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ORIGINAL ARTICLE

Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675)

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ABSTRACT

Introduction: To compare neurocognitive functioning in patients with SCLC who received prophylactic cranial irradiation (PCI) with or without hippocampus avoidance (HA).

Methods: In a multicenter, randomized phase 3 trial (NCT01780675), patients with SCLC were randomized to standard PCI or HA-PCI of 25 Gy in 10 fractions. Neuropsychological tests were performed at baseline and 4, 8, 12, 18, and 24 months after PCI. The primary end point was total recall on the Hopkins Verbal Learning Test—Revised at 4 months; a decline of at least five points from baseline was considered a failure. Secondary end points included other cognitive outcomes, evaluation of the incidence, location of brain metastases, and overall survival.

Results: From April 2013 to March 2018, a total of 168 patients were randomized. The median follow-up time was 26.6 months. In both treatment arms, 70% of the patients had limited disease and baseline characteristics were well

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Primary end point presented at the 38th Annual Meeting of the European Society for Radiotherapy and Oncology in Milano, Italy, on April 26 to 30, 2019, and at the 29th Annual Meeting for the European Respiratory Society in Madrid, Spain, on October 1, 2019. Safety end point presented at the 61st Annual Meeting of the American Society for Radiation Oncology in Chicago, Illinois, on October 2 to 6, 2019.

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balanced. Decline on the Hopkins Verbal Learning Test-Revised total recall score at 4 months was not significantly different between the arms: 29% of patients on PCI and 28% of patients on HA-PCI dropped greater than or equal to five points ($p = 1.000$). Performance on other cognitive tests measuring memory, executive function, attention, motor function, and processing speed did not change significantly different over time between the groups. The overall survival was not significantly different ($p = 0.43$). The cumulative incidence of brain metastases at 2 years was 20% (95% confidence interval: 12%–29%) for the PCI arm and 16% (95% confidence interval: 7%–24%) for the HA-PCI arm.

Conclusions: This randomized phase 3 trial did not find a lower probability of cognitive decline in patients with SCLC receiving HA-PCI compared with conventional PCI. No increase in brain metastases at 2 years was observed in the HA-PCI arm.

Keywords: SCLC; Prophylactic cranial irradiation; Hippocampus; Neurocognition; PCI

Introduction

Patients with SCLC have a very high incidence of brain metastases (BM) of more than 50% depending on the stage of the disease.[1,2] Those with BM have a dismal prognosis leading to an impaired quality of life. Prophylactic cranial irradiation (PCI) results to a highly significant reduction of BM and to a lesser extent to a higher overall survival (OS) but at the expense of side effects, of which long-lasting neurocognitive decline is feared the most.[3] Several interacting mechanisms to explain neurocognitive decline have been proposed, including vasculopathy, depletion of oligodendrocytes, central nervous system inflammation, and progenitor cell niche degradation in the hippocampus, a structure important for learning and memory.[4] The hippocampal function is indeed the most affected by PCI. Modern radiotherapy techniques such as intensity-modulated radiotherapy or volumetric-modulated arc therapy allow treating the entire brain to standard radiation doses, while keeping the dose to the hippocampi low.[5] Recent preclinical and clinical research suggests that hippocampal sparing may provide a useful intervention for reducing adverse cognitive effects of cranial irradiation.[6] A phase 2 study revealed encouraging results of hippocampal avoidance (HA) during whole-brain radiation therapy (WBRT) on cognitive function in patients with BM.[7] Furthermore, a recent phase 3 trial of HA during WBRT plus memantine for patients with BM from NSCLC revealed a lower incidence of neurocognitive decline and a better quality of life, but surprisingly not reduced the decline in hippocampal-related cognitive tests.[8] Moreover, a Spanish phase 3 trial, thus far only reported in abstract form, in patients with SCLC who were randomized to receive PCI or HA-PCI[9] reported a greater decline in memory in the PCI group compared with the HA-PCI group at 3, 6, and 12 months, but the impact on long-term cognitive outcome is unclear.

The aim of the current phase 3 study was to examine the preservation of cognitive function by HA in patients with SCLC receiving PCI. The primary end point of this trial was a decline on total recall of the Hopkins Verbal Learning Test-Revised (HVLT-R) at 4 months after PCI.[10] The total recall HVLT-R is established as the neurocognitive test of choice to evaluate the function of the hippocampus.[11] A decline was defined according to the reliable change index[12] as a drop of at least five points from baseline. Secondary end points included other cognitive outcomes, incidence and location of BM, progression-free survival, OS, and quality of life.

Materials and Methods

Patient Selection

Patients with histologic- or cytologic-proven SCLC, stages I to III ("limited stage") or stage IV ("extensive stage"), without clinical or radiologic evidence of BM on a contrast-enhanced magnetic resonance imaging (MRI) scan, and without progressive disease after chemoradiotherapy in stages I to III or after chemotherapy alone in stage IV were eligible. Patients younger than 18 years old and those with previous radiotherapy to the brain or receiving concurrently with PCI anticancer agents were excluded. The interval between the last chemotherapy and the start of PCI was at least 3 weeks. 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.

