Journal of the National Cancer Center xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of the National Cancer Center

journal homepage: www.elsevier.com/locate/jncc

Short Communication

Quality assurance and safety of hippocampal avoidance prophylactic cranial irradiation in the multicenter randomized phase III trial (NCT01780675)

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ARTICLE INFO

Keywords:
Hippocampus-avoidance profylactic cranial irradiation
Small cell lung cancer
Quality assurance
NCT01780675
Neurocognition

ABSTRACT

Objective: NCT01780675, a multicenter randomized phase III trial of prophylactic cranial irradiation (PCI) versus PCI with hippocampal sparing in small cell lung cancer (SCLC) investigated neurocognitive decline and safety. As part of quality assurance, we evaluated if HA-PCI was performed according to the NCT01780675 trial protocol instructions, and performed a safety analysis to study the incidence and location of brain metastases for patients treated with HA-PCI.

Methods: This retrospective analysis evaluated the quality of the irradiation given in the randomized controlled trial (RCT) comparing SCLC patients receiving PCI with or without hippocampal avoidance, using intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). The dose distribution for each patient receiving HA-PCI was retrieved and analyzed to evaluate if the treatment dose constraints were met. A questionnaire was sent out to all participating sites, and data on radiotherapy technique, pre-treatment dummy runs, phantom measurements and treatment electronic portal imaging device (EPID) dosimetry were collected and analyzed. As part of the safety analysis, the follow-up magnetic resonance imaging (MRI) or computerized tomography (CT) scans on which cranial disease progression was first diagnosed were collected and matched to the radiotherapy planning dose distribution. The matched scans were reviewed to analyze the location of the brain metastases in relation to the prescribed dose.

Results: A total of 168 patients were randomized in the NCT01780675 trial in 10 centers in the Netherlands and Belgium from April 2013 until March 2018. Eighty two patients receiving HA-PCI without evidence of brain metastases were analyzed. All patients were treated with 25 Gy in 10 fractions. Dummy runs and phantom measurements were performed in all institutions prior to enrolling patients into the study. The radiotherapy (RT) plans showed a median mean bilateral hippocampal dose of 8.0 Gy, range 5.4–11.4 (constraint ≤ 8.5 Gy). In six patients (7.3%) there was a protocol violation of the mean dose in one or both hippocampi. In four of these

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https://doi.org/10.1016/j.jncc.2023.05.004
Received 29 August 2022; Received in revised form 10 May 2023; Accepted 17 May 2023
Available online xxx

six patients (4.9%) the mean dose to both hippocampi exceeded the constraint, in 1 patient (1.2%) only the left and in 1 patient (1.2%) only the right hippocampal mean dose was violated (average median dose left and right 8.9 Gy). All patients met the trial dose constraint of $V_{115\%}$ *PTV* ≤ 1%; however the D_{max} *PTV* constraint of ≤ 28.75 Gy was violated in 22.0% of the patients. The safety analysis showed that 14 patients (17.1%) developed cranial progression. No solitary brain metastases in the underdosed region were found. Two out of 11 patients with multiple brain metastasis developed metastasis in the underdosed region(s).

Conclusions: The radiotherapy quality within the HA-PCI trial is performed according to the protocol guidelines. The dose constraints to the hippocampi are met in the vast majority of cases. In all patients, the volume of the brain for which a higher dose was accepted, is according to the trial. However, within this volume there are small areas with higher doses than advised.

