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Original Article

Health-related quality of life after prophylactic cranial irradiation for stage III non-small cell lung cancer patients: Results from the NVALT-11/DLCRG-02 phase III study

W.J.A. Witlox^{a,*}, B.L.T. Ramaekers^a, M.A. Joore^{a,b}, A.-M.C. Dingemans^c, J. Praag^d, J. Belderbos^e, C. Tissing-Tan^f, G. Herder^g, T. Haitjema^h, J.F. Ubbelsⁱ, J. Lagerwaard^j, S.Y. El Sharouni^k, J.A. Stigt^l, E.F. Smit^m, H. van Tinterenⁿ, V. van der Noortⁿ, H.J.M. Groen^o, D.K.M. De Ruyscher^{p,q}

^a Maastricht University Medical Centre⁺, Department of Clinical Epidemiology and Medical Technology Assessment; ^b Care and Public Health Research Institute (CAPHRI), Maastricht University; ^c Maastricht University Medical Center⁺, Department of Pulmonology, GROW Research Institute; ^d Erasmus University Medical Center, Department of Radiation Oncology, Rotterdam; ^e Netherlands Cancer Institute (NKI), Department of Radiation Oncology, Amsterdam; ^f Radiotherapy Institute Arnhem, Arnhem; ^g Antonius Hospital Nieuwegein, Department of Pulmonology, The Netherlands; ^h Medical Center Alkmaar, Department of Pulmonology; ⁱ University of Groningen, University Medical Center Groningen, Department of Radiation Oncology; ^j Free University Medical Center, Department of Radiation Oncology, Amsterdam; ^k University Medical Center Utrecht, Department of Radiation Oncology; ^l Isala Hospital, Department of Pulmonology, Zwolle; ^m Netherlands Cancer Institute (NKI), Department of Pulmonology, Amsterdam; ⁿ Netherlands Cancer Institute (NKI), Department of Biometrics, Amsterdam; ^o University of Groningen and University Medical Center Groningen, Department of Pulmonary Diseases; ^p Maastricht University Medical Centre⁺, Department of Radiation Oncology (Maastricht Clinic), GROW School of Oncology and Developmental Biology, The Netherlands; ^q KU Leuven, Radiation Oncology, Belgium

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ABSTRACT

Background and purpose: The NVALT-11/DLCRG-02 phase III trial (clinicaltrials.gov identifier: NCT01282437) showed that, after standard curative intent treatment, prophylactic cranial irradiation (PCI) decreased the incidence of symptomatic brain metastases (BM) in stage III non-small cell lung cancer (NSCLC) patients compared to observation. In this study we assessed the impact of PCI on health-related quality of life (HRQoL). In addition, an exploratory analysis was performed to assess the impact of neurocognitive symptoms and symptomatic BM on HRQoL.

Materials and methods: Stage III NSCLC patients were randomized between PCI and observation. HRQoL was measured using the EuroQol 5D (EQ-5D-3L), EORTC QLQ-C30 and QLQ-BN20 instruments at completion of standard curative intent treatment and 4 weeks, 3, 6, 12, 24 and 36 months thereafter.

Generalized linear mixed effects (GLM) models were used to assess the impact of PCI compared to observation over time on three HRQoL metrics: the EORTC QLQ-C30 global health status and the EQ-5D-3L utility and visual analogue scale (EQ VAS) scores.

Results: In total, 86 and 88 patients were included in the PCI and observation arm, with a median follow-up of 48.5 months (95% CI 39–54 months). Baseline mean HRQoL scores were comparable between the PCI and observation arm for the three HRQoL metrics. In the GLM models, none of the HRQoL metrics were clinically relevant or statistically significantly different between the PCI and the observation arm (*p*-values ranged between 0.641 and 0.914).

Conclusion: No statistically significant nor a clinically relevant impact of PCI on HRQoL was observed.

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Patients with non-small cell lung cancer (NSCLC) frequently develop brain metastases (BM) [1]. In patients with stage III NSCLC staged with a magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain, the incidence of BM is currently around 30%, and prognosis is typically poor [1]. Once BM have occurred, patients are treated with the intention to maintain their

health-related quality of life (HRQoL) during their remaining lifespan [2].