MRI Acquisition, Radiation Treatment Procedure, and Neuropsychological Assessment

In this trial, a high-resolution, three-dimensional T1-weighted MRI with excellent contrast between the gray and white matter (1.2-mm slice thickness) was made at baseline, 4 months, and 12 months to delineate the hippocampi and study hippocampal atrophy. In addition, pre- and postgadolinium T1 scans were used to detect BM. Furthermore, fluid-attenuated inversion recovery, diffusion tensor imaging, susceptibility weighted imaging, and resting-state functional MRI were acquired. All sequences of the MRI scanners of participating institutions were aligned and checked with phantom measurements.[13] Participating centers had to

do a dummy run on HA-PCI treatment planning of three cases to be approved for trial inclusion. Patients underwent a computed tomography (CT) simulation with immobilization. The baseline MRI scan was coregistered to the simulation CT scan. In patients randomized to the HA-PCI group, the left and right hippocampi were manually delineated according to the RTOG atlas: (https://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx). Patients were irradiated using image-guided radiotherapy to a total dose of 25 Gy in 10 fractions, five times a week. Treatment planning was performed using 6 or 10 megavolt photon beams. The objective in the HA-PCI group was to establish a mean dose in the left and right hippocampi of less than or equal to 8.5 Gy (biological dose $\leq$ 6.1 Gy for $\alpha/\beta = 2$ Gy), a D1% hippocampus less than or equal to 10 Gy, maximum dose (Dmax) planning target volume (PTV) of less than 28.75 Gy (115%), and V115% PTV less than or equal to 1%.

Neuropsychological tests assessing episodic memory, processing speed, executive function, attention, and fine motor function were performed at baseline and 4, 8, 12, 18, and 24 months after completion of PCI. The battery included the HVLT-R (HVLT-R total recall, delayed recall, recognition), Trail Making Test (TMT) A and B, Controlled Oral Word Association (COWA) test, Wechsler Adult Intelligence Scale III digit span and digit symbol, and the Lafayette's Grooved Pegboard test. The HVLT-R, TMT (A and B), and the COWA form the core tests recommended by cooperative groups in oncology.[14,15] The tests were administered and scored by trained and continuously supervised care providers, and all assessments were centrally reviewed by an experienced neuropsychological assistant blinded for treatment assignment.

Statistical Methods

A total of 50 patients per arm were sufficient to provide 82% to 95% power to detect an absolute difference of 30% in cognitive decline using Fisher's exact test. It was estimated that approximately 40% of patients could not complete the assessment at 4 months postradiation owing to death or progressive disease. To obtain 100 assessable patients, 168 patients were randomized. Randomization was stratified per institute and stage (I–III versus IV). A planned interim analysis took place in March 2017. Stopping rules for efficacy were set according to O'Brien-Fleming spending function. The interim analysis was evaluated by the Independent Data Monitoring Committee, which advised to continue. The database used for final analysis was locked in March 2020. The primary end point was available for 102 patients. Raw scores were used for all neuropsychological analyses. The primary end point was a decline on the HVLT-R total recall at 4 months after radiotherapy (minimum of 3.5 mo and maximum 6 mo after PCI) treatment. Decline from baseline of at least five points was considered a failure.[10,12] The primary end point was analyzed according to the assigned treatment arm. A p value less than 0.048 was considered statistically significant for the primary end point to account for the interim "peek." In a sensitivity analysis of primary end points, cognitive tests taken after disease progression (in the brain or elsewhere) were excluded. The time to occurrence of brain metastasis was calculated from date of randomization until detection which was found on a scan or determined by clinical symptoms. The cumulative incidence of BM was calculated accounting for death as a competing risk. The OS was calculated for all randomized patients from date of randomization to death from any cause. In addition to the primary end point analyses, the longitudinal profiles of all cognitive tests were analyzed for all randomized patients. Linear mixed models included time as categorical variable (with categories 0, 4, 8, 12, 18, and 24), arm and time $\times$ arm as fixed effects, and random intercept per patient to account for correlation. The tests were classified into specific timeslots using clustering specified in the statistical analysis plan (Supplementary Data). The overall interaction between time and arm was tested using the maximum likelihood ratio test with 5 df. In a sensitivity analysis, we also fitted the linear mixed models for all outcomes with the exact time of the test and its quadratic effect as continuous variables.

To mimic the analysis of the recent phase 3 trial (NRG CC001) in patients with brain metastasis from NSCLC who were randomly assigned to receive HA or not during WBRT plus memantine, the time to neurocognitive failure (NCF) was calculated for all patients. This was an unplanned analysis. Following Brown et al.,[8] the time to NCF was defined as time from randomization to failure on any of the following core cognitive tests: HVLT-R (total recall, delayed recall, recognition), TMT (A and B), and COWA test. Failures were defined as a reliable change from baseline according to cutoffs from published literature.[10,12,16,17] In accordance with the (NRG CC001) trial, cumulative incidences were calculated accounting for death as a competing risk. Treatment arms were compared using Fine and Gray test.

Results

Patients

Between April 2013 and March 2018, a total of 168 patients were recruited in 10 centers in the Netherlands and Belgium. A total of 84 patients were randomly assigned to receive PCI and 84 to receive HA-PCI. The median follow-up for alive patients was 24.8 months

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

	PCI (N = 84)	HA-PCI (N = 84)	Total (N = 168)
Age			
Median	64	63	64
Q1, Q3	59, 69	59, 70	59, 70
Min-Max	43-87	36-80	36-87
Sex			
1 = Male	44 (52%)	39 (46%)	83 (49%)
2 = Female	40 (48%)	45 (54%)	85 (51%)
Type of SCLC			
1 = Stage I-III	59 (70%)	59 (70%) 118 (70%)	
2 = stage IV	25 (30%)	25 (30%)	50 (30%)
Performance status			
Missing	7	1	8
0	20 (26%)	19 (23%)	39 (24%)
1	51 (66%)	60 (72%)	111 (69%)
2	5 (6%)	4 (5%)	9 (6%)
3	1 (1%)	0 (0%)	1 (1%)
HVLT-R. Total recall score			
Missing	5	1	6
Median	25	23	24
Q1, Q3	20, 30	20, 26	20, 27
Min-Max	10-35	12-33	10-35

HA, hippocampus avoidance; HVLT-R, Hopkins Verbal Learning Test—Revised; Max, maximum; Min, minimum; PCI, prophylactic cranial irradiation; Q1, quartile 1; Q3, quartile 3.