1. Introduction

Small cell lung cancer (SCLC) accounts for about 14% of all lung carcinomas worldwide, and has a 60% risk of progressing to distant organs, primarily the liver, bone and brain.[1,2] Patients with SCLC often receive prophylactic cranial irradiation (PCI) in order to reduce the incidence of brain metastasis and improve overall survival.[3,4] As hippocampal dose is associated with late-onset neurocognitive decline and metastases in the hippocampus are relatively rare, there exists a rationale for hippocampal avoidance during PCI.[5,6]

A multicenter randomized phase III trial (NCT01780675) was performed that investigated neurocognitive functioning and safety of PCI with or without hippocampus avoidance (HA) in SCLC patients. This trial, using avoidance of the hippocampus with the aim to reduce the incidence of neurocognitive side effects of PCI, could not detect a benefit.[7] However, other investigations into hippocampal avoidance in PCI as well as whole brain radiotherapy (WBRT) for brain metastases did detect a difference (RTOG0933, CC001).[8,9]

Treating the whole brain with standard radiotherapy doses while preserving the left and right hippocampi from receiving high doses requires a challenging delineation, radiotherapy planning and execution. Volumetric modulated arc therapy (VMAT) and intensity modulated radiotherapy (IMRT) are radiotherapy techniques that are able to generate hippocampus avoidance PCI (HA-PCI) treatment plans. However, the HA-PCI treatment plans require expertise of the radiation oncology team, as lowering the bilateral hippocampal dose automatically forces the dose to be higher in other areas of the brain, and hippocampus delineation is challenging.

This study investigated the quality of the HA-PCI treatment of patients treated within the trial since treatment deviations have been shown to directly impact primary outcome.[10] We evaluated if HA-PCI was performed according to the NCT01780675 trial protocol instructions. Additionally, we performed a safety analysis for patients treated with HA-PCI to study the incidence and location of brain metastases.

2. Materials and methods

Patients included had histologic or cytological proof of stage III-IV SCLC. Patients had no clinical or radiological signs of brain metastasis at inclusion. The study MRI scan protocol used defined high quality brain MRI scan acquisition at baseline and at 4 and 12 months. All sequences of the magnetic resonance imaging (MRI) scanners of participating institutions were aligned and assessed for multi-center and longitudinal reproducibility before the start of the study including physical and human phantom measurements.[11] All patients in this study were randomized from April 2013 until March 2018 and received cranial irradiation to a dose of 25 Gy delivered in 10 once-daily fractions. The treatment was performed using image guided irradiation, using VMAT or IMRT. In the HA arm, several dose constraints were formulated to ensure optimal dose distributions, as can be found in Table 1. Before participating in the trial all institutions received the study protocol containing the radiotherapy dose distribution constraints.

For each patient, the diagnostic MRI-scan at baseline was co-registered to the planning computerized tomography (CT) scan. The left and right hippocampus were manually delineated according to the RTOG atlas (https://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx) in patients randomized to the HA-PCI group. The hippocampus was then enlarged with 5 mm to generate the hippocampal avoidance zone. This area is used for dose fall-off, day-to-day setup inaccuracy, geometrical uncertainties, and inter-observer variation in hippocampus delineation.

Patients receiving HA-PCI were included in this quality analysis. In order to assess the overall quality of the performed HA-PCI radiotherapy treatments, we evaluated the treatment planning and execution step by step. The trial protocol included a specification for use of image guidance, but neither type nor frequency was specified. Therefore, a questionnaire was sent to all participating institutions regarding radiotherapy technique (IMRT or VMAT), type of image guidance (two-dimension [2D] or 3D) and the frequency (daily or weekly).

In order to evaluate the treatment plan quality, dummy runs were required for all participating institutions before enrolling patients in the trial. The dummy run consisted of three test planning CT scans with hippocampi and organ at risk (OAR) already delineated. The participating institutions were requested to plan a HA-PCI treatment according to the treatment planning dose constraints specified in the protocol (Table 1).