The effectiveness of prophylactic cranial irradiation (PCI) to reduce BM has been investigated in several randomized controlled trials (RCTs) [3–11]. The NVALT-11/DLCRG-02 trial [12] showed that the proportion of patients with symptomatic BM two years after PCI was reduced to 7.0% in the PCI arm, compared to 27.2% in the observation arm (*p* ≤ 0.001). However, no statistically significant difference in overall survival (OS) was observed between the arms (HR, 0.9 [95% confidence interval (CI), 0.62 to 1.29]). As PCI is also associated with neurocognitive toxicity, it could negatively

* Corresponding author at: Maastricht University Medical Center+ (MUMC+), Department of Clinical Epidemiology and Medical Technology Assessment, P. Debeyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

E-mail address: willem.witlox@mumc.nl (W.J.A. Witlox).

impact patients' HRQoL [10]. In the NVALT-11/DLRCG-02 trial, mainly grade 1 and 2 memory impairment (30% versus 8%) and cognitive disturbances (19% versus 3%) were increased in the PCI arm compared to observation. These side effects, together with the absence of an observed improvement in OS are the most likely reasons why PCI is not standard of care in stage III NSCLC. To inform this trade-off between the pros and cons of PCI, information about HRQoL is thus crucial. HRQoL can be evaluated using generic and disease-specific instruments, both of which were used in the NVALT-11/DLRCG-02 trial. The advantage of generic HRQoL instruments is that they can be used to evaluate HRQoL for many types of diseases and can easily be compared. However, generic HRQoL instruments have been criticized for their lack of sensitivity to detect small clinically important differences in treatment effects, for which disease-specific HRQoL instruments are usually more suitable [13]. Additionally, HRQoL metrics can be grouped based on the valuation perspective used (e.g. based on societal or patient preferences). For instance, the generic EuroQol-5D-3L (EQ-5D-3L) HRQoL instrument provides a patient valuation of HRQoL with a visual analogue scale (EQ VAS), as well as a HRQoL valuation from a societal perspective (by applying a so called tariff). In general, societal preferences are recommended for health economic evaluations (see for instance the Dutch guideline for economic evaluations in healthcare [14]).

In order to weigh the benefits of PCI by reducing symptomatic BM against the potential risk of neurocognitive decline, we here report the impact of PCI on generic and disease-specific HRQoL for stage III NSCLC patients included in the NVALT-11/DLRCG-02 phase III trial. In addition, we performed an exploratory analysis to assess the impact of neurocognitive symptoms and symptomatic BM on HRQoL.

Methods

Study

The primary results of the Dutch NVALT-11/DLRCG-02 randomized phase III trial have been reported previously [12]. In this trial, stage III NSCLC patients (staging included contrast-enhanced brain CT or MRI and a whole-body F-labeled fluorodeoxyglucose positron emission tomography-CT scan) were randomized between PCI and observation after standard curative intent treatment (mostly concurrent chemotherapy and radiotherapy) (Fig. 1). The primary endpoint of the study was the proportion of patients developing symptomatic BM within 24 months from randomization. Symptomatic BM were defined as a combination of key symptoms suggesting BM (signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures

and focal neurological symptoms) and MRI or CT proving evidence of BM. As specified in the study protocol, follow-up assessments were performed 4 weeks, 3, 6, 12, 24 and 36 months after completion of standard curative intent treatment, or earlier when symptoms of BM occurred. These assessments included both physician and patient reported measures. Brain imaging in order to detect BM was performed only after patients reported symptoms suggestive of BM or at the discretion of the treating physician. Once BM occurred, patients went off study and no additional information on HRQoL was collected. The study was conducted in agreement with the Declaration of Helsinki – Tokyo, Venice, Hong Kong, Somerset West, and Edinburgh amendments – and the laws and regulations of the Netherlands. The study was approved by the medical ethical committees of all participating hospitals in accordance with Dutch laws and regulations and was registered in The Netherlands Trial Registry (number NTR1601) and at clinicaltrials.gov (identifier: NCT01282437).

Health-related quality of life assessment

Generic HRQoL was measured using the EQ-5D-3L instrument. The EQ-5D-3L consists of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ VAS. The five dimensions can be answered with one of three possible responses (no problems, some problems or severe problems) [15]. These response scores were translated to utility scores using the Dutch tariff [16]. A utility score of 0 indicates death and a utility score of 1 indicates perfect health, while utility scores <0 indicate health states worse than death. A difference of 0.03 in EQ-5D-3L utility scores is considered clinically relevant [17].

