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Abstract

Background: In small cell lung cancer (SCLC), limiting the radiation dose in the hippocampus area during preventive cranial irradiation (PCI) can reduce nerve injury and cognitive decline. This study was done to compare changes in cognitive functions between hippocampal-protected (3D-H) and non-hippocampal-protected (3D) patients during PCI.

Materials and methods: the study group included 113 patients with SCLC qualified to PCI divided in two subgroups: 3D-H (n = 74) and 3D (n = 39). Two diagnostic and screening tests, Mini-Mental State Examination (MMSE) Short Scale and Montreal Cognitive Assessment

(MoCA) Scale, have been applied before the start of irradiation, immediately after and 3 months after PCI.

Results: The doses delivered to the volume of the left and right hippocampus were similar and amounted to 12.00 Gy and 12.05 Gy, respectively. There were no differences between 3D-H and 3D groups in the MoCA and MMSE tests at any time point. In both groups the values in MoCA and MMSE scales differed between time points I, II and III. The patients in the 3D-H group were less likely than patients in 3D group to experience significant cognitive decline on the MoCA scale ($p = 0.003$), but not on the MMSE scale ($p = 0.103$).

Conclusions: Following PCI, SCLC patients experience significant cognitive decline, even when the radiation dose in the hippocampal area is reduced. This trend continues for at least 3 months following the PCI. In hippocampal-protected patients significant cognitive decline assessed on the MoCA scale is less common than in non-hippocampal-protected patients.

Key words: preventive cranial irradiation, hippocampal sparing, small cell lung cancer, neurocognitive dysfunction

Introduction

Small cell lung cancer (SCLC), which accounts for 13–15% of all lung cancer cases, is an aggressive disease characterized by its early dissemination at diagnosis, high chemosensitivity, high radiosensitivity and rapid relapse [1, 2]. The tumor has a tendency to disseminate early resulting in 70–85% of patients being diagnosed with extensive disease (ESCLC) [1, 3, 4]. The common metastasis sites of SCLC include the lung, brain, bone, adrenal gland, liver, colorectum, and lymph nodes [5]. Approximately 10% of the patients with SCLC present with brain metastases at the time of diagnosis. Patients with cancer control outside the brain have a 60% actuarial risk of developing brain metastases within 2 to 3 years after starting treatment. The brain metastases shorten overall survival and harms the quality of life [6]. Brain MRI is the preferred imaging method to accurately judge the number, size, and location of brain tumors in patients with SCLC brain metastasis [7].

SCLC has no treatment options that produce durable responses. The two-drug combination of etoposide and cisplatin is a “gold standard” in primary treatment for both LSCLC and ESCLC. In LSCLC the rate of response to treatment is 70–80%, while in ESCLC it amounts to 60–70% [8]. The standard treatment for patients with LSCLC is to combine

chemotherapy with radiotherapy applied to the mediastinal region (CHT-RT) and preventive cranial irradiation (PCI) [8, 9]. Despite treatment, nearly all patients experience relapse shortly after treatment and median survival time only ranges from 7 to 10 months from the diagnosis, while that of patients with brain metastasis is only about 5 months [3, 6, 10].

For patients with LSCLC and ESCLC, PCI is used to eliminate undetectable brain micrometastases to prevent them from progressing into larger metastatic tumors [11]. The effectiveness of PCI has been well established in patients with SCLC after response to first-line therapy [12, 13]. In a meta-analysis of seven randomized trials evaluating the value of PCI, the risk of developing central nervous system metastases was reduced by more than 50% and the 3-year overall survival of complete responders was 20.7% with PCI versus 15.3% in the control group [14]. Due to the frequent occurrence of neuropsychological disorders following radiation therapy to the brain area, significant interest in the search for parameters predicting the occurrence of cognitive impairment is observed [15, 16]. A brain structure closely related to neurocognition is hippocampus. It plays an important role in memory coding, memory consolidation, and long-term learning. It is believed, that limiting the radiation dose in the hippocampus area can reduce nerve injury and cognitive decline by protecting hippocampal formation [17].