(interquartile range: 23.5–32.8 mo). Median age was 64 years (range: 36–87 y). Baseline characteristics are illustrated in Table 1. In each arm, 70% and 30% of patients had SCLC stages I to III and stage IV, respectively. Performance status at baseline was WHO 0 to 1 in 93% of the patients. At baseline, four patients had BM and were ineligible (Fig. 1). A total of 157 patients (96%) received 25 Gy in 10 fractions.

Radiotherapy Details

All treatment planning results for patients receiving HA-PCI treatment are found in Table 2. The median mean dose to the left and right hippocampi was 8.0 Gy (range: 5.4–11.4 Gy). This is lower than the trial constraint of less than or equal to 8.5 Gy. In only five patients (6.3%), the mean dose in one or both hippocampi was violated. In 12.5% and 13.8% for the right and left hippocampi, the Dmax was violated ($\leq$11 Gy instead of $\leq$10 Gy). All patients met the trial constraint of $V_{115\%}$ PTV less than or equal to 1%; however, the D_{max} PTV of less than or equal to 28.75 Gy was violated in 22.8% of the patients (median = 29.35 Gy).

Treatment Outcomes

Primary End Point: Failure on HVLT-R Total Recall. Data on the primary end point at 4 months were available for 102 patients: 46 patients in the PCI arm and 56 patients in the HA-PCI arm (Fig. 1). Of these patients, 29 (28%) dropped five points or more on the HVLT-R total recall. This was 29% in the PCI arm and 28% in the HA-PCI arm, which was not different between the arms (Fisher's exact test, $p = 1.000$, difference in proportions 0%, 95% confidence interval [CI]: −17.6–18.2). This result was consistent in the subgroups with stages I to III and stage IV disease. In the sensitivity analysis excluding tests taken after disease progression, the primary end point of 81 patients (35 patients in the PCI and 46 patients in the HA-PCI) was analyzed. Failure was observed in 26% and 28% of the patients, respectively ($p = 1.000$).

Neurocognitive Function: Longitudinal Profiles of All Neurocognitive Tests. No significant group differences between the treatment arms were observed in changes over time on any of the cognitive tests. Results of the HVLT-R total recall score (plots of the mean scores over time and fitted coefficients) are provided in Figure 2. Results for all the other cognitive tests can be found in the Supplement. Briefly, a decline was found on all subtests of the HVLT-R. At 24 months, the HVLT-R total score approached the baseline level again. Scores on the TMT A improved slightly over time in the PCI arm, whereas the scores declined in the HA-PCI arm. The interaction at 4 months was at the boundary of statistical significance ($p = 0.05$). TMT B scores declined in both arms; at 4 months, this decline was somewhat stronger in the HA-PCI arm compared with the PCI arm ($p = 0.07$). The COWA scores dropped initially for both groups but improved later. Digit span forward scores improved over time in the PCI arm, whereas in the HA-