For the assessment of disease-specific HRQoL, patients were asked to complete the EORTC QLQ-C30 and QLQ-BN20 instruments. The QLQ-C30 is a cancer-specific instrument, and consists of five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea/vomiting), six single items (dyspnea, loss of appetite, insomnia, constipation, diarrhea and financial problems) and a global health status scale [18]. The QLQ-BN20 is a brain cancer-specific supplement of the QLQ-C30, consisting of four multi-item scales (future uncertainty, visual disorder, motor dysfunction and communication deficits) and seven single-item scales (headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs and bladder control) [19]. Each item score is translated to a score between 0 and 100. For the functional scales, higher scores indicate better functioning, whereas higher symptom scores indicate more severe symptoms. A change or difference of 10 points has been suggested to be clinically relevant [20].

Fig. 1. Study design of the NVALT-11/DLRCG-02 study.

Statistical analysis

Patients' baseline characteristics and the proportions of HRQoL responses, as well as HRQoL scores of the EQ-5D-3L, EORTC QLQ-C30 and BN-20 were analyzed over time using descriptive statistics.

To address the research objectives, generalized linear mixed effects (GLM) models with random intercepts (with a Gaussian distribution and an identity link) were used to estimate the association between repeated measurements within individual subjects. The impact of PCI on HRQoL was analyzed using three metrics as dependent variables (EQ-5D-3L utility, EQ VAS and EORTC QLQ-C30 global health status). These analyses were performed using the intention-to-treat principle, including treatment allocation (PCI or observation), age, gender and smoking status as independent variables in the model. Backward elimination was used to select the best fitting regression model using an alpha of 0.05. The treatment allocation variable was forced into the model during this procedure. For consistency, an independent predictor was kept in the models of all HRQoL metrics if it significantly improved the model of at least one of the metrics.

To test the generalizability of the calculated EQ-5D-3L utility scores by the Dutch tariff, a sensitivity analysis was performed using the United Kingdom (UK) tariff [21]. Furthermore, in addition to the intention-to-treat analysis, the primary objective was also assessed using a per protocol analysis in which patients were grouped by the treatment received rather than by the treatment they were assigned to by randomization. All analyses were performed using Stata/SE 14.2, except for visualization of the results by boxplots, which was done using the ggplots2 package in R.

An exploratory analysis was performed to assess the impact of neurocognitive symptoms and symptomatic BM on HRQoL. This was done using the GLM approach as described above, with the addition of an independent variable to distinguish between patients (1) without neurocognitive symptoms and symptomatic BM, (2) with neurocognitive symptoms but without symptomatic BM, and (3) with both neurocognitive symptoms and symptomatic BM. This variable was also forced into the model, alongside the treatment variable, during the backward elimination procedure.

Results

Between 2009 and 2015, 87 patients were randomized to receive PCI, and 88 patients were randomized to the observation arm. One patient in the PCI arm was withdrawn from the study after randomization. The median follow-up was 48.5 months (95% CI, 39 to 54 months). Baseline characteristics (e.g. age, sex, smoking status, WHO performance status) were similar for both arms (Table 1).

Baseline HRQoL assessment was completed by 80.2% of the patients in the PCI arm and 84.1% of the patients in the observation arm. For both arms, the number of patients alive at a follow-up moment, as well as the number of patients alive reporting HRQoL, declined over time. The proportion of patients alive reporting HRQoL was lowest at 18 months for both arms, and ranged between 71.3% and 100.0% for the other time points (Fig. 2).

The dimensions of the EQ-5D-3L having the largest impact on HRQoL in both arms were the ability to perform usual activities and the degree to which patients experience pain/discomfort (Appendix A Table A1). Based on visual inspection of the EORTC QLQ-C30 functional scales and the EORTC QLQ-C30 and BN-20 symptom scales over time (Appendix A Figs. A1–A4), the mean cognitive functioning scores (PCI arm), mean physical functioning scores (both arms) and symptom scores of pain, insomnia (both arms) and appetite loss (observation arm) were below the corresponding mean EORTC reference values for NSCLC [22]. In contrast,

the mean emotional and role functioning scores were generally above their reference values in both arms.

