ACTA ONCOLOGICA
2022, VOL. 61, NO. 2, 185–192
https://doi.org/10.1080/0284186X.2021.1974553

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Outcomes of prophylactic cranial irradiation in patients with small cell lung cancer in the modern era of baseline magnetic resonance imaging of the brain

Mads Kjaergaard Held[a,b], Olfred Hansen[a,b,c], Tine Schytte[a,b], Karin Holmskov Hansen[b], Rana Bahij[b], Morten Nielsen[b,d], Tine Bjørn Nielsen[b,d] and Stefan Starup Jeppesen[a,b,c]

[a]Department of Clinical Research, University of Southern Denmark, Odense, Denmark; [b]Department of Oncology, Odense University Hospital, Odense, Denmark; [c]Academy of Geriatric Cancer Research (AgeCare), Odense, Denmark; [d]Laboratory of Radiation Physics, Odense University Hospital, Odense, Denmark

ABSTRACT

Background: For decades many patients with small cell lung cancer (SCLC) have been offered prophylactic cranial irradiation (PCI) to prevent brain metastases (BM). However, the role of PCI is debated in the modern era of increased brain magnetic resonance imaging (MRI) availability. BM in SCLC patients may respond to chemotherapy, and if a negative MRI is used in the decision to use of PCI in the treatment strategy, the timing of brain MRI may be crucial when evaluating the effect of PCI. This retrospective study investigates the impact of PCI outcomes in patients with SCLC staged with brain MRI prior to chemotherapy.

Materials and methods: This study included 245 patients diagnosed SCLC/mixed NSCLC-SCLC treated between 2012 and 2019. The population was analyzed separately for limited disease (LS-SCLC) and extensive disease (ES-SCLC). Patients were divided into groups based on baseline brain MRI prior to chemotherapy and PCI. The primary endpoint was time to symptomatic BM. Secondary endpoints were overall survival (OS), and progression-free survival (PFS).

Results: In patients with LS-SCLC staged with brain MRI the probability of developing symptomatic BM at one year was 4% vs. 22% ($p < 0.05$), median OS was 55 vs. 24 months ($p < 0.05$), and median PFS was 30 vs. 10 months ($p < 0.05$) with and without PCI, respectively. No differences in probability of symptomatic BM and survival outcomes were observed in ES-SCLC. In a multivariate regression analysis, no variables were statistically significant associated with the risk of developing symptomatic BM in patients with LS-SCLC and ES-SCLC. For patients with ES-SCLC staged with brain MRI, PS (HR = 3.33, CI; 1.41–7.89, $p < 0.05$) was associated with poor survival.

Conclusion: This study found that PCI in LS-SCLC patients staged with brain MRI had lower incidence of symptomatic BM and improved survival outcomes suggesting PCI as standard of care. Similar benefit of PCI in patients with ES-SCLC was not found.

ARTICLE HISTORY
Received 18 June 2021
Accepted 25 August 2021

KEYWORDS
Small-cell lung cancer; prophylactic cranial irradiation; brain magnetic resonance imaging; brain metastases; limited-stage small-cell lung cancer; extensive-stage small-cell lung cancer

Introduction

Lung cancer is the second most frequent type of cancer in the Nordic countries with 14.502 new cases each year on average from 2012 to 2016 [1]. Lung cancer is the most frequent cause of cancer specific death in developed countries [2].

Small-cell lung cancer (SCLC) is a very aggressive type of lung cancer with a median overall survival of 3 months for limited stage (LS-SCLC) and 6 weeks for extensive disease (ES-SCLC) [2]. Up to 80% of all patients with SCLC may develop brain metastases (BM) [3] which is associated with poor prognosis and often leads to focal neurological symptoms [4]. However, a study of 84 patients with BM from different types of cancers, showed that 24% had no symptoms [5]. In patients with SCLC 15% of patients with normal neurological findings may have asymptomatic BM [6], and such observations suggest that baseline magnetic resonance imaging (MRI) of the brain should be used in the staging procedures of patients with SCLC [6].

International guidelines recommend prophylactic cranial irradiation (PCI) for patients with LS-SCLC aged <70 years in a good performance status to prevent BM [7–9], and for patients with ES-SCLC response to the initial systemic treatment [8,9]. However, PCI results in ten extra attendances at the hospital and has potentially neurotoxic side effects and thus, shared decision making with the patient is recommended [8–10].