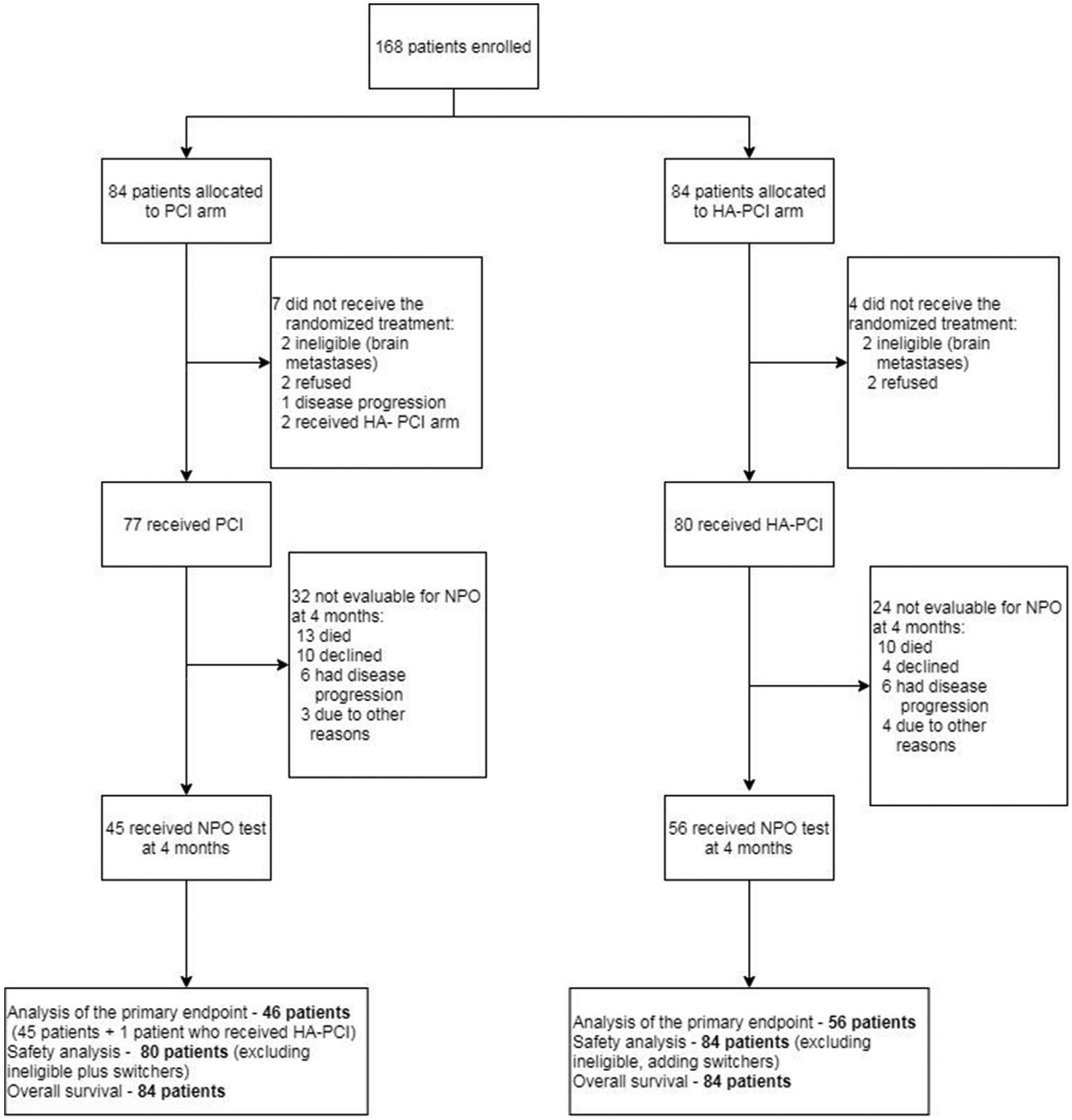

Figure 1. Trial profile. HA, hippocampus avoidance; NPO, neurocognitive testing; PCI, prophylactic cranial irradiation.

PCI arm, this score fluctuated during follow-up. Digit span backward scores also improved slightly over time for both arms. Digit symbol scores declined over time in both arms. Pegboard test scores (dominant and nondominant) declined over time in both arms.

CC001 Primary End Point Analyses Applied to NCT01780675 Data. In total, 89 patients experienced NCF: 52 in the HA-PCI arm and 36 in the PCI arm. A total of 59 patients died without NCF. The risk of NCF was significantly higher in the HA-PCI arm (hazard ration [HR] = 1.75, 95% CI: 1.15–2.66, Fine and Gray test, $p = 0.0088$) (Fig. 3). After 2 years of radiotherapy, 65% of the patients in the HA-PCI arm (95% CI: 55–76) and 45% of the patients in the PCI arm (95% CI: 34–56) experienced NCF, although most of the NCFs occurred in the first year.

Brain Metastases. Of 164 patients eligible for safety analysis, 31 patients, 14 in the HA-PCI arm and 17 in the PCI arm, developed BM. In 18 patients, BM were detected after intrathoracic or distant disease progression.

Table 2. Treatment Planning Constraints of All Patients Treated with HA-PCI

Total Number of Patients is 80

Constraints		Constraint Achieved		Constraint Violated	
		N (%)	Median (Range)	N (%)	Median (Range)
$V_{95\%}$PTV	≥95%	74 (92.5)	95 (95-97)	6 (7.5)	92 (90-94)
$V_{115\%}$PTV[a]	≤1%	79 (98.8)	0 (0-1)	0 (0.0)	– (–)
$D_{98\%}$PTV	≥18.75 Gy (75%)	76 (95.0)	20.83 (18.75-27.10)	4 (5.0)	18.15 (16.45-18.70)
$D_{1\%}$PTV	≤27.5 Gy (110%)	69 (86.3)	26.9 (25.3-27.5)	11 (13.8)	28.1 (27.6-29.8)
D_{max}PTV[a]	≤28.75 Gy (115%)	61 (77.2)	28.18 (25.30-28.74)	18 (22.8)	29.35 (28.80-31.67)
Mean dose hippocampus left	≤8.5 Gy (BED ≤ 6.1 Gy)	75 (93.8)	8.0 (5.4-8.5)	5 (6.3)	8.9 (8.7-11.4)
Mean dose hippocampus right	≤8.5 Gy (BED ≤ 6.1 Gy)	75 (93.8)	8.0 (5.7-8.5)	5 (6.3)	8.9 (8.6-10.7)
$D_{1\%}$hippocampus left	≤10 Gy	69 (86.3)	10 (7-10)	11 (13.8)	11 (11)
$D_{1\%}$ippocampus right	≤10 Gy	70 (87.5)	10 (7-10)	10 (12.5	11 (11)
D_{max} lenses[a]	≤10 Gy	76 (96.2)	9 (6-10)	3 (3.8)	12 (11-17)

[a]One missing.

BED, biologically effective dose; $D_{1\%}$, dose to 1%; $D_{98\%}$, dose to 98%; D_{max}, maximum dose; HA, hippocampus avoidance; PCI, prophylactic cranial irradiation; PTV, planning target volume; $V_{95\%}$, volume receiving 95% of the dose; $V_{115\%}$, volume receiving 115% of the dose.

