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Self-Reported Cognitive Function and Quality of Life in Patients With SCLC in the Hippocampal Avoidance Prophylactic Cranial Irradiation Versus Prophylactic Cranial Irradiation Randomized Phase 3 Trial (NCT01780675)

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ABSTRACT

Introduction: In the randomized controlled trial in patients with SCLC comparing standard prophylactic cranial irradiation (PCI) with hippocampal avoidance PCI (HA-PCI), we did not observe beneficial effects of HA-PCI on tested cognition. Here, we report findings on self-reported cognitive functioning (SRCF) and quality of life (QoL).

Methods: Patients with SCLC were randomized to receive PCI with or without HA (NCT01780675) and assessed at baseline (82 HA-PCI and 79 PCI patients) and at 4, 8, 12, 18, and 24 months of follow-up, using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EORTC QLQ—brain cancer module (BN20). SRCF was assessed with the cognitive functioning scale of the EORTC QLQ-C30 and the Medical Outcomes Study questionnaire. A change of 10 points was used for minimal clinically important differences. Percentages of patients classified with having improved, stable, or deteriorated SRCF were compared between groups using chi-square tests. Changes in mean scores were analyzed using linear mixed models.

Results: There was no significant difference in the percentage of patients with deteriorated, stable, or improved SRCF between the treatment arms. Depending on the evaluated time point, 31% to 46% and 29% to 43% of patients in the HA-PCI and PCI arm, respectively, reported a deteriorated SRCF on the basis of the EORTC QLQ-C30 and Medical Outcomes Study. QoL outcomes were not significantly different between the study arms, except for physical functioning at 12 months ($p = 0.019$) and motor dysfunction at 24 months ($p = 0.020$).

Conclusions: Our trial did not find beneficial effects of HA-PCI over PCI on SRCF and QoL. The cognitive benefit of sparing the hippocampus in the context of PCI is still a subject of debate.

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Drs. Belderbos and Schagen contributed equally as last authors.

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Introduction

SCLC is characterized by early dissemination, including the brain.[1] At time of death, 50% to 65% of patients with SCLC have been diagnosed with having brain metastases (BMs).[2–4] BMs are associated with a considerable reduction in quality of life (QoL) and life expectancy.[5] Once BMs have occurred, patients are treated palliatively, aiming to maintain their QoL during their remaining lifespan.

Prophylactic cranial irradiation (PCI) reduces the incidence of BM and may prolong the overall survival.[4,6,7] One of the concerns of PCI is the potential for cognitive impairment and its effect on QoL.[8,9]

The NVALT-11 DLRCG-02 trial, in which PCI was compared with observation in patients with NSCLC, revealed increased self-reported memory impairment (30% versus 8%, respectively) and cognitive disturbances (19% versus 3%, respectively).[10] Nevertheless, no statistically significant nor clinically relevant impact of PCI compared with no PCI on patients' overall QoL was reported.[11]

Hippocampal avoidance PCI (HA-PCI) has the potential to preserve cognitive function, which may retain patients' QoL. A recent phase 3 trial (NRG CC001) of HA during whole-brain radiotherapy (WBRT) plus memantine versus WBRT plus memantine in 518 patients with overt BM mainly from NSCLC reported a better preserved cognitive function assessed with neuropsychological tests (including the Hopkins Verbal Learning Test—Revised [HVLT-R], Controlled Oral Word Association, and Trail Making Test [TMT]-A and TMT-B) and fewer self-reported cognitive symptoms (measured with the EuroQol-5D-5L [EQ-5D-5L] and MD Anderson Symptom Inventory—Brain Tumor questionnaire) among patients treated with HA-WBRT plus memantine compared with patients in the WBRT plus memantine arm.[12] No other significant differences between arms were observed over time on several aspects of QoL (measured with the EQ-5D-5L).[12] The phase 3 PREMER trial conducted in 150 patients with SCLC without BM who were randomized to receive PCI or HA-PCI also revealed better preserved cognitive function assessed by the Free and Cued Selective Reminding Test in the HA-PCI compared with the PCI arm.[13] In contrast, no significant differences were observed between arms on any scale of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and brain cancer module (BN20) up to 24 months of follow-up.[13]