Furthermore, the dosimetry data as recorded in the electronic case report form (eCRF) of the patients included in the HA-PCI arm were collected and evaluated. To analyze if metastases were found in the underdosed regions (both hippocampi and the HA zone), the follow-up MRI or CT scan on which cranial disease progression first diagnosed was reviewed. These CT and/or MRI scans were first visually inspected by an expert, to check if metastases were found in an underdosed region. In case of metastasis in the proximity of the lower dose regions, the scans were matched to the radiotherapy planning dose distribution by an experienced technician using Mirada (medical imaging software). Isodose-lines were generated (corresponding with the radiotherapy planning dose constraints) of 8.5, 10 and 12.5 Gy to visualize the underdosed region. Furthermore, isodose lines of 18.75, 25, 27.5 and 28.75 Gy were used to visualize the planning target volume (PTV) coverage. Every matched scan was reviewed by one expert (radiation oncologists) to analyze the location of the brain metastases in relation to the dose distribution.

3. Results

A total of 168 patients were randomized in the NCT01780675 trial in 10 centers in the Netherlands and Belgium from April 2013 until March 2018. No significant difference was found in neurocognitive function between the two treatment arms at 4 months.[7] A total of 82 patients receiving HA-PCI without evidence of brain metastases at baseline were analyzed.

Table 2 showed the image guided radiotherapy techniques that were used. The irradiation was performed using 6 or 10 megavolt (MV) photon beams. Out of the 10 participating institutions (7 in the Netherlands and 3 in Belgium), 9 centers used VMAT and 1 center used IMRT. Two

Table 1
Treatment planning dose constraints.

Variable	Constraint	Definition
D_{mean} *hippocampi*	≤ 8.5 Gy (BED ≤ 6.1 Gy)	Mean biological dose on hippocampi
$D_{1\%}$ *hippocampi*	≤ 10 Gy	Dose on 1% of hippocampi
$V_{95\%}$ *PTV*	≥ 95%	PTV receiving 95% of prescribed dose
$V_{115\%}$ *PTV*	≤ 1%	PTV receiving 115% of prescribed dose
$D_{98\%}$ *PTV*	≥ 18.8 Gy (75%)	Dose on 98% of PTV
$D_{1\%}$ *PTV*	≤ 27.5 Gy (110%)	Dose on 1% of PTV
D_{max} *PTV*	≤ 28.8 Gy (115%)	Max dose within PTV
D_{max} *lenses*	≤ 10 Gy	Max dose on lenses

Abbreviations: BED, biologically effective dose; PTV, planning target volume.

Table 2
HA-PCI radiotherapy execution specifications.

Specification	Institutions, No. (%)
Radiotherapy technique	
IMRT	1 (10.0)
VMAT	9 (90.0)
Type of imaging	
2D	2 (20.0)
3D	8 (80.0)
Frequency of imaging	
Daily	9 (90.0)
Not daily	1 (10.0)

Abbreviations: 2D, two-dimension; 3D, three- dimension; IMRT, intensity modulated radiotherapy; VMAT, volumetric modulated arc therapy.

centers used 2D image guidance (kV imaging) and 8 centers used 3D image guidance during the treatment (7 cone beam CT-scans and 1 MegaVolt CT). The imaging was done daily except for one institution that performed daily imaging for the first four fractions and weekly imaging thereafter.

All participating institutions performed three treatment planning dummy runs. One institution used a constraint for the hippocampi that was incorrect. A D_{max} *PTV* of < 130% was used in this dummy run instead of D_{max} *PTV* < 115%. Therefore, this dummy run was excluded from the analysis. The other nine centers performed the dummy runs according to the trial constraints. For one institution we were unable to retrieve the dummy run results. Table 3 showed the frequency that a treatment planning constraint was violated for the three dummy runs. Six out of eight institutions (75%) did not violate the constraints during any of the three dummy runs. One institution violated only the D_{max} *PTV* constraint for all three dummy runs. Another institution violated multiple constraints for at least one of the three dummy runs. The D_{max} *PTV* two times and PTV, and $D_{1\%}$ hippocampus right were violated in one out of three dummy runs in this institution. Violation of a constraint in two out of three runs was interpreted as a notable violation. This occurred in two institutions for the D_{max} *PTV* constraint which exceeded the allowed maximum dose to the PTV with 1–5%.