The cumulative incidence of BM at 2 years (Fig. 4) was 16% (95% CI: 7–24) in the HA-PCI arm and 20% (95% CI: 12–29) in the PCI arm (HR = 0.83, 95% CI: 0.42–1.65, Fine and Gray test, $p = 0.60$). Of the 31 patients who developed BM, 74% had multiple BM. In 16 of the 31 patients, BM were asymptomatic; in 13 patients, they were symptomatic; and in two patients, this was unknown. None of the patients with a single metastasis developed a metastasis within the hippocampus or underdosed region. We analyzed 11 patients with multiple BM using matched diagnostic follow-up MRI scans and planning CT scans in the HA-PCI group (using a mutual information algorithm) and found five patients with a metastasis within the hippocampus or 5-mm margin region (four within the hippocampus and 5-mm margin region and one with a metastasis in the 5-mm margin region only).

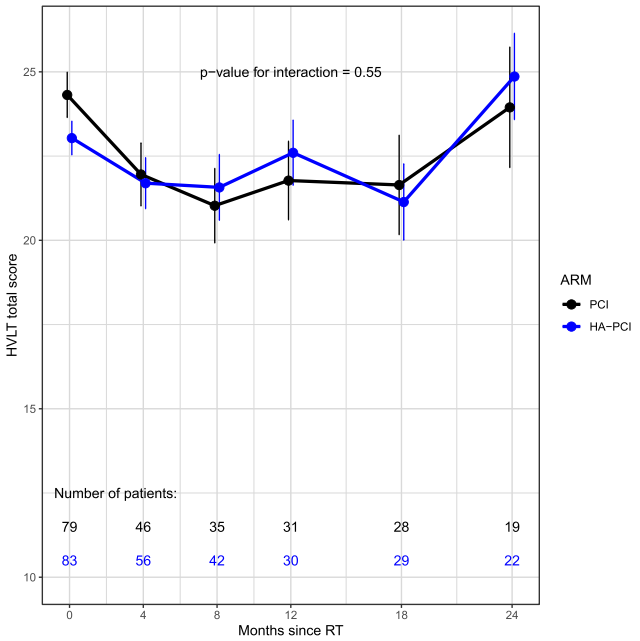

Figure 2. Mean scores of HVLT-R total recall over time. HVLT-R, Hopkins Verbal Learning Test—Revised; HA, hippocampus avoidance; PCI, prophylactic cranial irradiation; RT, radiotherapy.

OS. At the data cutoff, 102 of 168 patients had died (49 patients in the HA-PCI arm and 53 patients in the PCI arm) (Fig. 5). There was no difference in OS between the arms (median OS of 18.5 and 19.9 mo for HA-PCI and PCI arm, respectively; HR = 0.93, 95% CI: 0.63–1.37, log-rank $p = 0.70$). Subgroup analysis of patients with stages I to III and stage IV also revealed no difference in OS between the HA-PCI and PCI arms (Fig. 5*B* and *C*).

Discussion

Our trial failed to find a difference in the percentage of patients who declined on a word-list learning test between those who received HA-PCI compared with those who received standard PCI. In addition, our longitudinal analyses on all cognitive tests did not find a difference in the trajectory over time between the arms. However, the trial did find that HA is safe. No difference was observed between the arms in the incidence of BM or in OS rates, neither in patients with stages I to III or stage IV disease. Although it is believed that BM are almost never observed in the hippocampus,[18] we did find five patients with multiple BM in the HA-PCI arm including BM localized in the underdosed region. This is

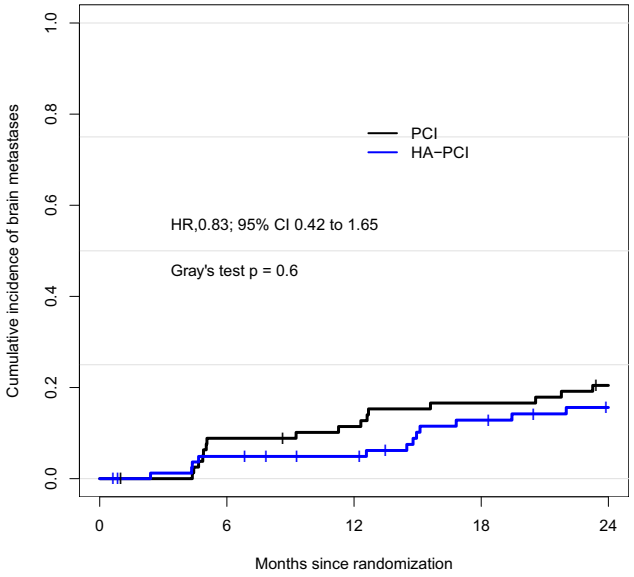

Figure 3. Cumulative incidence of BM. BM, brain metastases; CI, confidence interval; HA, hippocampus avoidance; HR, hazard ratio; PCI, prophylactic cranial irradiation.

largely in line with the original safety analysis, which predicted a risk of 8.6%.[19] All patients received an MRI scan before the irradiation. BM were observed during the first 24 months in 20% and 16% of the patients randomized to PCI and HA-PCI, respectively. This is similar to the 22% reported in the RTOG 0212 trial for stages I to III SCLC.[20]