In patients receiving PCI, subjective psychological tests are used to assess cognitive functions. The tools used to assess cognitive function include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) [16]. The MMSE scale is the most popular and most frequently used diagnostic tool, which allows for a comprehensive evaluation of cognitive impairment in clinical research and community settings. It consists of 30 questions which enable a quantitative assessment of numerous aspects of cognitive functioning, i.e. memorisation, reading, naming and counting. The MoCA is a screening tool that detects Mild Cognitive Impairment (MCI) [18]. It assesses abstraction, short-term memory, visuospatial function, executive functions, language, verbal fluency, allopsychic orientation and attention. In the MoCA test the maximum number of points that can be scored is 30 [18]. It is especially useful for patients who complain about memory problems and achieve a normal score on the MMSE scale [19].

The aim of this study was to compare changes in cognitive functions between hippocampal-protected and non-hippocampal-protected patients with SCLC during PCI.

Materials and methods

The prospective two-center study on adult SCLC patients was conducted at the Copernicus Memorial Hospital of Lodz and in Oncology Center of Radom between 1 April 2019 – 29 January 2023. The patients had been subjected to Platinum-based chemotherapy. After completion of chemotherapy the presence of brain metastases was excluded based on imaging scans. The patients were qualified to PCI. Initial evaluation included 133 patients who met all the above mentioned inclusion criteria. After recruitment was completed and data summarized 20 patients were excluded due to: the lack or low quality of the MRI scan (n = 10), the use of drugs affecting cognitive functions (n = 6) and the isolation due to SARS-CoV-2 infection (n = 4). Finally, 113 patients were included into the study group. The patients were divided into two groups: with hippocampal protection during PCI (3D-H) and without hippocampal protection during PCI (3D). The 3D-H group included 74 patients (64.49%) and the 3D group, 39 patients (35.51%). The characteristics of the study group are presented in Table 1.

The process of planning radiotherapy and irradiation was similar in both groups. The patients were fitted with orfit masks to immobilise their heads during irradiation. A treatment plan was developed based on a head CT scan with image fusion with a contrast-enhanced MRI scan. During the treatment planning process, the treated volume included the brain and critical organs: the right and left optic nerves, the optic nerve junction, lenses and eyeballs on both sides, the brain stem, the left hippocampus (LH) and the right hippocampus (RH) were contoured. Once the treatment plan was approved, the patients received PCI to a total dose of 25 Gy fractionated into 2.5 Gy doses, receiving one fraction per day and five fractions per week.

The first part of the evaluation survey was conducted with a clinical psychologist during a medical consultation preceding PCI. Clinical data and treatment history of the patients were included in the questionnaire. The survey involved the evaluation of cognitive functions according to MoCA 7.2 (the cut-off point adopted was < 26 points) and according to MMSE; a score of 20–25 points was assumed to indicate mild cognitive impairment. A re-evaluation of patients' cognitive functions according to the MoCA and MMSE scales took place in the first week following the completion of PCI. It was repeated three months after the completion of irradiation. A CT scan of the brain was performed three months following the completion of PCI. A clinically significant cognitive decline was defined as a MoCA and MMSE score at least 2 points worse than baseline at the last assessed time point [20]. Age,

sex and level of education were assessed as additional factors with a possible impact on cognitive functions.

Statistical analysis

The data were statistically elaborated using the Statistica 13.1 PL software (Statsoft Inc., Tulsa, OK, USA). Nominal variables were expressed as percentages and analyzed using the Chi-square test with appropriate corrections (the Yates's correction for continuity or the Fisher exact test), if needed. The normality of the distribution of continuous variables was verified with the Shapiro-Wilk test. Continuous variables were presented as medians with 25% to 75% values and compared using the Mann-Whitney U test. They were compared using the Mann-Whitney U test or for three groups, using the Friedman test. The Kaplan-Meier survival curves were calculated and statistical analysis of survival was performed with the log-rank test and Cox models. A multivariable analysis was performed with the application of general linear models. The „p" value below 0.05 was considered statistically significant.

The study was approved by the Bioethics Commission of the Medical University of Lodz, No. RNN/05/19/KE.

Results

The doses delivered to the volume of the LH and RH were similar and amounted to 12.00 (11.30–13.00) Gy and 12.05 (11.40–12.80) Gy, respectively. There was no correlation between the average dose for the RH and LH and the total dose for both hippocampus and the decrease in cognitive functions ($p = 0.364$; $p = 0.382$; $p = 0.400$, respectively).