The main objective of the Dutch-Flemish phase 3 trial was to investigate the benefit of HA-PCI on memory function in patients with SCLC compared with standard PCI using the HVLT-R total score.[14] No differences between the treatments were found at 4 months. Furthermore, no differences were found for other additional cognitive outcomes, despite an observed reduction in hippocampal atrophy in the HA-PCI compared with the PCI arm.[15] Nevertheless, both treatment modalities were associated with considerable brain injury.[15] Here, we report the study's secondary objectives: comparing patients' QoL, in particular their self-reported cognitive performance (SRCF) between HA-PCI and PCI.

Materials and Methods

Patient Selection

Eligibility criteria of the multicenter phase 3 trial (NCT01780675) have been published before.[14] In short, patients were included when they (1) had histologic- or cytologic-proven SCLC, stages I to III ("limited stage") or stage IV ("extensive stage"), (2) had clinical or radiologic evidence of BM on a contrast-enhanced magnetic resonance imaging scan, and (3) had no progressive disease after first-line chemoradiotherapy in stages I to III or after chemotherapy alone in stage IV.[14] Patients were excluded when they (1) are younger than 18 years, (2) had previous radiotherapy to the brain, or (3) received anticancer agents concurrently with PCI. All patients gave written informed consent. This trial (NCT01780675) was conducted according to the Declaration of Helsinki and approved by the Medical Ethics Committee of the Netherlands Cancer Institute.

Patients first received four courses of platinum-etoposide alone (stage IV) or concurrent chemoradiotherapy (stages I–III) followed by PCI. The interval between the last chemotherapy and the start of PCI was at least 3 weeks. The detailed magnetic resonance imaging acquisition and radiation treatment procedures have been previously described.[14,15] Briefly, patients were irradiated with a total dose of 25 Gy in 10 fractions, five times a week. The mean dose of the hippocampal avoidance zone of the HA-PCI was limited to 8.5 Gy.

QoL Assessment

Questionnaires were administered at baseline and at 4, 8, 12, 18, and 24 months after completion of (HA) PCI in the same session as the neuropsychological assessment. QoL and symptom burden were assessed by the

following: (1) The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), a 30-item questionnaire applicable for patients with cancer in general.[16] In addition to the domain of cognitive functioning (SRCF), four domains were selected for the current analyses, which are as follows: physical functioning, emotional functioning, role functioning, and fatigue. On the basis of the literature, we expected that these domains were relevant to the patients' daily life.[13,17] (2) The EORTC QLQ-Brain Cancer Module 20 (EORTC QLQ-BN20),[18] a 20-item questionnaire specific for patients with brain cancer, from which four domains were selected on the basis of similar studies involving patients with SCLC or NSCLC and BM, which are as follows:[19,20] motor dysfunction, future uncertainty, visual disorder, and communication deficit. For both the EORTC QLQ-C30 and BN20, symptoms in the past week were scored in a range from 1 (not at all) to 4 (very much). All raw scores were linearly transformed and scored from 0 to 100. A higher score on the functional domains indicated higher QoL, whereas a higher score on the symptom domains indicates poorer QoL. (3) The cognitive functioning questionnaire from the Medical Outcomes Study (MOS). The six-item questionnaire assessed day-to-day problems in cognitive functioning, asking patients whether in the past month they became confused, reacted slowly to things, had difficulty reasoning, were forgetful, had trouble keeping attention, or had difficulty concentrating. Symptoms in the past month were scored in a range from 1 (not at all) to 6 (all of the time). Scores were transformed to a range of 0 to 100, with higher scores indicating better cognitive functioning.

Statistical Analyses

Power calculation for the primary study cognitive outcome has been previously described.[14] In total, 168 patients were randomized. In this current study, QoL data were available for 161 patients. Patients' baseline characteristics, the proportion of QoL responses, and the QoL scores were analyzed over time using descriptive statistics.

