive function and neuropsychological tests results in a group of irradiated and non-irradiated brain tumour patients [21]. In this analysis we report these findings only for the irradiated patients included in this study. Statistically significant correlations ($r = 0.27$ – 0.54 , $p = 0.02$ to < 0.01) were found between the PAOFI Memory, PAOFI Language and PAOFI HLCF subscales and the following neuropsychological tests: TMT A (processing speed), TMT B (executive function), HVLT-R total (verbal learning and memory), HVLT-R delayed (delayed recall), COWAT animal (word fluency), COWAT letter S (word fluency) and WAIS coding (processing speed) with higher levels of self-reported cognitive impairment being associated with lower performance on the neuropsychological tests. STROOP interference (executive function) was correlated with the PAOFI Language subscale ($r = 0.29$, $p = 0.01$), but not with PAOFI Memory or PAOFI HLCF subscales. For the PAOFI Motor subscale there was a correlation to TMT A ($r = 0.49$, $p = 0.02$), but no other tests (Supplementary Table 4).

Discussion

This cross-sectional study aimed to explore associations between RT dose and various PROs, with a primary focus on HRQoL and self-reported cognitive function. Our study demonstrated several associations between RT doses to the brain and HRQoL, fatigue, and self-reported cognition suggesting that RT dose may have negative and noticeable effects on a patient's daily life. Patients in the present study who had received a higher radiation dose to the total brain, brainstem and hippocampus, temporal lobes and thalamus scored poorer on HRQoL and more problems in the areas of cognition involving memory and higher level cognitive functioning. Furthermore, patients who had received higher RT doses to the brainstem, hippocampus, temporal lobes and thalamus experienced severe fatigue.

Studies examining the association between RT dose and PROs are in general inconsistent. In one study where prescription total dose was high (59.4 Gy), there was a correlation [18] whilst another with lower dose (< 50.4 Gy) did not find associations between RT and HRQoL [17]. Klein et al. found that RT was not associated with lower levels of self-reported cognitive function [20]. Tabrizi et al. found that dose to hippocampus did not differ in patients with or without reported toxicity in low grade glioma treated with proton therapy receiving 54 Gy [22]. Compared with the present study, these differences could be explained by the inclusion of various PROs measures, tumour types, differences in RT regimens and follow-up. In these studies, only one [17] used the EORTC QLQ-C30 to examine HRQoL. The other PRO measures used also differed from the present study. The differences in the instruments used could be one explanation for the between-study differences in associations generally found in the literature between RT dose and PROs.

In the present study, higher levels of depression, anxiety, stress and fatigue were associated with impaired HRQoL and self-reported cognitive functioning. Given the correlational nature of our analyses, it is difficult to distinguish the effects of RT from those of stress and fatigue symptoms. However, the findings are suggestive of the importance of considering the potential impact of RT dose on HRQoL and self-reported cognition when determining treatment regimens. In addition, they also highlight the importance of screening for depression, anxiety, stress and fatigue when assessing HRQoL and self-reported cognitive functions in brain tumour patients, since they are associated with these functions.

Our results show that patients who maintained employment scored better on HRQoL and reported better cognitive functioning than patients who had given up work due to their brain tumour. Again, due to the nature of the study, we are unable to determine what caused the reduced HRQoL – the experience of cognitive decline or the loss of work. Epilepsy status, on the other hand, was not associated with HRQoL or self-reported cognition which is in contrast to previous studies showing an

association between epilepsy (or being on antiepileptic drugs) and reduced self-reported cognition and HRQoL [20,24].

In comparison to a reference cohort of a healthy Danish population, and brain tumour patients in other studies, the patients in our study reported fairly high HRQoL [4,24,46,47]. These relatively high HRQoL scores may be explained by a so-called “response shift” – a situation in which patients who experience a change in health over time become more ready to accept their situation, potentially influencing their appraisal of HRQoL in a favourable way [4]. Taphoorn et al. reported improvement in HRQoL over time after RT in glioma patients supporting such a response shift [10].