Points scored in the MoCA and MMSE tests in studies I, II, and III are shown in Table II. There were no differences between 3D-H and 3D groups in the MoCA and MMSE tests at any time point. In both groups of patients the values in MoCA and MMSE scales differed between time points I, II and III (Fig 1 and 2).

Based on the results of the MoCA and MMSE tests at time point I, patients in the 3D-H and 3D groups were divided into those with significant cognitive decline and those without significant cognitive decline after PCI. In the 3D-H group 48 patients (64.86%) experienced no significant cognitive decline on the MoCA scale, while in the 3D group there were 13 patients (33.33%). Patients in the 3D-H group were statistically less likely than patients in 3D

group to experience significant cognitive decline on the MoCA scale (p = 0.003; Fig. 3). Such a relationship was not observed on the MMSE scale (p = 0.103).

There was a negative correlation between age of the patients and the scores in MoCA tests from time point I to III (r = –0.26; p = 0.005; Fig. 4A). Patients who experienced clinically significant cognitive decline during PCI on the MoCA scale were older than those who did not (p = 0.028, Fig. 4B). The analysis showed no relationship between sex of patients and both clinically significant cognitive decline (p = 0.110) and the scores in MoCA tests (p = 0.112). It was shown that patients with higher education experienced a smaller decrease in cognitive functions compared to patients with primary, vocational and secondary education in MoCA tests (p = 0.018, p = 0.016, p = 0.013, respectively; Fig. 5).

In multivariate analysis of 113 patients, the lack of protection of the hippocampus turned out to be a statistically significant risk factor for the occurrence of clinically significant cognitive decline, taking into account the level of education, sex and age of patients [odds ratio (OR) = 4.98; 95% confidence interval (CI) = 1.83–13.52; p = 0.002]. Another significant independent factor associated with cognitive decline was education: patients with higher education were less likely to experience cognitive decline compared to patients with primary education (OR = 0.06, 95% CI = 0.01–0, 31; p < 0.001). The age and sex of patients were not statistically significant in multivariate analysis. The exact results are presented in Table 3.

Discussion

Few studies on hippocampal sparing during PCI (PCI — HA) in SCLC have been conducted so far and the recommendations for hippocampal tolerance doses during brain irradiation were developed based on the results of the RTOG 0933 trial in patients with brain metastases with a prognosis of survival of more than 6 months, who received Whole Brain Radiotherapy (WBRT) [21]. The total dose (TD) below 7.8 Gy, the maximum dose (D max) below 15.3 Gy and the dose delivered to the entire hippocampus not exceeding 10 Gy were established [21]. The median doses to the hippocampi in our study were 12.00 Gy (LH) and 12.05 Gy (RH), and the dose 15.3 Gy was not exceed in any case. The NRG CC-003 study is currently recruiting [22]. Eligible patients have a diagnosis of SCLC with at least a partial response after CHT-RT and no brain metastases on MRI. According to the study protocol, the maximum dose delivered to the hippocampus should be lower than 13.5 Gy, however, doses below 15 Gy are acceptable, as they are similar to those administered in our study. The results

of the NRG CC-003 study may prove significant in terms of obtaining an unambiguous fractional dose and total dose that would make it possible to preserve the function of the limbic system.

The effect of brain irradiation on cognitive functions has been studied many times, but the observations of various authors do not allow to draw clear conclusions. The results of meta-analyses indicate slight deterioration in cognitive functions in SCLC patients following PCI, which mainly affects short-term memory, learning, and problems with minor sensorimotor functions [23, 24]. According to Soltman et al., cognitive dysfunction causes deterioration of the quality of life of SCLS patients [25]. Our results show, that even in patients who receive a reduced dose of radiation to the hippocampus, scores in MoCA and MMSE scales deteriorate during PCI and the trend continues for three months after the irradiation. Wang et al. observed further deterioration of neurocognitive function over a period of two years [26].

We did not show a protective effect of hippocampal protection on neurocognitive functions, because the differences in neurocognitive functions assessed in the MoCA and MMSE scales between the groups were not statistically significant at any time point. This may have been due to the follow-up period after PCI being too short. In the same period of time Wang et al. also did not show such a relationship, and only the following months of observation showed statistically significant less decline in cognitive functions in patients with hippocampal protection compared to patients irradiated without dose limitation to the hippocampal area [26]. Additionally, according to Tan et al., we used the criterion of two-point “clinically significant” decreases in the MoCA and MMSE scores [20]. We showed a higher frequency of clinically significant decrease in cognitive functions in the MoCA test in patients without hippocampal protection compared to those with hippocampal protection (33.33% *vs.* 64.86%). However, the MMSE analysis did not confirm this relationship. These results can suggest that more than 3 months of follow-up is required to reveal the benefits of hippocampal protection during PCI.