Baseline mean HRQoL scores were comparable between PCI and observation for EQ-5D-3L utility (PCI: 0.80, observation: 0.79), EQ VAS (PCI: 63.2, observation: 65.0), and EORTC QLQ-C30 global health status (PCI: 62.9, observation: 63.7). The three HRQoL metrics suggested similar patterns between the PCI and the observation arm that were stable over time (Fig. 3a and Appendix A Table A2).

After backward elimination, next to treatment allocation, smoking status was also included in the final GLM models. Age and gender did not have a statistically significant impact on HRQoL and were eliminated from the model. All GLM models showed that over time, none of the HRQoL metrics were neither clinically relevant nor statistically significantly different between the PCI and the observation arm (*p*-values ranged between 0.641 and 0.914) (Table 2). Results of the per protocol analysis were similar to the intention-to-treat analysis (Appendix A Table A3). For all GLM analyses, results of the sensitivity analysis using EQ-5D-3L scores based on the UK tariff were similar to the results using the Dutch tariff (Appendix A Table A4).

The post-hoc exploratory analysis showed a statistically significant and clinically relevant lower HRQoL (utility score: -0.169 , $p < 0.001$, EQ VAS: -13.022 , $p < 0.001$, global health status: -10.207 , $p = 0.007$) in patients with both neurocognitive symptoms and symptomatic BM ($n = 2$ observations in PCI arm and $n = 23$ observations in no PCI arm) compared to patients without neurocognitive symptoms and symptomatic BM ($n = 343$ observations in PCI arm and $n = 384$ observations in no PCI arm). Additionally, the utility score was clinically relevant lower (-0.044 , $p = 0.059$) and the EQ VAS was statistically significantly lower (-4.154 , $p = 0.040$) in patients who developed neurocognitive symptoms without symptomatic BM ($n = 85$ observations in PCI arm and $n = 32$ observations in no PCI arm) compared to patients without neurocognitive symptoms and symptomatic BM (Table 3, Fig. 3b).

Discussion

We assessed the impact of PCI compared to observation on generic and disease-specific HRQoL in stage III NSCLC patients randomized in the NVALT-11/DLCRG-02 trial [12].

No clinically relevant nor statistically significant HRQoL differences were found between PCI and observation. HRQoL was both statistically significantly and clinically relevant lower in patients with both neurocognitive symptoms and symptomatic BM compared to patients without neurocognitive symptoms and symptomatic BM. For patients with neurocognitive symptoms without symptomatic BM this was only observed in generic HRQoL.

Most symptomatic BM were observed in the observation arm, whereas the observed number of neurocognitive symptoms without symptomatic BM was higher in the PCI arm. Hence, it is likely that the HRQoL benefit of PCI in reducing the number of patients with symptomatic BM was outweighed by the increased number of patients with neurocognitive symptoms. On the other hand, the increased disease-free survival in patients receiving PCI should be taken into account [11]. Therefore, there should be room for shared decision-making.

An alternative explanation of finding comparable HRQoL scores between both arms, and also a potential limitation of this study, might be that patients who developed symptomatic BM dropped out of the analysis and thus HRQoL might be potentially overestimated overall. However, if applicable this is likely to be more prominent in the observation arm as more symptomatic BM occurred in this arm. Furthermore, the NVALT-11/DLCRG-02 trial was not powered to detect a statistically significant difference between the study arms, as HRQoL was a secondary endpoint.

Table 1
Baseline characteristics of the patients per arm.