The treatment plan results of all patients treated in the HA-PCI arm were depicted in Table 4. The median mean bilateral hippocampal dose of all patients was 8.0 Gy, range 5.4–11.4 Gy (constraint ≤ 8.5 Gy). In six patients (7.3%) there was a protocol violation of the mean dose in one or in both hippocampi. In four of the six patients (4.9%) the mean dose to both hippocampi exceeded the constraint, in one patient (1.2%) only the left and in one patient (1.2%) only the right hippocampal mean dose was violated (median mean dose left and right 8.9 Gy). All patients met the trial constraint of $V_{115\%}$ *PTV* ≤ 1%; however, the D_{max} *PTV* of ≤ 28.75 Gy was violated in 22.0% of the patients. Fig. 1 showed the dose distribution of a HA-PCI treatment plan.

Out of the 82 patients in the HA-PCI arm, the 14 patients (17.1%) developing brain metastases were shown in Table 5. Patients in the HA-PCI arm did not have a higher risk to develop brain metastases compared to conventional PCI.[7] In 11 of the 14 follow-up scans made to diagnose intracranial progression MRI scans were available, 3 of the scans were CT scans of the brain. In 10 out of the 14 patients, neurological symptoms led to additional brain imaging (MRI or CT scan). Four of the patients were not experiencing symptoms and the progression was diagnosed on a trial follow-up MRI-scan.

In case of metastases in the proximity of the lower dose regions, the MRI or CT scan were matched to the planning CT-scan. Then the scan was visually inspected by an expert to see if the metastases were located in the underdosed region. In 13 of the 14 patients the MRI scan and/or CT-scan was retrieved. We were unable to retrieve one follow-up (FU) MRI-scan of a patient recently diagnosed with brain metastasis. Three patients (21.4%) had progression of a solitary lesion on the FU MRI-scan, 11 patients (78.6%) showed progression of multiple lesions. Seven of the patients (63.6%) with multiple metastasis had 2–5 lesions, 1 patient (9.1%) had lesions in the range 5–15, 2 patients (18.2%) had >15 lesions visible on the FU-scan. None of the solitary metastases were located in the HA region. One patient had an infratentorial solitary metastasis and two patients had a supratentorial solitary metastasis. Two of the 11 patients with multiple brain metastases had metastases in the HA-region (underdosed areas). Patient 1 had approximately a total of 30 metastases, of which 2 metastases in the left hippocampus, 1 in the left HA-area and 1 in the right HA-area. Patient 2 had a total of two metastases, of which one large tumor covered both the left hippocampus and the left HA-area.

4. Discussion

Neurocognitive deterioration is an important side effect that influences the quality of life (QOL) of patients receiving PCI. On the other hand, the development of brain metastases is detrimental for the patient's QOL as well.[12,13] The phase III randomized trial of PCI with or without HA in SCLC (NCT01780675) with the aim to reduce the incidence of neurocognitive side effects of PCI, could not detect a benefit.[7] At 4 and 8 months, no difference in cognitive decline according to the total recall of Hopkins Verbal Learning Test-Revised (HVLT-R) was seen. The Spanish PREMER phase III randomized study demonstrated less cognitive deterioration with HA-PCI in SCLC but had only 118 patients randomized.[8]

The results of the NRC 001 phase III trial randomizing hippocampus avoidance WBRT versus WBRT in patients with brain metastases from solid tumors with concurrent use of Memantine, revealed better preserved neurocognitive function.[9] Despite many differences in the patients selected and treatment characteristics, it is surprising that this trial showed a preserved neurocognitive function in the HA-WBRT group compared to the WBRT group.[9] Because of the discrepancy in outcome of neurocognitive decline between the HA-PCI and HA-WBRT study, it is crucial to evaluate the quality of the radiotherapy treatment given in the HA-PCI arm.

We performed an analysis on the quality of the radiotherapy that was given in the HA group within the HA-PCI study. This is the first study evaluating the quality of this complex new treatment technique.