Analyses were performed on individual and group level. For all three questionnaires, the following analyses are performed: (1) analyzing mean scores at each time interval and (2) analyzing clinical minimally important differences from baseline versus follow-up scores, using 10 points as cutoff for deterioration or improvement in scores.[21] Differences in percentage of patients that reported deteriorated, improved, or stable scores between the arms were investigated using Fisher's exact test.

On the group level, linear mixed models were used for all the three questionnaires, adding an interaction term for time by group to check for differences between the arms. Level of significance was set at p less than 0.05. Statistical analyses were performed using R-studio.

Results

Study Patients

Figure 1 reveals a flowchart of patients completing the SRCF and QoL questionnaires over time. According to intention to treat, 79 of 83 patients (95%) treated with PCI and 82 of 84 patients (98%) treated with HA-PCI completed the questionnaires at baseline. This

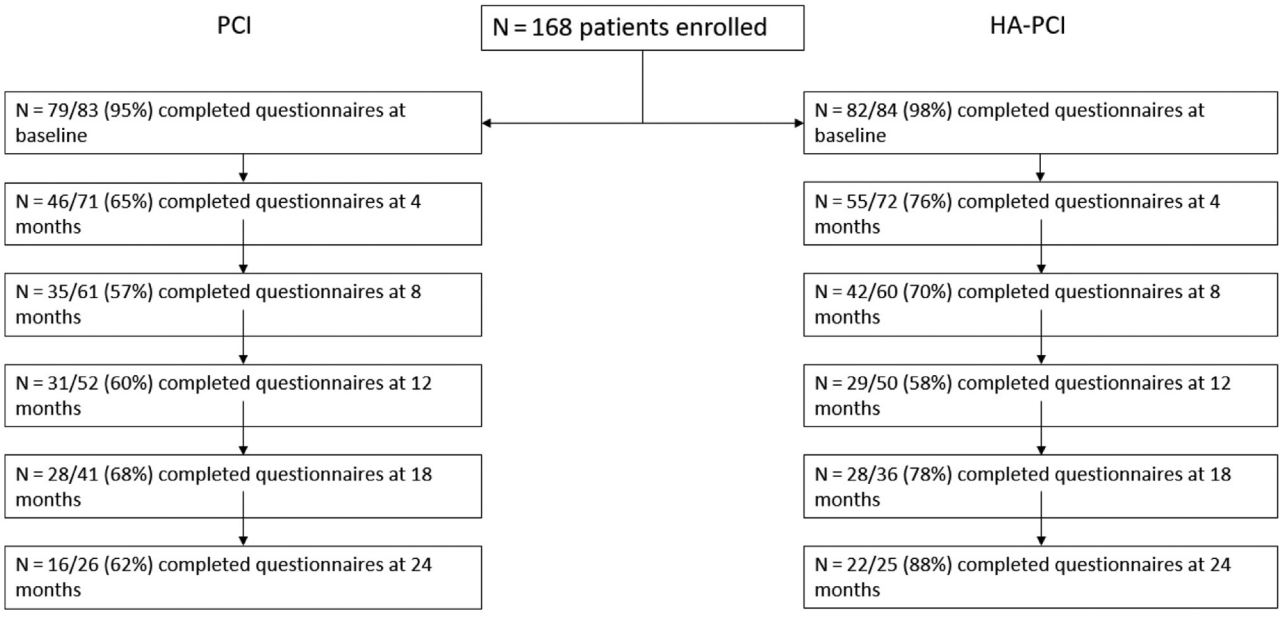

Figure 1. Flowchart. HA-PCI, hippocampal avoidance prophylactic cranial irradiation; PCI, prophylactic cranial irradiation.

decreased to 16 of 26 patients (62%) treated with PCI and 22 of 25 patients (88%) treated with HA-PCI at the final 24 months of follow-up. Reasons for dropout were mainly deceased, decline, and disease progression.