The prevailing view is that the MoCA test offers a better chance of identifying an impairment of cognitive function than the MMSE test [27, 28]. It was confirmed in our study. As clinically significant cognitive decline was not found in the MMSE scale, the assessment of the impact of the age, sex and education of patients on the occurrence of clinically significant cognitive decline was carried out only on the scores of the MoCA test. Similarly to Borland et al. [29], we also proved that older age and lower education level were correlated

with a lower score in MoCA test after treatment. Borland et al. [29] found that female sex correlates with lower decrease of cognitive functions following PCI, but it was not confirmed in our material. Additionally, Wu et al. found that the results of the MoCA test, but also the MMSE, were dependent on the duration of patient education, and higher level of education correlated with higher scores in both tests [27]. Rambe et al. assessed this relationship only on the MMSE scale obtaining similar results [30]. These observations show that, especially with longer follow-up of patients with SCLC after PCI than in our study, the use of both the MoCA and MMSE tests is justified.

The results of our study are original and interesting. Patients in the study group were treated according to the same protocol, at the same facility, and by the same team of radiation oncologists, which adds to the value of the results. The observation that the PCI leads to a reduction in both MoCA and MMSE scores and that the process continues for at least three months after the irradiation of the brain area is especially valuable. However, the present study has its limitations. The first one is the small number of patients in the study group and the second is short time of the follow up. The actual value of our results should be confirmed in studies on large groups with patient randomisation.

Conclusions

We concluded, that following PCI, SCLC patients experience significant cognitive decline, even when the radiation dose in the hippocampal area is reduced. This trend continues for at least 3 months following the completion of PCI. In hippocampal-protected patients significant cognitive decline assessed on the MoCA scale is less common than compared to non-hippocampal-protected patients. The older age and low education are risk factors of significant cognitive decline following PCI.

Conflict of interests

Authors declare no conflict of interests.

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Figure 1. Changes in cognitive functions over time in a hippocampal-protected (3D-H) (**A**) and non-hippocampal-protected (3D) (**B**) subgroups on a Montreal Cognitive Assessment MoCA scale