Table 3
Dummy run violation per institution.

Constraint	The number of dummy runs violating dose constraints per institution							
Institution	1	2	3	4	5	6	7	8
D_{mean} *hippocampus left*	0	0	0	0	0	0	0	0
D_{mean} *hippocampus right*	0	0	0	0	0	0	0	0
$D_{1\%}$ *hippocampus left*	0	0	0	0	0	0	0	0
$D_{1\%}$ *hippocampus right*	**1**	0	0	0	0	0	0	0
$V_{95\%}$ *PTV*	0	0	0	0	0	0	0	0
$V_{115\%}$ *PTV*	0	0	0	0	0	0	0	0
$D_{98\%}$ *PTV*	0	0	0	0	0	0	0	0
$D_{1\%}$ *PTV*	**1**	0	0	0	0	0	0	0
D_{max} *PTV*	**2**	0	0	0	**3**	0	0	0
D_{max} *lenses*	0	0	0	0	0	0	0	0

Abbreviations: PTV, planning target volume.

Table 4
Treatment dose constraint violation for all patients receiving HA-PCI (n = 82).

Constraint		Constraint achieved			Constraint violated		
		No. (%)	Median (Gy)	Range	No. (%)	Median (Gy)	Range
D_{mean} *one/both hippocampi*	≤ 8.5 Gy (BED ≤ 6.1 Gy)	76 (92.7)	8.0	5.4–8.5	6 (7.3)	8.9	8.6–11.4
Left	≤ 8.5 Gy (BED ≤ 6.1 Gy)	77 (93.9)	8.0	5.4–8.5	5 (6.1)	8.9	8.7–11.4
Right	≤ 8.5 Gy (BED ≤ 6.1 Gy)	77 (93.9)	8.0	5.7–8.5	5 (6.1)	8.9	8.6–10.7
$D_{1\%}$ *one/both hippocampi*	≤ 10 Gy	70 (85.4)	10	7–10	12 (14.6)	11	–
Left	≤ 10 Gy	71 (86.6)	10	7–10	11 (13.4)	11	–
Right	≤ 10 Gy	72 (87.8)	10	7–10	10 (12.2)	11	–
$V_{95\%}$ *PTV*	≥ 95%	76 (92.7)	95	95–97	6 (7.3)	92	90–94
$V_{115\%}$ *PTV*	≤ 1%	82 (100)	0	0–1	0 (0)	–	–
$D_{98\%}$ *PTV*	≥ 18.8 Gy (75%)	78 (95.1)	20.7	18.8–27.1	4 (4.9)	18.2	16.5–18.7
$D_{1\%}$ *PTV*	≤ 27.5 Gy (110%)	71 (86.6)	26.8	25.3–27.5	11 (13.4)	28.1	27.6–29.8
D_{max} *PTV*	≤ 28.8 Gy (115%)	64 (78.0)	28.1	25.3–28.7	18 (22.0)	29.4	28.8–31.7
D_{max} *lenses*	≤ 10 Gy	79 (96.3)	9	6–10	3 (3.7)	12	11–17

Abbreviations: BED, biologically effective dose; HA-PCI, hippocampus avoidance-prophylactic cranial irradiation; PTV, planning target volume.