We assessed associations between self-reported cognition and objectively assessed functions as measured by neuropsychological assessments. In a previous publication we found statistically significant associations between self-reported cognition as assessed by the PAOFI and objectively-assessed cognitive functions in the domains of verbal learning and memory, processing speed, verbal fluency and executive function in a group of radiated and non-irradiated brain tumour patients [21]. In the present study focusing on the irradiated group only, we found that these associations are maintained. The agreement between the patients' perceptions of their cognitive functions and cognitive test scores supports the use of PAOFI as an important tool in follow-up after RT for brain tumours. Nonetheless, we do consider PAOFI and testing to be complementary. Measures of perceived cognitive problems can provide important data that supports and adds to objective neuropsychological testing by increasing our understanding of the life activities that may be disrupted by cognitive deficits after RT [15].

The high participation rate and sample size are strengths of the present study. We used validated PRO questionnaires regarding a broad spectrum of issues known to impact brain tumour patients [9,19,20,21]. There are, however, some limitations. The lack of pre-treatment status due to the cross-sectional study design and the heterogeneous patient cohort limit the interpretability of the findings. Moreover, there are no recommended standardised cut-off scores for the quality of life and self-reported cognition measures used for patients treated for a brain tumour. Given the exploratory and hypothesis-generating nature of the study, we undertook broad testing of associations between PROs and RT doses to different brain structures, but did not adjust for multiple comparisons, due to the limited sample size and the fact that the specific PROs may not be independent of each other. This carries a risk of type 1 errors.

Furthermore, in recent years, a connectionist view, i.e., one where functionally linked and topographically distributed large scale networks underlie cognition [48], has challenged the localizationist perspective taken in this study. Cognitive deficits in glioma patients have been found associated with altered brain functional connectivity [49,50]. Global functional connectivity is lower in patients with IDH wild-type compared to diffuse glioma with IDH mutation, leading to poorer cognitive function [49]. While the localizationist perspective has been used to define organs at risk, brain connectomics have matured into a well-established tool for investigating the cerebral networks underlying cognition [50]. Herbert and Duffau propose an alternative meta-networking theory, which holds that complex cognitions and behaviour arise from the spatiotemporal integration of distributed specialized networks underlying cognition [48]. From a connectionist perspective, analyzing association between PROs and radiation dose in the brain and its substructures such as hippocampi, frontal lobes, temporal lobes etc. may be inadequate and too simplistic [48]. In the future, a redefinition of organs at risk may be needed.

Nevertheless, there is little established knowledge on PRO dose–effect relationships in the brain in general. The results of this study may still provide important information that can guide future studies in this field. PROs of treatment related side-effects and their associations with radiation doses to the brain and its sub-structures can provide important information on radiation tolerance to the brain and sub-structures. Such information provides evidence regarding which brain sub-structures are

likely to be associated with specific side-effects and it can then be translated into dose-volume constraints used in RT planning. Furthermore, when assessing brain tumour patients' cognitive function, the assessment of patient reports of cognitive problems gives health care providers important complementary information to standard neuropsychological testing by increasing our understanding of the life activities that may be disrupted by cognitive deficits after RT.

5. Conclusion

High radiation doses to specific brain structures may be associated with impaired HRQoL and self-reported cognitive function with potentially negative implications to patients' daily lives. Patient-reported outcomes of treatment-related side-effects and their associations with radiation doses to the brain and its sub-structures may provide important information on radiation tolerance to the brain and sub-structures. These findings require further validation in prospective trials with pre-treatment assessment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Prof Morten Høyer received support for the present study from the Danish Cancer Society (R124-Rp15398). Dr. Ali Amidi receives support from the Danish Cancer Society (R174-A11447-17-S52) and Dr. Lisa M. Wu from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie program (754513) and the Aarhus University Research Foundation.

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

ClinicalTrials.gov number: ID NCT04118426.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.09.006>.