Baseline characteristics are described in Table 1. Median age was 64 (range: 36–87) years. In both arms, 71% of the patients had SCLC stages I to III and 29% had stage IV SCLC. Most patients had a performance status of 1 (61% [PCI] versus 71% [HA-PCI]).

SRCF Measured With the EORTC QLQ-C30

At an individual level, there was no significant difference in percentage of patients who reported deteriorated, stable, or improved SRCF between the treatment arms at each time point: $p = 0.771$ at 4 months, $p = 0.338$ at 8 months, $p = 0.538$ at 12 months, $p = 0.779$ at 18 months, and $p = 0.831$ at 24 months (Table 2). Dependent on the evaluated time point, a deterioration in SRCF was reported by 33% to 41% of patients treated with PCI compared with 36% to 45% of patients treated with HA-PCI. Improvement was reported by 7% to 24% and 10% to 23% of patients, respectively. Mean scores of SRCF of the EORTC QLQ-C30 are presented in Figure 2.

At group level, mixed effect modeling for SRCF revealed no significant interaction between treatment arm and time ($p = 0.71$) (Fig. 2).

SRCF Measured With the MOS

At an individual level, there was no significant difference in the percentage of patients who reported deteriorated, stable, or improved SRCF between the treatment arms at each time point: $p = 0.869$ at 4 months, $p = 0.184$ at 8 months, $p = 0.100$ at 12 months, $p = 0.879$ at 18 months, and $p = 0.123$ at 24 months (Table 2). Dependent on the evaluated time point, a deterioration in SRCF was reported by 29% to 43% of patients treated with PCI compared with 31% to 46% of patients treated with HA-PCI. Improvement was reported by 17% to 38% and 14% to 29% of patients, respectively. Mean scores of SRCF of the MOS are presented in Figure 3.

Table 1. Baseline Characteristics According to PCI and HA-PCI Group of All Randomized Patients

	PCI (N = 79)	HA-PCI (N = 82)	Total (N = 161)
Age			
Median	64	63	64
Q1, Q3	59, 69	59, 70	59, 70
Min-max	43-87	36-80	36-87
Sex, n (%)			
Male	42 (53)	38 (46)	80 (50)
Type of SCLC, n (%)			
Stages I-III	56 (71)	58 (71)	114 (71)
Stage IV	23 (29)	24 (29)	47 (29)
Performance status, n (%)			
0	20 (25)	19 (23)	39 (24)
1	48 (61)	58 (71)	106 (66)
2	5 (6)	4 (5)	9 (5)
3	1 (1)	0 (0)	1 (1)
Missing	5 (7)	1 (1)	6 (4)
Cognitive functioning			
Mean	78	85	82
Physical functioning			
Mean	70	74	72
Emotional functioning			
Mean	78	80	79
Role functioning			
Mean	63	70	67
Fatigue			
Mean	43	34	39
Motor dysfunction			
Mean	14	8	11
Future uncertainty			
Mean	27	26	27
Visual disorder			
Mean	12	8	10
Communication deficit			
Mean	10	8	9

HA, hippocampus avoidance; Max, maximum; Min, minimum; PCI, prophylactic cranial irradiation; Q1, quartile 1; Q3, quartile 3.

Table 2. Percentage of Patients With Deteriorated/Improved SRCF and Difference Between Both Treatment Arms at Each Time Point