Characteristics		PCI (n = 86)	Observation (n = 88)	Total (n = 174)
Mean age (SD)		61 (8.35)	62 (7.68)	61 (7.99)
Sex (M)		58 (67%)	56 (64%)	114 (66%)
Smoking status	Current	35 (41%)	25 (28%)	60 (34%)
	Former	46 (53%)	60 (68%)	106 (61%)
	Never	4 (5%)	3 (3%)	7 (4%)
	Unknown	1 (1%)	0	1 (1%)
WHO performance status	0	32 (37%)	34 (39%)	66 (38%)
	1	50 (58%)	49 (56%)	99 (57%)
	2	4 (5%)	5 (6%)	9 (5%)
	Unknown	1 (1%)	0	1 (1%)
Histology	Adenocarcinoma	31 (36%)	41 (47%)	72 (41%)
	Squamous cell carcinoma	33 (38%)	29 (33%)	62 (36%)
	Large cell carcinoma	19 (22%)	13 (15%)	32 (18%)
	NOS	3 (3%)	5 (6%)	8 (5%)
Stage	IIIA	41 (48%)	52 (59%)	93 (53%)
	IIIB	44 (51%)	36 (41%)	80 (46%)
	Unknown	1 (1%)	0	1 (1%)
Prior treatment with curative intent	Concurrent CRT	56 (65%)	55 (62%)	111 (64%)
	Concurrent CRT and induction chemotherapy	16 (19%)	13 (15%)	29 (17%)
	Sequential CRT	6 (7%)	12 (14%)	18 (10%)
	Concurrent CRT followed by surgery	1 (1%)	1 (1%)	2 (1%)
	Concurrent CRT and induction chemotherapy followed by surgery	3 (3%)	4 (5%)	7 (4%)
	Other	3 (3%)	4 (5%)	7 (4%)
	NA	1 (1%)	0 (0%)	1 (1%)

Percentages may not total 100 due to rounding.

Abbreviations: CRT = chemoradiotherapy, M = male, NA = not applicable, NOS = not otherwise specified, PCI = prophylactic cranial irradiation, SD = standard deviation, WHO = World Health Organization.

Fig. 2. Expected and actual number of patients reporting HRQoL for the PCI arm (A) and observation arm (B) over time. The dots represent the averages over time. Footnote Fig. 2: The expected number of patients reporting HRQoL was defined as the total number of patients alive at an assessment point. The actual number of patients reporting HRQoL was defined as the expected number of patients reporting HRQoL minus the number of patients with incomplete/missing HRQoL instruments. An HRQoL measurement was considered incomplete/missing if global health status of the EORTC QLQ-C30 was missing or if one of the EQ-5D-3L dimensions or VAS was missing. Subsequently, the proportion of patients reporting HRQoL was calculated by dividing the actual number of patients reporting HRQoL by the expected number of patients reporting HRQoL per assessment point.

This seems more profound at later time points where the number of living patients decreased substantially. Nevertheless, we computed the power to detect (in a t-test) a clinically relevant difference between arms one month after randomization under the assumption that the standard deviations for the various HRQoL measures would be the same as those observed at baseline (that is: 0.2 points for the EQ-5D-3L utility, 16 points for the EQ-VAS and 19 points for the EORTC QLQ-C30 global health status). This yielded powers of 15%, 98% and 91% respectively for the three HRQoL measures.

The mean EQ-5D-3L utility scores were generally higher over time than the mean scores of the EQ VAS and EORTC QLQ-C30 global health status. Although there are differences in methods of elicitation, perspective and conceptualization between the EQ-5D-3L and EORTC QLQ-C30, this finding might suggest that the five dimensions of the EQ-5D-3L could not fully capture all relevant PCI (side)effects on HRQoL, and shows the importance of assessing HRQoL using both generic and disease-specific instruments and adopting a societal perspective as well as a patient perspective on the valuation of HRQoL.

Only a few studies previously assessed the impact of PCI on HRQoL in patients with NSCLC. Sun et al. [23] and Li et al. [9], including a total of 340 and 156 eligible stage III NSCLC patients respectively, measured disease-specific HRQoL (EORTC QLQ-C30, QLQ-BN20 and FACT-L). In line with our results, both studies showed that the disease-specific HRQoL was not statistically significantly different between PCI (30 Gy in 15 once-daily and 10 once-daily fractions, respectively) and observation (Appendix A, Table A5).

In small cell lung cancer (SCLC), multiple RCTs [24–26] examined the impact of PCI on HRQoL. The studies of Wolfson et al. [24] and Le Pechoux et al. [25] in patients with limited stage SCLC did not find any statistically significant difference in HRQoL between PCI delivered to a higher or lower dose (25 Gy in 10 once-daily fractions or 36 Gy in 18 once-daily or 24 twice-daily fractions). However, no observation arm was included in these RCTs. The study of Slotman et al. [26], which was done in patients with metastatic SCLC, showed a negative impact of PCI (20 Gy in 5

Fig. 3a. Boxplots visualizing the EQ-5D-3L utility score and scores of the EQ VAS and EORTC QLQ-C30 between PCI and observation. The open dots represent the averages over time. Abbreviations Fig. 3a: PCI = prophylactic cranial irradiation, VAS = visual analogue scale.