References

- [1] Saad S, Wang TJC. Neurocognitive Deficits After Radiation Therapy for Brain Malignancies. *Am J Clin Oncol* 2015;38(6):634–40. <https://doi.org/10.1097/COC.0000000000000158>.
- [2] Redmond KJ, Mahone EM, Terezakis S, et al. Association between radiation dose to neuronal progenitor cell niches and temporal lobes and performance on neuropsychological testing in children: a prospective study. doi: 10.1093/neuonc/nos303.
- [3] Hahn CA, Zhou S-M, Raynor R, Tisch A, Light K, Shafman T, et al. Dose-dependent effects of radiation therapy on cerebral blood flow, metabolism, and neurocognitive dysfunction. *Int J Radiat Oncol Biol Phys* 2009;73(4):1082–7. <https://doi.org/10.1016/j.ijrobp.2008.05.061>.
- [4] Dirven L, Aaronson NK, Heimans JJ, Taphoorn MJB. Health-related quality of life in high-grade glioma patients. *Chin J Cancer*. 2014;33(1):40–5. <https://doi.org/10.5732/cjc.013.10214>.
- [5] Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Int J Radiat Oncol Biol Phys* 2017;26(5):617–24. <https://doi.org/10.1002/pon.v26.510.1002/pon.4046>.
- [6] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016;131(6):803–20. <https://doi.org/10.1007/s00401-016-1545-1>.
- [7] Ostrom QT, Gittleman H, Xu J, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro Oncol*. 2016;18:v1–v75. doi: 10.1093/neuonc/nov207.
- [8] Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol* 2016;17(9):e383–91. [https://doi.org/10.1016/S1470-2045\(16\)30321-7](https://doi.org/10.1016/S1470-2045(16)30321-7).
- [9] McAleer MF, Brown PD. Neurocognitive function following therapy for low-grade gliomas. *Semin Radiat Oncol*. 2015;25(3):210–8. <https://doi.org/10.1016/j.semradi.2015.02.005>.
- [10] Taphoorn MJB, van den Bent MJ, Mauer MEL, Coens C, Delattre J-Y, Brandes AA, 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):5723–30. <https://doi.org/10.1200/JCO.2007.12.7514>.
- [11] Coomans MB, Dirven L, Aaronson NK, et al. Symptom clusters in newly diagnosed glioma patients: which symptom clusters are independently associated with functioning and global health status? *Neuro Oncol*. 2019;21(11):1447–1457. doi: 10.1093/neuonc/noz118.
- [12] Armstrong TS, Dirven L, Arons D, Bates A, Chang SM, Coens C, et al. Glioma patient-reported outcome assessment in clinical care and research: a Response Assessment in Neuro-Oncology collaborative report. *Lancet Oncol* 2020;21(2):e97–103. [https://doi.org/10.1016/S1470-2045\(19\)30796-X](https://doi.org/10.1016/S1470-2045(19)30796-X).
- [13] Haldbo-Classen L, Amidi A, Lukacova S, Wu LM, Oettingen GV, Lassen-Ramshad Y, et al. Cognitive impairment following radiation to hippocampus and other brain structures in adults with primary brain tumours. *Radiother Oncol* 2020;148:1–7. <https://doi.org/10.1016/j.radonc.2020.03.023>.
- [14] Chelune GJ, Heaton RK, Lehman RAW. Neuropsychological and personality correlates of patients' complaints of disability. *Adv Clin Neuropsychol* 1986;3: 95–126. https://doi.org/10.1007/978-1-4613-2211-5_4.
- [15] Schwartz CE, Kozora E, Zeng Q. Towards patient collaboration in cognitive assessment: Specificity, sensitivity, and incremental validity of self-report. *Ann Behav Med* 1996;18(3):177–84. <https://doi.org/10.1007/BF02883395>.
- [16] Lisa M. Wu, Jane Austin, Jada G. Hamilton, Luis Isola, Scott Rowley, Rachel Warbet, Gary Winkel WHR, Rini C. Self-efficacy beliefs mediate the relationship between subjective cognitive functioning and physical and mental well-being after hematopoietic stem cell transplant. *Psychooncology*. 2012;21(11):1175–1184. doi: 10.1002/pon.2012.