	EORTC QLQ-C30 Cognitive Functioning			MOS Cognitive Functioning		
	PCI	HA-PCI	*p* Value	PCI	HA-PCI	*p* Value
4 mo	(n = 45)	(n = 54)	0.771	(n = 46)	(n = 55)	0.869
Deterioration	17 (38)	20 (37)		16 (35)	17 (31)	
Improvement	9 (20)	8 (15)		10 (22)	11 (20)	
Stable	19 (42)	26 (48)		20 (43)	27 (49)	
8 mo	(n = 33)	(n = 42)	0.338	(n = 35)	(n = 42)	0.184
Deterioration	13 (39)	16 (38)		10 (29)	16 (38)	
Improvement	8 (24)	5 (12)		6 (17)	12 (29)	
Stable	12 (36)	21 (50)		19 (54)	14 (33)	
12 mo	(n = 30)	(n = 29)	0.538	(n = 31)	(n = 29)	0.100
Deterioration	10 (33)	13 (45)		11 (35)	10 (34)	
Improvement	6 (20)	3 (10)		11 (35)	4 (14)	
Stable	14 (47)	13 (45)		9 (29)	15 (52)	
18 mo	(n = 27)	(n = 28)	0.799	(n = 28)	(n = 28)	0.879
Deterioration	11 (41)	11 (39)		12 (43)	13 (46)	
Improvement	2 (7)	4 (14)		6 (21)	4 (14)	
Stable	14 (52)	13 (46)		10 (36)	11 (39)	
24 mo	(n = 16)	(n = 22)	0.831	(n = 16)	(n = 22)	0.123
Deterioration	6 (38)	8 (36)		6 (38)	7 (32)	
Improvement	2 (12)	5 (23)		6 (38)	3 (14)	
Stable	8 (50)	9 (41)		4 (25)	12 (55)	

Note: All values are n (%).
EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; HA, hippocampal avoidance; PCI, prophylactic cranial irradiation; n, number; MOS, Medical Outcomes Study.

At group level, mixed effect modeling for cognitive functioning measured with the MOS revealed no significant interaction between treatment arm and time (p = 0.94) (Fig. 3).

QoL Measured With the EORTC QLQ-C30

At an individual level, there were no significant differences in the percentage of patients reporting deteriorated, stable, or improved role or emotional functioning after receiving treatment with PCI or HA-PCI. The same was found for fatigue. For physical functioning, a significant difference between the treatment arms was observed only at 12 months: 23% (n = 7) of patients in the PCI arm reported a deterioration in physical functioning, compared with 14% (n = 4) of patients in the HA-PCI arm (p = 0.019). Furthermore, 48% (n = 15) of patients in the PCI arm reported improved physical functioning compared with 21% (n = 6) of the patients in the HA-PCI arm at 12 months.

At group level, mixed effect modeling for symptoms of fatigue, role, and emotional and physical functioning revealed no significant interaction between group and time (Supplementary Fig. 1).

QoL Measured With EORTC QLQ-BN20

At an individual level, domains of future uncertainty, visual disorder, and communication deficit had no significant differences in the percentage of patients who deteriorated, remained stable, or improved over time between the two treatment arms. An exception was motor dysfunction at the 24 months of follow-up, in which a significant difference between the two treatment arms was observed: 33% (n = 5) of the patients treated with PCI reported a deterioration, whereas this was 23% (n = 5) for HA-PCI (p = 0.020). Furthermore, 60% of the patients in the PCI arm (n = 9) reported improved motor dysfunction compared with 27% in the HA-PCI arm (n = 6). The percentage of patients who deteriorated or improved over time on all EORTC QLQ-C30 and BN20 scales is reported in Supplementary Table 1.

At group level, no significant interaction between treatment arm and time was found for future uncertainty, visual disorder, motor dysfunction, and communication deficit (Supplementary Fig. 2).

Discussion

Much research is being conducted HA-PCI to preserve cognition. This trial previously reported no observed beneficial effects of HA-PCI compared with PCI on tested cognition in patients with SCLC. Here, we report the findings on SRCF and QoL. This trial did not find a clinically relevant nor statistically significant benefit in SRCF, using the EORTC QLQ-C30 and the MOS in patients with SCLC treated with HA-PCI compared with PCI.