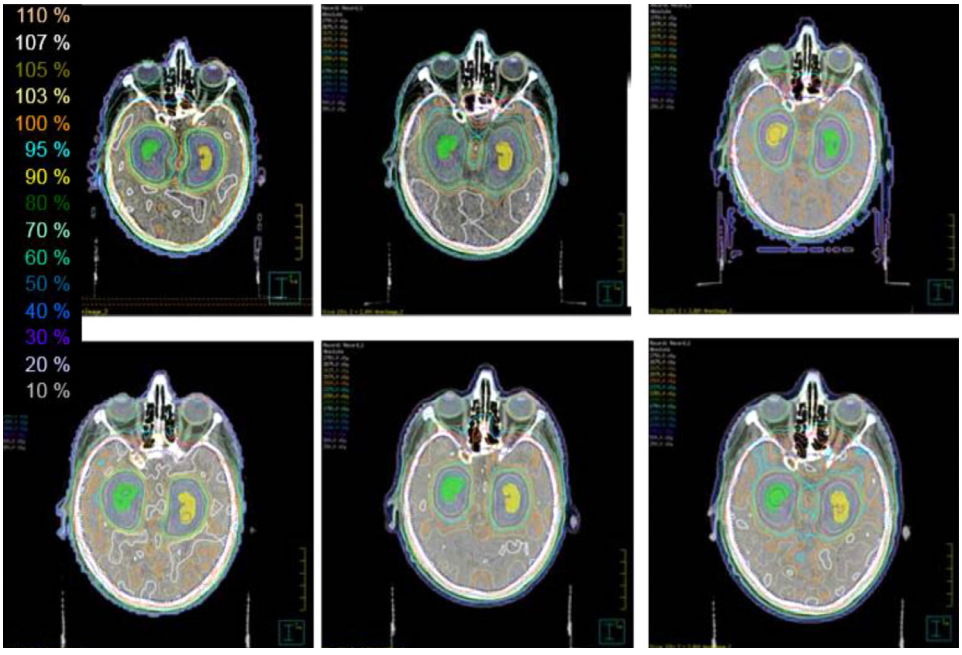

Fig. 1. Dose distribution of HA-PCI treatment plan. The hippocampi was presented as green and yellow rings. Around the hippocampi, the underdosed region is visible in blue/purple. Within the PTV some "hotspots" (higher dosed regions) up to 107% (according to the ICRU guideline) of the prescribed dose were observed. HA-PCI, hippocampus avoidance-prophylactic cranial irradiation; ICRU, International Committee for Radiological Units; PTV, planning target volume.

Through an analysis of the dosimetry data extracted from the eCRF, we compared the radiotherapy planning dosimetry data with the study protocol treatment planning constraints. Especially the hippocampi dose constraints were well achieved. Since the hippocampus seems to be a parallel organ,[14] the mean dose to the hippocampi is the main constraint to indicate hippocampal sparing. This constraint was met in the vast majority of treatment plans. There was a notable rate of dose violations found in the maximum dose allowed to the PTV (D_{max} *PTV* ≤ 28.75 Gy). However, these violations were seen in very small volumes (hotspots), since there was no violation at all of the $V_{115\%}$ *PTV* constraint, allowing

Table 5
Characteristics of cranial progression in HA-PCI patients.

	Solitary (n = 3)	Multiple (n = 11)
Tumor Characteristics		
Number of metastasis, No. (%)		
1	3 (100)	0
2–5	0	7 (63.6)
5–15	0	1 (9.1)
> 15	0	2 (18.2)
Unknown	0	1 (9.1)
Location tumor, No. (%)		
Infratentorial	1 (33.3)	0
Supratentorial	2 (66.6)	3 (27.3)
Infra and supratentorial	0	7 (63.6)
Unknown	0	1 (9.1)
Radiotherapy dose region, No. (%)		
Only regular dose region	3 (27.3)	8 (72.7)
Only underdosed region	0	0
Regular and underdosed	0	2 (18.2)
Unknown	0	1 (9.1)
Diagnostics		
Modality, No. (%)		
MRI	3 (100)	8 (72.7)
CT	0	3 (27.3)
Reason scan, No. (%)		
Symptomatic/extra scan	1 (33.3)	9 (81.8)
Asymptomatic/study scan	2 (66.7)	2 (18.2)

less than 1% of the volume of the PTV to receive this maximum dose. This finding might be important because overdosing in normal brain tissue might adversely influence neurocognitive functioning.