- [17] Dirven L, Reijneveld JC, Taphoorn MJB, Coens C, El-Badawy SA, Tzuk-Shina T, et al. Clinical investigation impact of radiation target volume on health-related quality of life in patients with low-grade glioma in the 2-year period post treatment: a secondary analysis of the EORTC 22033–26033 radiation oncology. *Int J Radiat Oncol Biol Phys* 2019;104(1):90–100. <https://doi.org/10.1016/j.ijrobp.2019.01.003>.
- [18] Kiebert GM, Curran D, Aaronson NK, Bolla M, Menten J, Rutten EHJM, et al. Quality of life after radiation therapy of cerebral low-grade gliomas of the adult: results of a randomised phase III trial on dose response (EORTC trial 22844). *Eur J Cancer* 1998;34(12):1902–9. [https://doi.org/10.1016/S0959-8049\(98\)00268-8](https://doi.org/10.1016/S0959-8049(98)00268-8).
- [19] Hendrix P, Hans E, Griessnauer CJ, Simgen A, Oertel J, Karbach J. Neurocognitive function surrounding the resection of frontal WHO Grade I meningiomas: a prospective matched-control study. *World Neurosurg* 2017;98:203–10. <https://doi.org/10.1016/j.wneu.2016.10.095>.
- [20] Klein M, Heimans JJ, Aaronson NK, van der Ploeg HM, Grit J, Muller M, 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):1361–8. [https://doi.org/10.1016/S0140-6736\(02\)11398-5](https://doi.org/10.1016/S0140-6736(02)11398-5).
- [21] Haldbo-Classen L, Amidi A, Wu LM, Lukacova S, Oettingen GV, Gottrup H, et al. Long-term cognitive dysfunction after radiation therapy for primary brain tumors. *Acta Oncol (Madr)* 2019;58(5):745–52. <https://doi.org/10.1080/0284186X.2018.1557786>.
- [22] Tabrizi S, Yeap BY, Sherman JC, Nachtigall LB, Colvin MK, Dworkin M, et al. Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma. *Radiother Oncol* 2019;137: 95–101. <https://doi.org/10.1016/j.radonc.2019.04.027>.
- [23] Lambrecht M, Eekers DBP, Alapetite C, Burnet NG, Calugaru V, Coremans IEM, et al. Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus. *Radiother Oncol* 2018;128(1):26–36. <https://doi.org/10.1016/j.radonc.2018.05.001>.
- [24] Aaronson NK, Taphoorn MJB, Heimans JJ, Postma TJ, Gundy CM, Beute GN, et al. Compromised health-related quality of life in patients with low-grade glioma. *J Clin Oncol* 2011;29(33):4430–5. <https://doi.org/10.1200/JCO.2011.35.5750>.
- [25] Danish Neuro Oncology Group. DNOG - Contouring guidelines. www.dnog.dk.
- [26] Daniëlle Eekers, Lieke In T Ven, Erik Roelofs, Alida Postma EGT. EPTN International Neurological Contouring Atlas. doi: 10.17195/candat.2017.08.1.
- [27] Baumann M, Begg AC BS et al. Basic Clinical Radiobiology. Vol 86. 4. edition. (Albert JM and van der K, ed.). Boca Raton, FL 33487-2742: CRC Press. Taylor and Francis Group; 2010. doi: 10.3109/09553002.2010.496030.
- [28] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, 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):365–76. <https://doi.org/10.1093/jnci/85.5.365>.
- [29] Kasper B. The EORTC QLQ-C30 summary score as a prognostic factor for survival of patients with cancer: a commentary. *Oncologist* 2020;25(4):2019–20. <https://doi.org/10.1634/theoncologist.2019-0749>.
- [30] Giesinger JM, Kieffer JM, Fayes PM, Groenewold M, Petersen MA, Scott NW, et al. Replication and validation of higher order models demonstrated that a summary