Several reasons may explain the current negative findings: First, a biological dose of 6 Gy to the hippocampus without a neuroprotective agent might be too high and still causes neuroprogenitor cells to die.[21] Second, other brain areas such as the amygdala, which support cognitive functions, were not spared. Although we performed rigorous quality assurance on the radiotherapy preparation and execution of the HA-PCI treatment, it could be that the hippocampi were not delineated correctly as there was no central quality control on the hippocampus delineation. We did however publish an interobserver delineation study of the hippocampi performed among seven trial investigators in five cases.[22] Although there were interobserver variations in the posterior and anterior medial hippocampal regions, the mean dose constraint for the hippocampi would still have been met in all cases owing to the generous 5 mm margin used in the trial. Furthermore, all participating centers performed a dummy run planning to get approval for trial inclusion. The treatment plans complied with the trial constraints in the vast majority of cases. As the hippocampus is more a parallel than a serial organ, we may assume that achieving the mean hippocampal dose constraint is more important than the small volumes (<1% of the PTV) with overdosing. Our study was designed and powered to detect a 30% difference in cognitive failure at 4 months, on the basis of the available literature at the start of the trial. More recent studies evaluating HA-WBRT and HA-PCI have been designed with larger sample sizes to detect smaller differences, for example the NRG CC001 phase 3 trial.9 In this study, the same neuropsychological tests (i.e., the international core neuropsychological tests) were used as in this study.

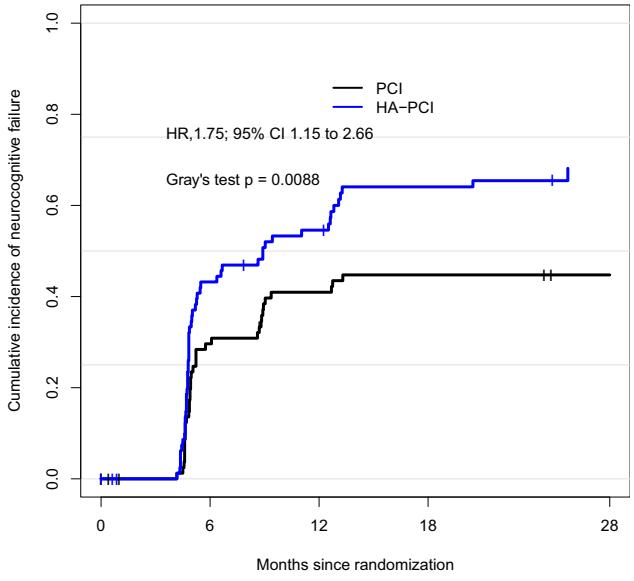

Figure 4. Cumulative incidence of NCF. CI, confidence interval; HA, hippocampus avoidance; HR, hazard ratio; NCF, neurocognitive failure; PCI, prophylactic cranial irradiation.

In this trial, 518 patients with BM from solid tumors were randomized to receive WBRT or HA-WBRT, and in both arms, memantine was part of the treatment strategy. This study observed an approximate 10% difference in cognitive failure rates favoring those with HA-WBRT plus memantine. Looking at the CI for the difference in our primary end point, we cannot rule out a much smaller than anticipated effect. This could lead to the simple conclusion that our study is underpowered and as such cannot contribute to the discussion on the relevance of hippocampal sparing for cognition. There are, however, several important issues that prevent us from drawing this conclusion. First of all, the much larger NRG CC001 trial also did not find a significant difference in the percentage of patients with cognitive failure at 4 months using our primary (memory specific) end point of HVLT-R total recall (34.9% [n = 109] versus 29.0% [n = 93] of WBRT + memantine versus HA-WBRT + memantine, $p = 0.38$). Second, when we apply the primary end point of the NRG CC001 trial, which is defined as a cognitive failure on any of six neuropsychological tests (measuring memory,