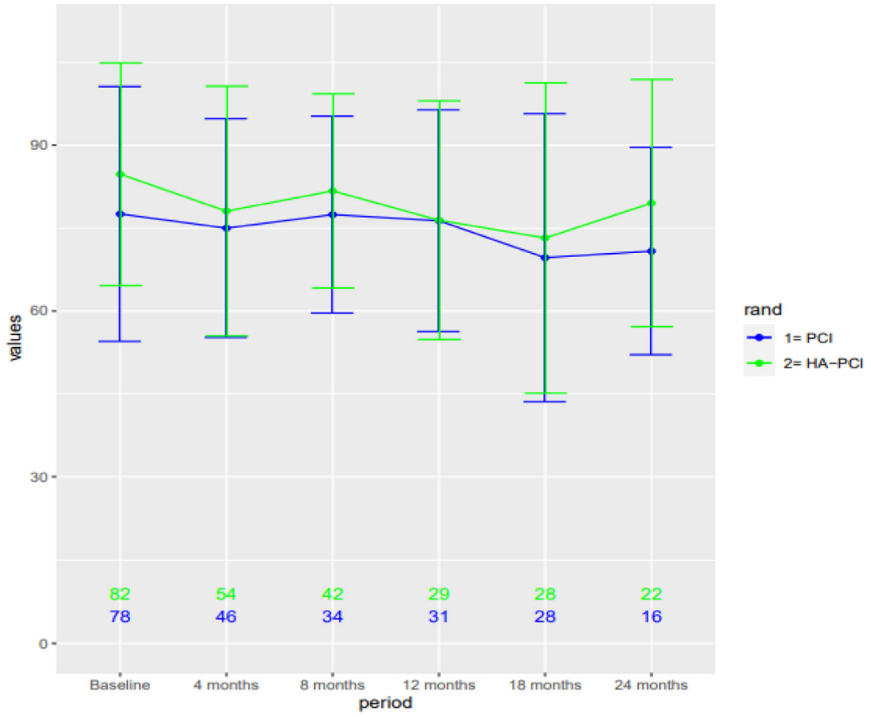

Figure 2. Mean scores of EORTC QLQ-C30 for self-reported cognitive functioning. EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

There was also no clinically relevant nor statistically significant benefit for patients treated with HA-PCI regarding overall QoL. With two exceptions, no significant differences between arms were found for self-reported physical functioning, emotional functioning, role functioning, and fatigue, neither at the individual nor at the group level. The exceptions were a significant difference in physical functioning at 12 months and a significant difference in motor functioning at 24 months (more patients improved and deteriorated over time in the PCI arm and more patients remained stable in the HA-PCI arm). Given the large number of comparisons

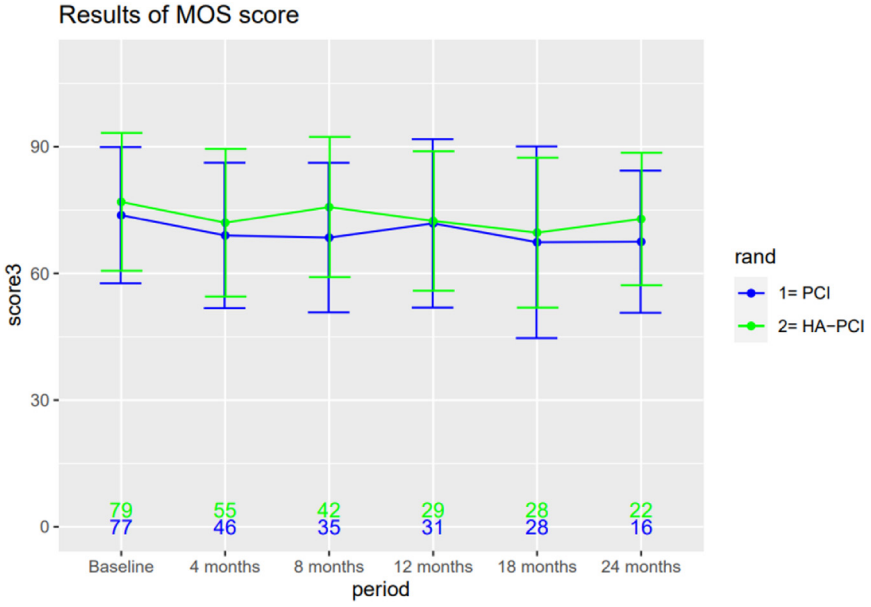

Figure 3. Mean scores of the MOS for cognitive functioning. HA, hippocampal avoidance; MOS, Medical Outcomes Study; PCI, prophylactic cranial irradiation.