- score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol* 2016;69:79–88. <https://doi.org/10.1016/j.jclinepi.2015.08.007>.
- [31] Richardson-Vejlgaard R, Dawes S, Heaton RK, Bell MD. Validity of cognitive complaints in substance-abusing patients and non-clinical controls: The Patient's Assessment of Own Functioning Inventory (PAOFI). *Psychiatry Res* 2009;169(1): 70–4. <https://doi.org/10.1016/j.psychres.2008.06.018>.
- [32] Van Dyk K, Ganz PA, Ercoli L, Petersen L, Crespi CM. Measuring cognitive complaints in breast cancer survivors: psychometric properties of the patient's assessment of own functioning inventory. *Support Care Cancer* 2016;24(12): 4939–49. <https://doi.org/10.1007/s00520-016-3352-6>.
- [33] Facit. Facit-F. English. 2007;(November):4-5. <http://www.facit.org/FACITOrg/Questionnaires>.
- [34] Redd WH, Valdimarsdottir H, Wu L, et al. Fatigue : a preliminary study. 2015;23 (12):1431-1434. doi:10.1002/pon.3553.Systematic.
- [35] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361–70. <https://doi.org/10.1111/j.1600-0447.1983.tb09716.x>.
- [36] Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes*. 2003;1:6-9. doi: 10.1186/1477-7525-1-29.
- [37] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24(4):385. <https://doi.org/10.2307/2136404>.
- [38] Eskildsen A, Dalgaard VL, Nielsen KJ, Andersen JH, Zachariae R, Olsen LR, et al. Cross-cultural adaptation and validation of the danish consensus version of the 10-item perceived stress scale. *Scand J Work Environ Heal* 2015;41(5):486–90. <https://doi.org/10.5271/sjweh.3510>.
- [39] State of New Hampshire Employee Assistance Program. Perceived Stress Scale Score Cut Off. State New Hampsh Empl Assist Progr. 1983;2. doi: 10.1037/t02889-000.
- [40] Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8(3):271–6. <https://doi.org/10.2466/pms.1958.8.3.271>.
- [41] Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test? Revised: normative data and analysis of inter-form and test-retest reliability. *Clin Neuropsychol (Neuropsychology, Dev Cogn Sect D)*. 1998;12(1):43–55. <https://doi.org/10.1076/clin.12.1.43.1726>.
- [42] Thurstone LL. Primary mental abilities. *Science*. 1948;108(2813):585. <http://www.ncbi.nlm.nih.gov/pubmed/18933605>. Accessed August 22, 2018.
- [43] Solutions S. Wechsler Adult Intelligence Scale — Fourth Edition (WAIS – IV). San Antonio. 2014;91(1):1-3. doi: 10.1016/j.ejcb.2011.01.011.
- [44] Wiens AN, Fuller KH, Crossen JR. Paced auditory serial addition test: adult norms and moderator variables. *J Clin Exp Neuropsychol* 1997;19(4):473–83. <https://doi.org/10.1080/01688639708403737>.
- [45] Stroop Ridley. Studies of Interference in Serial Verbal Reactions. 1935.
- [46] Gustafsson M, Edvardsson T, Ahlström G. The relationship between function, quality of life and coping in patients with low-grade gliomas. *Support Care Cancer* 2006;14(12):1205–12. <https://doi.org/10.1007/s00520-006-0080-3>.
- [47] Juul T, Petersen MA, Holzner B, Laurberg S, Christensen P, Grønvald M. Danish population-based reference data for the EORTC QLQ-C30: associations with gender, age and morbidity. *Qual Life Res* 2014;23(8):2183–93. <https://doi.org/10.1007/s11136-014-0675-y>.
- [48] Guillaume Herbet, Hugues Duffau. Physiological Reviews Revisiting the functional anatomy of the human brain : toward a meta-networking graphical abstract authors revisiting the functional anatomy of the human brain : toward a meta-networking theory of cerebral functions. 2020;1181-1228. doi: 10.1152/physrev.00033.2019.
- [49] Derks J, Kulik S, Wesseling P, Numan T, Hillebrand A, van Dellen E, et al. Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity. *Brain Behav*. 2019;9(4):e01204. <https://doi.org/10.1002/brb3.2019.9.issue-410.1002/brb3.1204>.
- [50] Noll KR, Chen HS, Wefel JS, Kumar VA, Schomer DF. Alterations in functional connectomics associated. 2021;88(3):544-551. doi: 10.1093/neuros/nyaa453.