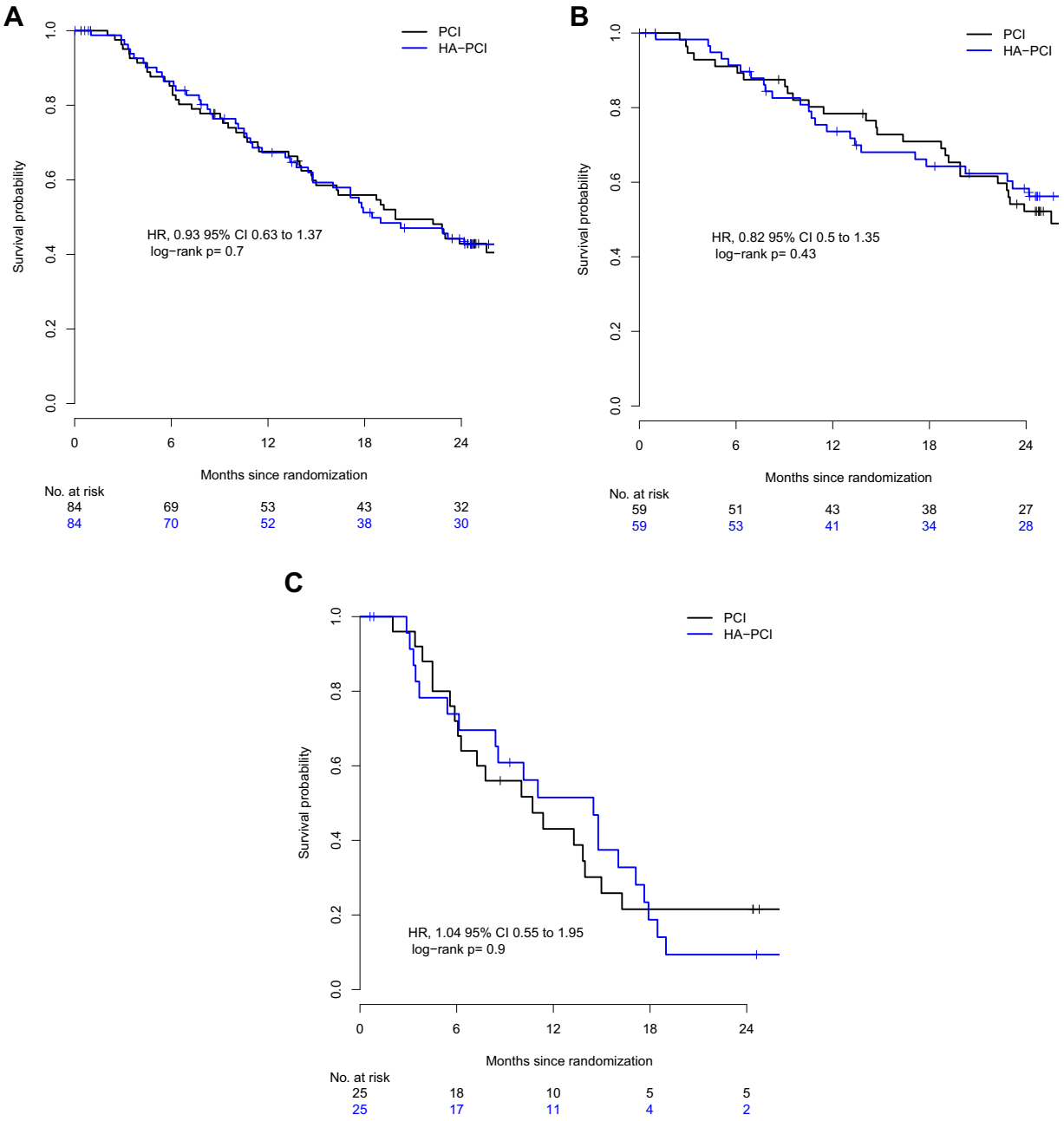

Figure 5. OS for (*A*) all randomized patients, (*B*) those with stages I to III, and (*C*) those with stage IV. CI, confidence interval; HA, hippocampus avoidance; HR, hazard ratio; OS, overall survival; PCI, prophylactic cranial irradiation.

executive function, and processing speed) on any of six follow-up assessments, we actually found a significant difference in time to cognitive failure favoring the patients with SCLC who received standard PCI compared with those who received HA-PCI. These two important observations (i.e., negative findings in both trials when applying the NCT01780675 primary end point and conflicting findings across trials when applying the NRC CC001 end points) force us to look beyond the conclusion that our trial lacks power to detect benefits of hippocampal sparing. In an attempt to further understand the divergent conclusions of these trials, we should consider differences between the trials in patient population and dose distributions that could potentially explain these results (Table 3). Regional overdosing of small areas outside the hippocampi is an inevitable consequence of any WBRT plan with hippocampal sparing. These hot spots might be associated with brain injury and cognitive decline.[23] In our trial, both the total dose to the brain and the mean dose to the hippocampi were lower compared with those of the NRG CC001 trial. It might

Table 3. Differences Between the NRG CC001 WBRT Trial and the NCT01780675 PCI Trial

	NCT01780675 HA-PCI Trial	NRG CC001 HA-WBRT Trial
Diagnosis	SCLC	Solid tumors (no SCLC, germ cell, or lymphoma)
BM at baseline	No	Yes
RT dose and fractionation	25 Gy/10 fractions	30 Gy/10 fractions
Quality assurance HA technique	Pre-enrollment benchmark	Pre-enrollment benchmark
Pretreatment review of hippocampal contouring	No	Yes
Delineation according to RTOG atlas	Yes	Yes
PTV max dose	28.75 Gy	40 Gy
(BED assuming $\alpha/\beta = 2$ Gy)	35 Gy (to <1% of the PTV)	60 Gy (to <2% of the PTV)
$D_{1\%}$ PTV	≤27.5 Gy	–
$D_{2\%}$ PTV	–	≤37.5 Gy
$D_{98\%}$ PTV	≥18.75 Gy	≥25.00 Gy
Mean hippocampus dose (BED assuming $\alpha/\beta = 2$ Gy)	<8.5 Gy 6.05 Gy	<9 Gy 6.52 Gy
Treatment execution: Image guidance	Weekly/daily 3D	Daily 2D or 3D required
Baseline HVLT-R points	Median 24	–
Previous anticancer therapy	Chemotherapy or chemoradiation >4 wk before start PCI	Prior chemotherapy or radiosurgery/ surgical resection of BM allowed
Concurrent daily memantine[a] 20 mg	No	Yes
Test moment (mo)	Baseline, 4, 8, 12, 18, 24	Baseline, 2, 4, 6, 12
Test scores	Raw scores	Raw scores and standardized

[a]Memantine is an excitatory neurotransmitter in cortical and hippocampal neurons.
2D, two-dimensional; 3D, three-dimensional; BED, biologically effective dose; BM, brain metastases; $D_{1\%}$, dose to 1%; $D_{2\%}$, dose to 2%; $D_{98\%}$, dose to 98%; HA, hippocampus avoidance; HVLT-R, Hopkins Verbal Learning Test- Revised; Max, maximum; PCI, prophylactic cranial irradiation; PTV, planning target volume; RT, radiotherapy; WBRT, whole-brain radiation therapy.