The effect on outcomes of PCI in patients with SCLC is thus still debated. A randomized study by Slotman et al. demonstrated that PCI reduced the probability of developing BM and increased survival outcomes in ES-SCLC with no brain MRI performed prior to treatment or PCI [11]. Another study of patients with ES-SCLC suggested the effect of PCI on preventing development of BM was small with no survival if a brain MRI was performed prior to PCI after chemotherapy [11].

CONTACT Mads Kjaergaard Held mads-held@hotmail.com Odense University Hospital, Kløvervaenget 19, Entrance 99, Odense C, 5000, Denmark

BM in SCLC may respond to chemotherapy [12], and if a negative MRI is used in the decision to use of PCI in the treatment strategy, the timing of brain MRI may be crucial when evaluating the effect of PCI.

The aim of the present study was to compare the incidence of symptomatic BM and the survival after PCI in patients with SCLC staged with brain MRI prior to chemotherapy.

Materials and methods

Study design, participants, and study size

All patients diagnosed with cytologically/histologically proven SCLC or mixed NSCLC-SCLC treated at the Department of Oncology at Odense University Hospital, Denmark from January 2012 to December 2019 were registered prospectively. In total, 493 patients were identified. Excluded from the study were 248 patients not candidates for PCI: BM diagnosed at baseline ($N = 51$), age 71 years or older ($N = 171$), no chemotherapy ($n = 3$), progressive disease within 2 months of diagnosis ($n = 20$). The final study population was 245 patients. All analyses will be performed separately for patients with LS-SCLC or ES-SCLC in groups depending on whether baseline brain MRI was performed (PCI + MRI, No-PCI + MRI) or not (PCI-MRI, No-PCI-MRI).

Diagnostic setup

All patients had a PET-CT scan performed unless if it would delay the start of antineoplastic treatment. The use of baseline brain MRI as a staging procedure changed during the study period. From 2012 to 2015 MRI was used up front for patients with neurological symptoms. From 2016 to 2018 baseline brain MRI was recommended for patients with LS-SCLC prior to antineoplastic treatment as part of the staging procedures. From 2019 the use of baseline MRI also included patients with ES-SCLC. In this study, baseline brain MRI was defined as MRI performed from 4 weeks prior to the SCLC diagnosis to 1 week after commencement of the first cycle of chemotherapy. Brain MRI was not repeated after chemotherapy prior to tentative PCI.

Treatment

The standard treatment for patients with LS-SCLC with performance score 0-2 was four cycles of cisplatin/carboplatin and intravenous etoposide concomitant to either hyperfractionated accelerated radiotherapy 45 Gy/30 fractions treated twice daily, 45 Gy/25 F treated once daily, or 60 Gy/40 F for some patients with LS-SCLC included in the THORA protocol [13]. For patients in poor performance status, a modified treatment schedule of chemotherapy and irradiation was offered. For patients with ES-SCLC the standard treatment consisted of up to six cycles of carboplatin and peroral etoposide or monotherapy with peroral etoposide.

At our institution, PCI 25 Gy in 10 fractions (F) was offered to patients with SCLC aged <71 not progressed on chemotherapy except for patients considered unfit due to poor performance status, comorbid conditions, or presence of severe white matter lesions at baseline MRI. Standard use of MRI in the diagnostic setup, was gradually introduces for patients with SCLC before initiating since 2012. PCI was applied in between two cycles of chemotherapy or after completing the full course of chemotherapy.

Follow-up

All patients had a planned follow-up with a CT scan of the thorax and upper abdomen after 5 weeks, and thereafter every third month for 2 years, and then every sixth month for 3 years. Brain MRI was only performed if neurological symptoms appeared and was not performed as a standard procedure in the follow-up period.

Outcomes

The primary endpoint of the study was time from the time of cytologically/histologically confirmed diagnosis of SCLC to symptomatic BM confirmed radiologically. Secondary endpoints were overall survival (OS) and progression-free survival (PFS). OS was defined as the time of diagnosis of SCLC until death of any cause. PFS was defined as the time of diagnosis of SCLC to radiologically or histologically proven progression of SCLC or death of any cause. In few cases, progression was only determined clinically when the condition of patients did not allow further examinations or treatment.