and the small sample sizes (n = 16 in the PCI arm and n = 22 in the HA-PCI arm at 24 mo of follow-up) at the later measurement points, we think that this statistical significance at a single time point is not clinically significant. Nevertheless, independent of treatment, more than one-third of patients treated with PCI and HA-PCI reported a deterioration of cognitive function at any given time point, regardless of treatment arms.

These findings are consistent with the primary end point of the trial, revealing that compared with PCI alone, HA-PCI did not preserve learning and memory, nor other aspects of cognitive functioning.[14]

Two other phase III randomized trials also have investigated the potential benefit of HA-PCI/WBRT compared with regular PCI/WBRT.[12,13] Our results differ from the positive yet also conflicting findings of these two randomized trials: in the PREMER trial (patients with SCLS), it was found that compared with PCI, HA-PCI preserved objective cognitive functioning assessed by Free and Cued Selective Reminding Test but not SRCF,[12] and in the NRG CC001 trial (patients with BM), it was found that compared with WBRT plus memantine, HA-WBRT plus memantine better preserved cognition both objectively assessed (including the HVLT-R, COW, and TMT-A and TMT-B) and self-reported cognitive symptoms (measured with the EQ-5D-5L and MD Anderson Symptom Inventory—Brain Tumor questionnaires).[13] Interestingly, all three trials reported that there were no significant differences between treatment arms regarding QoL, including global health status, physical functioning, emotional functioning, role functioning, fatigue, and pain/discomfort.

Conducted in parallel to the NRG CC001, the phase II/III trial of HA during PCI for SCLC was developed—the NRG CC003.[22] This trial has completed the accrual phase, and the results are eagerly awaited as it would add evidence to the discussion about the use of HA-PCI in patients with SCLC.

Similar to other trials, the interpretation of our results is hampered by the high dropout rates at later time points. Nevertheless, this dropout was balanced between both treatment arms and reflects the aggressive natures of SCLS and as such daily clinical practice. Another limitation is that as secondary end points, the trial was not powered to detect a statistically significant difference between arms for SRCF and QoL, especially at later time points. Nevertheless, this was similar as for other trials such as the PREMER and NRC CC001 trial.

Furthermore, the same cutoff of 10 points is used for all subscales to measure minimal clinically important differences. This cutoff is often used in studies of QoL.[21] Nevertheless, different subscales might require different cutoff points. Furthermore, the same cutoff of 10 points was used to determine deterioration or improvement of scores, while scoring changes into trivial, small, medium, or large improvement or deterioration might be more informative. Therefore, this cutoff may be too simplistic, and clinically meaningful change can be underestimated.

In conclusion, in line with previously published primary results of the NCT01780675 trial that reported no reduced probability of cognitive decline in patients receiving HA-PCI compared with PCI, we did not observe a statistically significant nor a clinically significant benefit of HA-PCI versus PCI regarding SRCF and QoL among patients with SCLC.

Credit Authorship Contribution Statement

E.A.C. Albers: Conceptualization, Methodology, Visualization, Roles/writing—original draft.

H. Zeng: Methodology, Writing—review and editing.

D.K.M. De Ruysscher: Funding acquisition, Investigation, Writing—review and editing.

M.A. Kuenen: Data curation, Project administration, Resources.

R. Kessels: Formal analysis, Methodology.

L.E.L. Hendriks: Writing—review and editing.

J.S.A. Belderbos: Funding acquisition, Investigation, Writing—review and editing.

S.B. Schagen: Conceptualization, Funding acquisition, Supervision, Writing—review and editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100506.

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