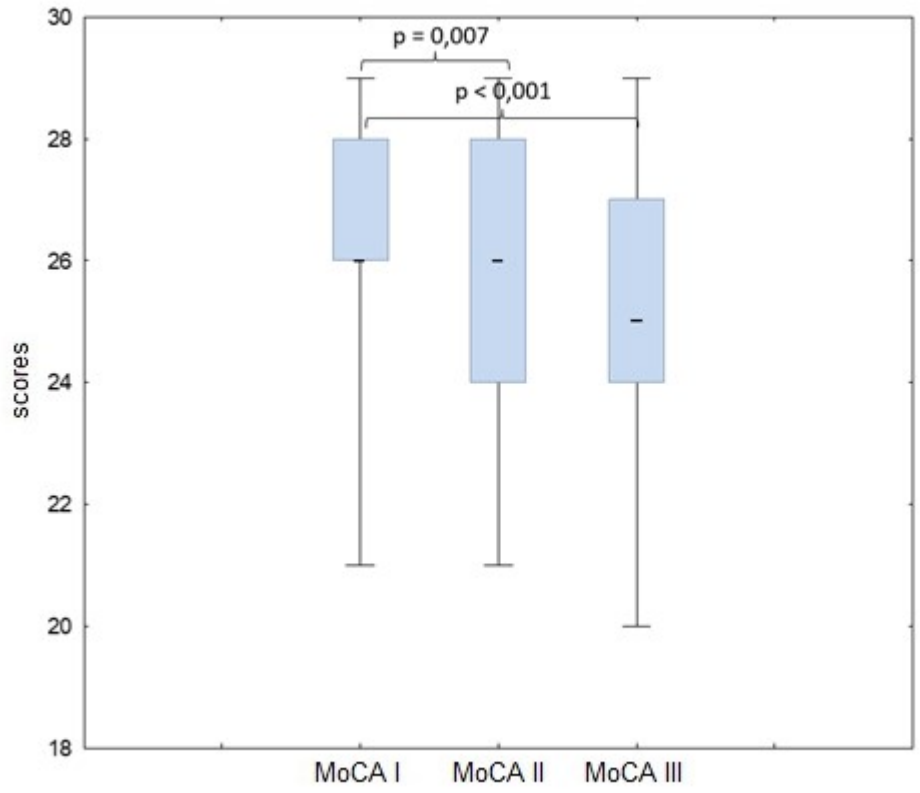

Figure 2. Changes in cognitive functions over time in a hippocampal-protected (3D-H) (**A**) and non-hippocampal-protected (3D) (**B**) subgroups on a Mini-Mental State Examination (MMSE) Short Scale

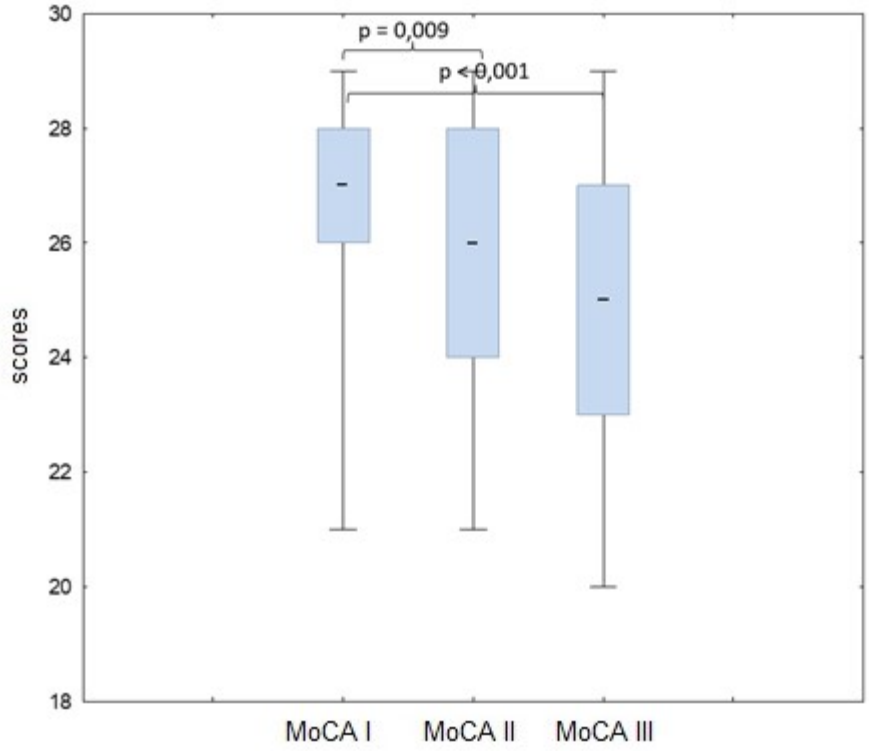

Figure 3. Comparison of the frequency of clinically significant cognitive decline on the Montreal Cognitive Assessment (MoCA) scale between hippocampal-protected (3D-H) and non-hippocampal-protected (3D) groups