Statistical methods

All groups were tested for differences using *T*-test/Mann-Whitney test on numerical data. The categorical data were tested using Chi-square test. Kaplan-Meier methods were used for survival analyses and Log-rank test was used for testing the survival outcomes for significant differences. The database was last updated for vital status on the 10th of August 2021. Multivariate analysis was performed using forward generated cox regression to describe the effect of confounders. If univariate analysis indicated possible association to the outcome ($p < 0.25$) it was included in the multivariate analysis. Interactions between variables and interaction with time were tested. A two-tailed p-value of less than 0.05 was considered significant for all analyses.

Ethics

The study was registered on the Region of Southern Denmark's record of data processing activities (J.no. 20/6923). All personal data were handled in accordance with EU GDPR, The Danish Data Protection Act, and The Danish Health Act. The principles of the Helsinki Declaration were followed. Permission to access the patient files for analysis was granted by the Danish Patient Safety Authority with reference no SMMO and identifier no. 13-1521-99.

Results

Of the 245 patients included in this study, 111 had LS-SCLC. Of these, 49 patients were staged with baseline brain MRI, and 63 patients received PCI. Of the remaining 134 patients with ES-SCLC, 29 patients were staged with brain MRI, and 54 patients received PCI. The median follow-up time for the total study population was 23 months (range 2–112). For both LS-SCLC and ES-SCLC groups of patients staged with brain MRI, the PCI groups were in a better performance status and younger than the patients in the groups with no PCI. For further baseline characteristics of groups with baseline brain MRI see Table 1, and without baseline brain MRI see appendix 1. In the study population, the fraction of patients who had a staging brain MRI performed increased from 13% in 2012–2015, to 38% in 2016–2018, and 86% in 2019.

Limited stage small cell lung cancer

There was a statistically significant difference in the probability of developing symptomatic BM at one year of 4% vs. 22% ($p < 0.05$) in the PCI + MRI and No-PCI + MRI groups (Figure 1(a)). For the group of patients not staged with MRI the probability of developing BM was 14% and 20% ($p = 1.00$) with and without PCI, respectively.

In a multivariate cox regression analysis for patients with LS-SCLC staged with brain MRI, no variables were statistically significantly associated with the risk of developing symptomatic BM (Table 2).

As illustrated in Figure 2(a), there was a statistically significant difference in median OS (mOS) for patients with LS-SCLC staged with brain MRI of 55 months vs. 24 months ($p < 0.05$) with and without PCI. For comparison, in the groups of patients not staged with brain MRI the mOS was 27 months and 20 months ($p = 0.16$) with and without PCI, respectively. When staged with brain MRI the median PFS (mPFS) was 30 months vs. 10 months ($p < 0.05$) in patients with and without PCI (appendix 2).

A multivariate cox regression analysis of OS in patients with LS-SCLC staged with brain MRI found no variables statistically significantly associated with survival (appendix 3).

Extensive stage small cell lung cancer

The probability of developing symptomatic BM at one year was 12% and 21% ($p = 0.77$) in patients staged with baseline brain MRI with and without PCI, respectively (Figure 1(b)). For comparison, patients not staged with brain MRI the probability of developing symptomatic BM at 1 year was 29% vs. 44% ($p = 0.14$) with and without PCI, respectively. A multivariate cox regression analysis of patients with ES-SCLC staged with brain MRI, found no variables associated with probability of developing symptomatic BM (Table 2).

When staged with brain MRI the mOS was 13 months vs. 11 months ($p = 0.62$) in patients with and without PCI (Figure 2(b)). For comparison, patients without baseline brain MRI had a mOS of 12 months vs. 9 months ($p = 0.11$) with and without PCI. No statistically significant difference was found comparing mPFS in patients staged with baseline brain MRI with and without PCI with a mPFS of 9 months and 8 months ($p = 0.82$) (Appendix 2). In a multivariate cox regression analysis of OS in patients with ES-SCLC staged with brain MRI performance status ≥ 2 (HR = 3.33, CI; 1.41–7.89, $p < 0.05$) was associated with decreased survival (Appendix 3).

Discussion

In this single-institutional study with 78 consecutive MRI staged patients with SCLC included in a cohort of 245 patients diagnosed between 2012 and 2019, we investigated the PCI outcomes prior to and in the modern era of brain MRI as a staging procedure.

Limited stage small cell lung cancer

This study found a statistically significant lower probability of developing symptomatic BM and increased survival outcomes in patients with LS-SCLC treated with PCI compared to patients without PCI, when staged with brain MRI. The same was not found in patients staged without brain MRI.