Table 2

Results of the generalized linear mixed effects models of the EQ-5D- (utility score and VAS) and EORTC QLQ-C30 (global health status) HRQoL instruments.

Impact of PCI	HRQoL instrument	HRQoL outcome measure	Treatment (PCI vs observation)	Smoking status	
				former vs never	current vs never
	EQ-5D-3L	Utility score	Coefficient	0.130	0.107
			95% CI	(0.009, 0.250)	(−0.017, 0.230)
			P-value	0.035	0.090
	EQ-5D-3L	VAS	Coefficient	7.816	7.358
			95% CI	(−2.072, 17.704)	(−2.754, 17.470)
			P-value	0.121	0.154
	EORTC QLQ-C30	Global health status	Coefficient	10.610	9.325
			95% CI	(−0.598, 21.818)	(−2.139, 20.789)
			P-value	0.064	0.111

Abbreviations: 95% CI = 95% confidence interval, PCI = prophylactic cranial irradiation, HRQoL = health-related quality of life, vs = versus.

or 8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions, or 30 Gy in 10 or 12 fractions) on HRQoL after three months compared with observation, and similar HRQoL scores at six and nine months. However, brain imaging was not mandatory in this trial and patients with metastases may not be comparable to those without detectable metastases at the time of diagnosis, as in our study (Appendix A, Table A5).

The role of PCI in prolonging long-term OS and strategies to reduce neurocognitive symptoms initiated by PCI, such as hippocampal sparing techniques or pharmacological interventions such as memantine, are promising future areas of

research [27–29]. Two recent studies by Belderbos et al. [30] and Gondi et al. [31], only reported in abstract form, show contradictory results regarding hippocampal sparing radiation techniques.

In conclusion, we did not observe a statistically significant nor a clinically relevant impact of PCI on HRQoL. Generic and disease-specific HRQoL were statistically significant and clinically relevant lower in patients with both neurocognitive symptoms and symptomatic BM, whereas for patients with neurocognitive symptoms without symptomatic BM this was only observed in generic HRQoL.

Table 3
Results of the exploratory analysis, assessing the impact of neurocognitive symptoms and symptomatic BM using generalized linear mixed effects models of the EQ-5D (utility score and VAS) and EORTC QLQ-C30 (global health status) QoL instruments.

QoL instrument			Treatment (PCI vs observation)	Smoking status		NCS and/or symptomatic BM	
				former vs never	current vs never	NCS w/o BM vs no NCS	NCS with BM vs no NCS
Impact of neurocognitive symptoms and symptomatic BM	EQ-5D-3L Utility score	Coefficient	0.009	0.131	0.114	−0.044	−0.169
		95% CI	(−0.040, 0.057)	(0.012, 0.251)	(−0.009, 0.236)	(−0.090, 0.002)	(−0.246, −0.091)
		P-value	0.726	0.032	0.069	0.059	<0.001
	EQ-5D-3L EQ VAS	Coefficient	−0.358	7.895	7.965	−4.154	−13.022
		95% CI	(−4.351, 3.635)	(−1.933, 17.724)	(−2.090, 18.020)	(−8.118, −0.190)	(−19.828, −6.216)
		P-value	0.861	0.115	0.121	0.040	<0.001
	EORTC QLC-C30 Global health status	Coefficient	−0.922	10.703	9.757	−2.712	−10.207
		95% CI	(−5.453, 3.610)	(−0.486, 21.891)	(−1.691, 21.204)	(−7.123, 1.698)	(−17.668, −2.747)
		P-value	0.690	0.061	0.095	0.228	0.007

Abbreviations: 95% CI = 95% confidence interval, NCS = neurocognitive symptoms, PCI = prophylactic cranial irradiation, QoL = quality of life, symptomatic BM = symptomatic brain metastases, vs = versus, w/o = without.

Fig. 3b. Boxplots visualizing the impact of neurocognitive symptoms and symptomatic BM on the three HRQoL metrics. The open dots represent the averages over time. Abbreviations Fig. 3b: BM = brain metastases, NCS = neurocognitive symptoms, VAS = visual analogue scale.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.10.016>.

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