be that hippocampal sparing is only useful when higher doses to the brain are delivered. In our trial, we allowed maximal 1% of the brain to receive 28.75 Gy, whereas in the NRG CC001 trial, this was 40 Gy to less than 2% of the brain tissue. Patients included in our trial had, in contrast to the CC001 trial, no neurologic symptoms or MRI-detected BM at baseline and memantine was not part of the treatment. We cannot rule out that a beneficial effect of HA in the CC001 was achieved or boosted by the concomitant memantine use, which we did not prescribe. Clearly, our understanding of the relationship between dose to the hippocampus and cognitive function is still incomplete. The normal tissue complication probability model published by Gondi et al.[24] was recently tested in a group of patients with low-grade glioma on the basis of dose to the bilateral hippocampi.[25] The hippocampus normal tissue complication probability model did not perform as expected in predicting cognitive decline. In our study, PCI with or without HA was associated with cognitive decline in 28% of the patients with SCLC in our trial at 4 months. This risk needs to be balanced against the potential benefit of PCI in general in terms of BM incidence. Recently, the health-related quality of life of patients with NSCLC treated in a randomized phase 3 trial of PCI or no PCI was reported.[26] In this trial, no statistically significant or clinically relevant impact of PCI was observed. PCI definitely reduces the incidence of BM, but more research is needed to avoid cognitive decline. Current research on HA-PCI is ongoing in the phase 3 NRG CC003 trial.

In conclusion, in our trial, avoidance of the hippocampus with the aim to reduce the incidence of neurocognitive side effects of PCI did not lead to a beneficial effect for patients, and based on these results, we believe that hippocampus sparing should not be offered to patients receiving PCI outside of clinical trials. The trial did find that HA-PCI is safe.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.12.024.

References

1. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *N Engl J Med*. 1999;341:476–484.
2. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation extensive small-cell lung cancer. *N Engl J Med*. 2007;357:664–672.
3. Péchoux CL, Sun A, Slotman BJ, De Ruysscher D, Belderbos J. Prophylactic cranial irradiation patients lung cancer. *Lancet Oncol*. 2016;17:e277–e293.

4. Pazzaglia S, Briganti G, Mancuso M, Saran A. Neurocognitive decline following radiotherapy mechanisms and therapeutic implications. *Cancers (Basel)*. 2020;12:146.
5. Wang S, Zheng D, Zhang C, et al. Automatic planning on hippocampal avoidance whole-brain radiotherapy. *Med Dosim*. 2017;42:63–68.
6. Tomé WA, Gökhan Ş, Gulinello ME, et al. Hippocampal-dependent neurocognitive impairment following cranial irradiation observed in pre-clinical models: current knowledge and possible future directions. *J Radiol*. 2016;89:20150762.
7. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32:3810–3816.
8. Brown PD, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG Oncology CC001. *J Clin Oncol*. 2020;38:1019–1029.
9. De Dios NR, Murcia M, Counago F, et al. Phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer. *J Radio Oncol*. 2019;105:S35–S36.
10. Benedict RH, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test–Revised: normative data and analysis of inter-form and test–retest reliability. *Neuropsychol*. 1998;12:43–55.
11. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10:1037–1044.
12. Wefel JS, Cloughesy T, Zazzali JL, et al. Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab. *Neuro Oncol*. 2011;13:660–668.
13. Deprez S, de Ruiter MB, Bogaert S, et al. Multi-center reproducibility of structural, diffusion tensor, and resting state functional magnetic resonance imaging measures. *Neuroradiology*. 2018;60:617–634.
14. Lin NU, Lee EQ, Aoyama H, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. *Lancet Oncol*. 2013;14:e396–e406.
15. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12:703–708.
16. Ruff RM, Light RH, Parker SB, Levin HS. Benton controlled oral word association test: reliability and updated norms. *Arch Clin Neuropsychol*. 1996;11:329–338.
17. Levine AJ, Miller EN, Becker JT, Selnes OA, Cohen BA. Normative data for determining significance of test-retest differences on eight common neuropsychological instruments. *Clin Neuropsychol*. 2004;18:373–384.
18. Han YM, Cai G, Chai WM, et al. Radiological distribution of brain metastases and its implication for the hippocampus avoidance in whole brain radiotherapy approach. *Br J Radiol*. 2017;90:20170099.
19. Gondi V, Tome WA, Marsh J, et al. Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. *Radiother Oncol*. 2010;95:327–331.
20. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011;81:77–84.
21. Son Y, Yang M, Wang H, Moon C. Hippocampal dysfunctions caused cranial irradiation: a review of the experimental evidence. *Brain Behav Immun*. 2015;45:287–296.
22. Bartel F, van Herk M, Vrenken H, et al. Inter-observer variation of hippocampus delineation in hippocampal avoidance prophylactic cranial irradiation. *Clin Transl Oncol*. 2019;21:178–186.
23. Mayinger M, Kraft J, Lohaus N, et al. Leukoencephalopathy after prophylactic whole-brain irradiation with or without hippocampal sparing: a longitudinal magnetic resonance imaging analysis. *Eur J Cancer*. 2020;124:194–203.
24. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys*. 2012;83:e487–e493.
25. Jaspers J, Mèndez Romero A, Hoogeman MS, et al. Evaluation of the hippocampal normal tissue complication model in a prospective cohort of low grade glioma patients-an analysis within the EORTC 22033 clinical trial. *Front Oncol*. 2019;9:991.
26. Witlox WJA, Ramaekers BLT, Joore MA, et al. 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. *Radiother Oncol*. 2020;144:65–71.