The efficacy of PCI for patients with LS-SCLC with brain MRI performed after initial systemic treatment have been investigated in four cohort studies [14–17]. Three of these studies did not demonstrate a statistically significant benefit of PCI concerning development of BM or survival. However, one study found a statistically significant reduction in probability of BM at 1 year from 32% to 4% [17]. For comparison the current study found a similar reduction of PCI from 22% to 4% in patients staged with brain MRI. In contrast to all four studies the present study found a statistically significant difference in mOS of 31 months and in mPFS of 20 months between patients with baseline brain MRI with and without PCI. The differences compared to the previous studies may be due to the timing of brain MRI as a staging procedure in our study excluding patients with asymptomatic BM prior to chemotherapy. However, one of the cohort studies did perform baseline brain MRI prior to chemotherapy in addition to the restaging brain MRI after chemotherapy and found a non-significant decrease in probability of BM and no survival benefit [16].

Studies have found that PCI may not be favorable in patients with LS-SCLC stage I. In the current study patients of all stages were included. Patients with stage I SCLC in the current study are likely to have received PCI due to good overall condition, this could improve outcomes in the PCI group [18,19]. A reason for poorer survival and BM outcomes in the group of patients staged with brain MRI without treatment of PCI may be due to clinical selection of patients for PCI. The clinician was most likely not to offer PCI to a patient in poor performance status, with comorbid conditions, or with severe white matter lesions at baseline MRI.

Extensive stage small cell lung cancer disease

For both groups of patients with ES-SCLC staged with and without brain MRI in the current study, there was no

Table 1. Baseline characteristics of the study population staged with brain MRI.

	LS-SCLC ($N = 49$) PCI + MRI ($N = 28$)	No-PCI + MRI ($N = 21$)	*p*-Value	ES-SCLC ($N = 29$) PCI + MRI ($N = 11$)	No-PCI + MRI ($N = 18$)	*p*-Value
Age (years)			$p < 0.05$			$p < 0.05$
Median	62.2	65.5		60.2	65.1	
Range	46.9–70.7	57.1–71.0		47.2–70.0	52.4–70.9	
Sex			N/S			N/S
Female	16 (57%)	10 (48%)		6 (55%)	8 (44%)	
Male	12 (43%)	11 (52%)		5 (45%)	10 (56%)	
WHO performance score			$p < 0.05$			N/S
0–1	25 (89%)	9 (43%)		9 (82%)	9 (50%)	
2	3 (11%)	7 (33%)		2 (18%)	6 (33%)	
3–4	0 (0%)	5 (24%)		0 (0%)	3 (17%)	
PET-CT baseline	28 (100%)	20 (95%)	N/S	11 (100%)	16 (89%)	N/S
Use of tobacco at inclusion			N/S			N/S
Currently smoker or stopped within 10 years	23 (82%)	19 (90%)		11 (100%)	16 (89%)	
Stopped smoking > 10 years ago or never smoked	5 (28%)	2 (10%)		0 (0%)	2 (11%)	
Initial systemic regime			N/S			N/S
Carboplatin/Cisplatin & Etoposide	28 (100%)	21 (100%)		10 (91%)	18 (100%)	
Mono Etoposide	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Other regimensMono Topotecan	0 (0%)	0 (0%)		1 (9%)	0 (0%)	
Thoracic radiation			$p < 0.05$			N/S
45 GY/30 F*	24 (86%)	10 (48%)		2 (20%)	1 (6%)	
60 GY/40 F*	3 (11%)	2 (10%)		0 (0%)	0 (0%)	
45 GY/25 F	0 (0%)	2 (10%)		0 (0%)	1 (6%)	
Other regimens	1 (4%)	5 (25%)		4 (36%)	5 (28%)	
No radiation	0 (0%)	2 (10%)		5 (45%)	11 (61%)	
Time from diagnose to PCI (days)						
Median	91			121		
Range	62–118			77–187		
Follow-up time (months)			N/S			N/S
Median	33	26		15	15	
Range	9–64	3–73		9–27	3–42	
Histologi			N/S			$p = 0.06$
SCLC	28 (100%)	21 (100%)		9 (82%)	18 (100%)	
Mixed NSCLC-SCLC	0 (0%)	0 (0%)		2 (18%)	0 (0%)	

*10 fractions weekly.