VMAT combined with daily 3D imaging was the most frequently used technique to execute the HA-PCI treatment plans. The pre-treatment dummy runs were mostly performed according to the trial protocol dosimetry constraints; however, two institutions violated a constraint at least 2 out of 3 times. The dosimetry constraint was violated by both institutions with 1–5% of the allowed dose, according to the readout in Pinnacle V16.2 (Philips Medical Systems, Best, the Netherlands), the treatment planning system used at the reviewing institution. These treatment plans did not show violations of these constraints when analyzed at their local sites with the local treatment planning system. This is due to small differences in dose-volume histogram (DVH) sampling methods in different treatment planning systems. Therefore, these dummy runs were approved and these institutions were allowed to include patients in the trial. These two institutions included a total of 15 out of 82 patients in the HA arm (18%) which accounted for 26 out of 73 total violations in this study (36%).

The NCT01780675 study previously reported that patients in the HA-PCI arm did not have a higher risk to develop brain metastases, and no solitary brain metastases in the underdosed regions were reported.[10] The frequency of brain metastases in the underdosed region in patients that developed multiple brain metastases (the majority) was analyzed in detail in this study. The current analysis included patients with solitary as well as multiple metastases by matching the dose distributions with the FU MRI scan on which the brain metastases were first detected. This showed a relatively low percentage of lesions developing in the underdosed regions, as 2% of the patients in the HA-arm developed metastasis in the underdosed regions. One of these patients had approximately 30 total brain metastases, and the other patient had 2 brain metastases in total.

A strong point of the trial, was the quality assurance procedure of the high-resolution, three-dimensional T1-weighted MRI (1.2 mm slice thickness) to delineate the hippocampi and detect brain metastases. All sequences of the MRI scanners of participating institutions were aligned and checked with phantom measurements.[11] A minor point was the absence of a central pre-treatment review of the hippocampus delineation. However, we organized meetings and a dummy run procedure to train the physicians in the trial.[15] The results showed observer variation to be acceptable, with some observers delineating too big. The RTOG-atlas hippocampus outlining protocol describes to exclude the fimbria and amygdala, which was included in some cases. Therefore, these inter-observer variations (localized in the posterior and medial anterior border of the hippocampus) were mainly enlarging the hippocampus area to spare. This would have a beneficial effect on neurocognitive functioning in the HA-PCI arm and negatively affected the incidence of brain metastases. Moreover, in our previous publication on this trial we demonstrated that hippocampal atrophy was prevented in the HA-arm, which also demonstrated that we succeeded in sparing the hippocampus.

In general, the HA-PCI treatment planning and execution was performed well. The preparation was done thoroughly, with all institutions performing dummy runs and phantom measurements before enrolling patients into the trial. The execution of the radiotherapy plans largely met the study protocol requirements.[16]

5. Conclusions

The quality of the radiotherapy preparation and execution within the HA-PCI trial was generally performed according to the protocol guidelines. The dose constraints to the hippocampi were met in the vast majority of cases. The volume of the brain for which a higher dose was accepted was according to the trial prescription in all patients; however, within this volume there were small areas with higher doses than advised.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Ethics statement

This study is a retrospective analysis of the quality of the irradiation given in the randomized controlled trial comparing SCLC patients receiving PCI with or without HA (NCT01780675). All patients gave written informed consent prior to entering the NCT01780675 randomized controlled trial. The trial was conducted according to the Declaration of Helsinki and approved by the Medical Ethics Committee of the Netherlands Cancer Institute.

Consent for publication

The patients whose medical images are presented in this manuscript provided consent for publication of their medical images for the manuscript. Only de-identified data and images are used in this manuscript.

Author contributions

O.C., J.B. and M.R. conducted the study conception and design. O.C., A.W., P.H., W.C., S.H., L.P., Z.K., J.J., G.K., J.U., W.E. and D.R. collected the data. O.C., J.B., A.W. and M.R. analyzed and interpretated the results. O.C. and J.B. prepared the draft manuscript. All authors reviewed the results and approved the final version of the manuscript.

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