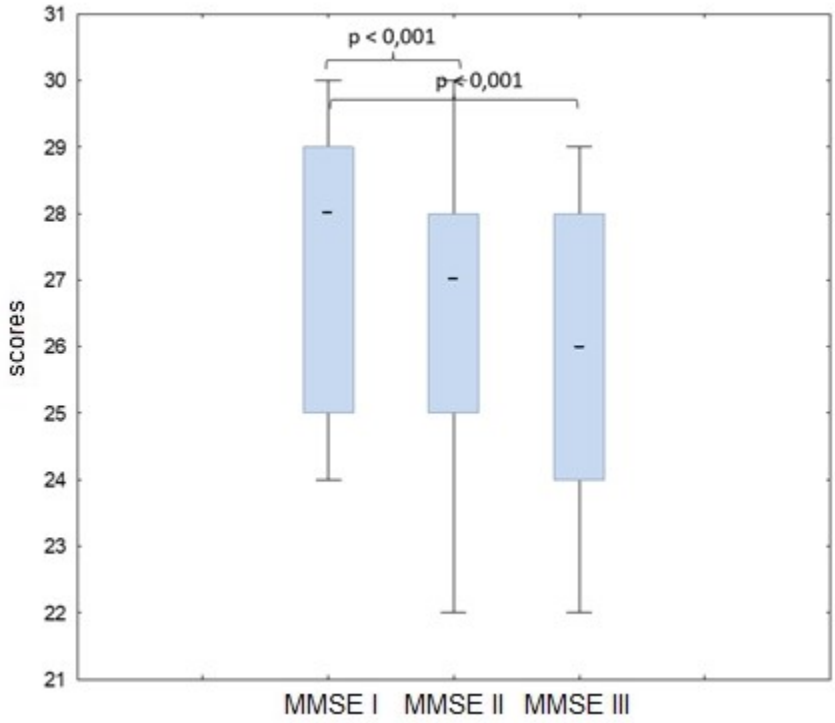

Figure 4. Relationship between age and cognitive decline after PCI on the Montreal Cognitive Assessment (MoCA) scale (A). Influence of age on the occurrence of significant cognitive decline on a scale MoCA (B)

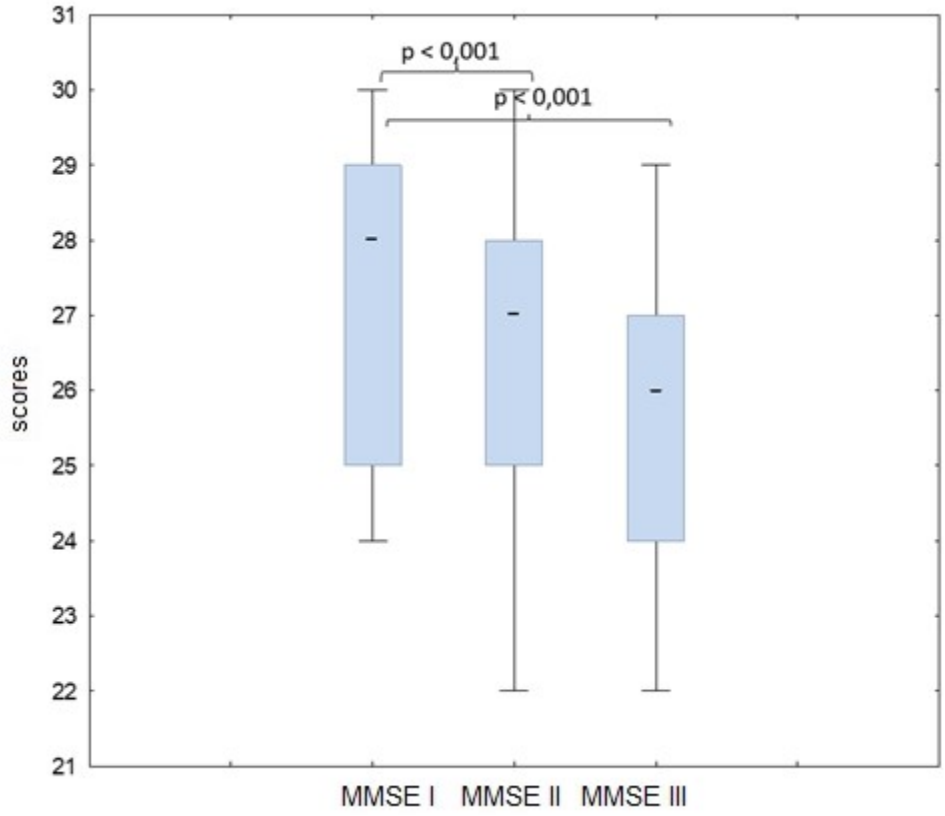

Figure 5. The relationship between education of the patients and the deterioration of cognitive functions