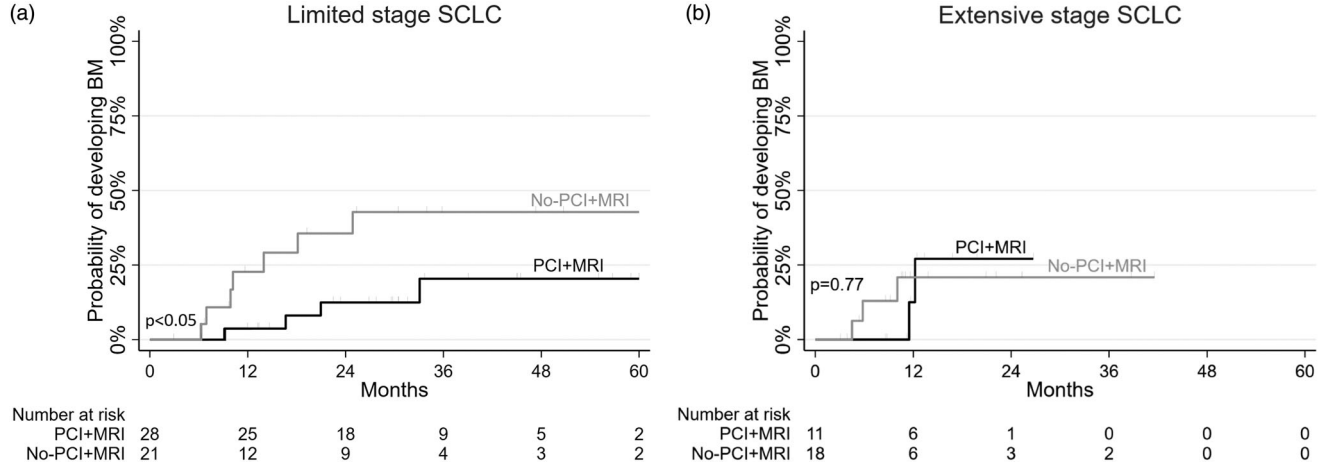


Figure 1. (a,b) Kaplan-Meier plot of probability of developing symptomatic brain metastases when treated with and without PCI, in patients staged with brain MRI with limited (1a) and extensive stage small cell lung cancer (1 b).

difference in outcomes of the probability of developing BM or survival in patients treated with and without PCI.

In a study by Takahashi et al. patients with ES-SCLC were randomized to PCI or no PCI [11]. It demonstrated that PCI reduced the probability of developing BM from 59% to 33% at one year. This is higher for both groups compared to our study. The patients in the study by Takahashi et al. had brain MRI performed after chemotherapy and prior to PCI and in the follow-up period at 3-month intervals for 12 months, at 18 months and 24 months. It has been demonstrated in previous studies, that BM may be asymptomatic in up to 24% of patients with SCLC [5,6]. The higher rate of BM diagnosed may partly be explained by the frequent screening with brain MRI in the follow-up period since patients in our study only had brain MRI performed if neurological symptoms occurred.

Another explanation of the lower risk of developing BM in the current study may be found in the selection of patients.

Table 2. Uni- and multivariate cox regression of probability of developing symptomatic brain metastases over time for patients staged with brain MRI with limited and extensive stage disease small cell lung cancer.

	Limited stage SCLC						Extensive stage SCLC					
	Univariate model			Multivariate model			Univariate model			Multivariate model		
	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI
PCI	0.31	0.06	0.09–1.06	0.60	0.18	0.29–1.25	0.76	0.77	0.13–4.59	—	—	—
Performance status 2+	1.02	0.98	0.27–3.84	—	—	—	1.79	0.53	0.30–10.84	—	—	—
Age (per year)	0.98	0.47	0.92–1.04	—	—	—	0.94	0.34	0.84–1.06	—	—	—
Male	1.26	0.52	0.62–2.56	—	—	—	0.57	0.54	0.10–3.46	—	—	—
Ex-smoker /never smoker	0.57	0.25	0.22–1.49	0.49	0.16	0.18–1.33	0.22	0.19	0.02–2.10	—	—	—