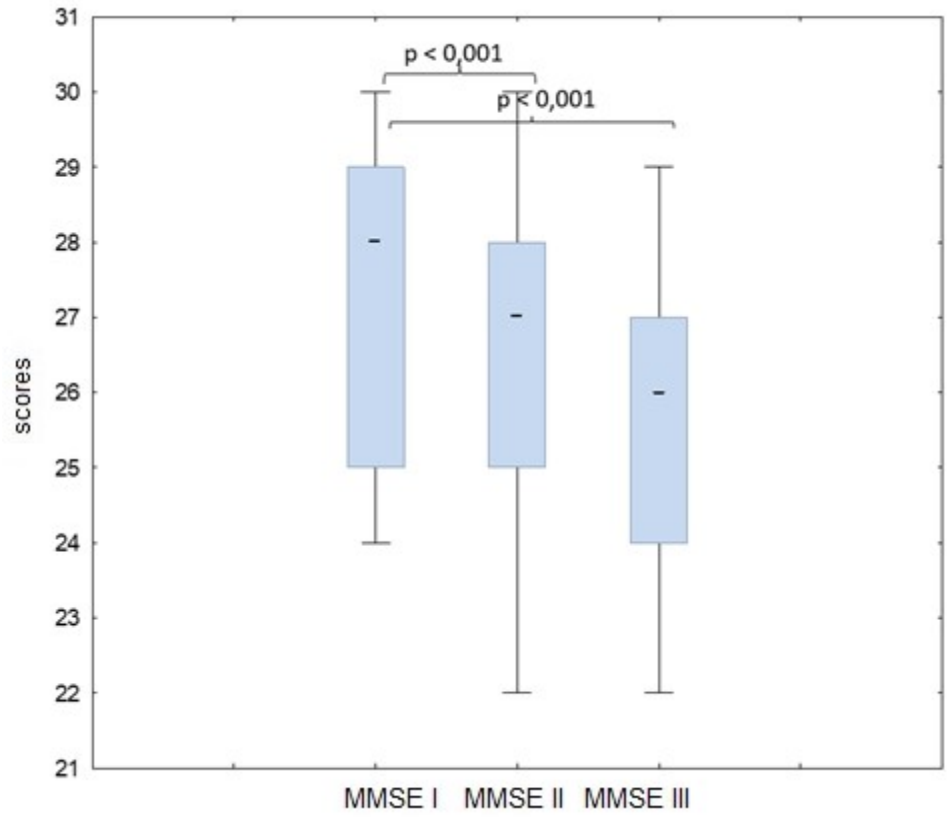

Table 1. Characteristics of the study group

Parameter		**3D-H group N = 74 (%) Median (25%-75%)**	**3D group N = 39 (%) Median (25%-75%)**
Research Center	Lodz	63 (85.14%)	13 (33.33%)
	Radom	11 (14.86%)	26 (66.67%)
Age [years]	–	65.00 (61.00-69.00)	68.00 (62.00–73.00)
Gender	Women	36 (48.65%)	21 (53.85%)
	Men	38 (51.35%)	18 (46.15%)
Education	primary level	15 (20.27%)	8 (20.51%)

	vocational	16 (21.62%)	9 (23.08%)
	secondary	25 (33.78%)	13 (33.33%)
	university	18 (24.33%)	9 (23.08%)

3D-H-group — patients with hippocampal sparing during preventive cranial irradiation (PCI); 3D-group — patients without hippocampal sparing during PCI

Table 2. Scores in Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) scales in studies I, II, and III

Parameter		**3D-H group Median (25–75%)**	**3D group Median (25–75%)**	**p**
MoCA	I	26.0 (26.0–28.0)	27.0 (26.0–28.0)	0.455
	II	26.0 (24.0–28.0)	26.0 (24.0–28.0)	0.927
	III	25.0 (24.0–27.0)	25.0 (23,0–27.0)	0.795
MMSE	I	28.0 (25.0–29.0)	28.0 (25.0–29.0)	0.802
	II	27.0 (25.0–28.0)	27.0 (25.0–28.0)	0.570
	III	26.0 (24.0–28.0)	26.0 (24.0–27.0)	0.417

MMSE — Mini-Mental State Examination, MoCA — Montreal Cognitive Assessment

Table 3. Relationship of clinical variables to clinically significant cognitive decline during preventive cranial irradiation (PCI) in multivariate analysis

Parameter	**Level of reference**	**Odds ratio (95% CI)**	**p**
Hippocampal protection	Not vs Yes	4.98 (1.83–13.53)	0.002
Education	secondary vs primary	0.87 (0.28–2.75)	0.812
	vocational vs	0.84 (0.24–2.99)	0.790

	primary		
	university vs primary	0.06 (0.01–0.31)	< 0.001
Age	–	0.96 (0.89–1.03)	0.265
Sex	Women vs Men	0.46 (0.19–1.13)	0.092

CI — confidence interval