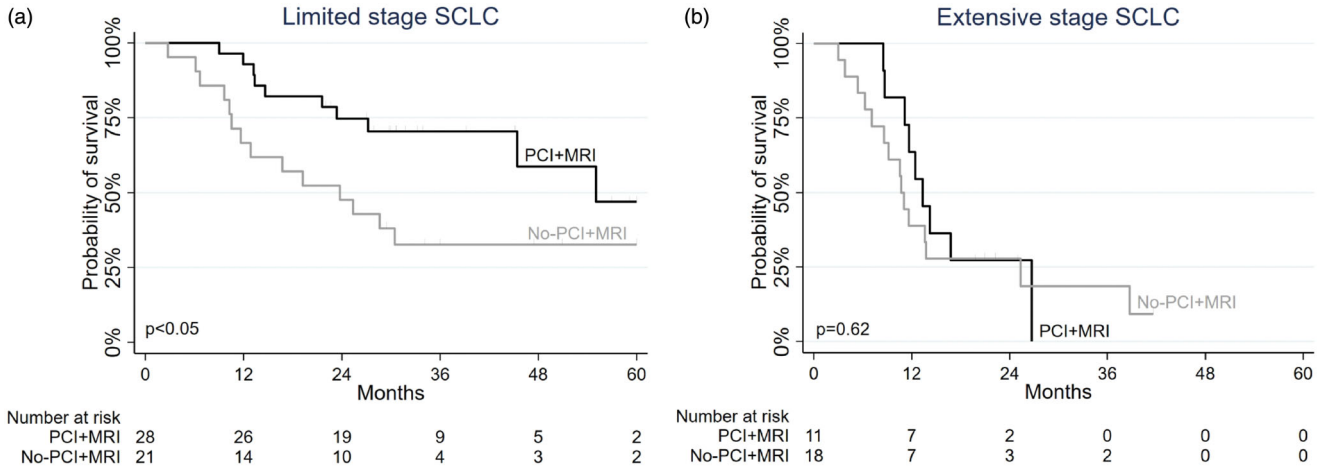


Figure 2. (a,b) Kaplan-Meier plot of probability of overall survival when treated with and without PCI, in patients staged with brain MRI with limited stage (2a) and extensive stage small cell lung cancer (2 b).

The patients in our study had a brain MRI performed prior to chemotherapy, thus, all patients with BM at baseline were excluded. Some patients in the Takahashi study where brain MRI was performed prior to PCI may have had asymptomatic BM at diagnosis but had complete response in the brain due to antineoplastic treatment. This may have affected the outcomes in Takahashi et al.'s study especially in the group without PCI. However, caution should be used when interpreting the outcomes of the current study due to the size of subgroups and the retrospective study design. It would have been ideal if patients in our study also had a restaging brain MRI performed prior to PCI for comparison with the Takahashi study.

Overall discussion of study results

There are some limitations of this study. One is selection bias e.g., the presence of WML is a poor prognostic factor concerning functionality and may also influence survival [20]. At our department patients with extensive WML were not offered PCI. This may have decreased survival outcomes in the No-PCI + MRI group and could explain the difference in survival rates between PCI + MRI and No-PCI + MRI. However, this still cannot explain the difference in risk of developing BM.

Another source of potential bias in the current study is the retrospective data collection from patient charts. Multivariate analysis was made to overcome confounders, unavoidably some unmeasured confounders will still occur. To remove the most important confounders from the study, patients who did not meet the criteria for being able to receive PCI were excluded. Thus, patients were excluded if they were older than 71, had progressive disease or died within 2 months, had BM at baseline, or did not receive chemotherapy [8]. Some patients experienced an improvement in performance status after first cycles of chemotherapy. Thus, patients were not excluded due to poor baseline performance status, contrary to the Slotman study and Takahashi study.

Takahashi et al. did not exclude by age, and Slotman et al. excluded patients aged >74, but this difference is not expected to impact the results, which the multivariate analysis confirms.

Restrictions with a chronological age cutoff to offer PCI is controversial. However, shared decision-making regarding PCI for patients with increasing age in good performance status and without comorbidity should be considered. However, chronic neurotoxicity for this group of patients is still a big concern at our department even though hippocampus avoidant treatment is performed.

Two randomized studies are investigating brain MRI surveillance alone in comparison with PCI with brain MRI surveillance [21,22]. The latter study is already including patients. But until results from these randomized studies are available, we believe that this study report valuable information on the outcome of PCI in the modern era of MRI, and PCI should still play an important role in patients with LS-SCLC with baseline brain MRI. According to the findings of

this study and to literature on the subject, PCI should be used with caution and shared decision-making in accordance with the relevant risk-benefit ratio.

Conclusion

This study found that PCI improved survival outcomes and decreased risk of symptomatic BM after PCI in patients with LS-SCLC staged with brain MRI, suggesting that PCI should be considered as standard of care. For patients with ES-SCLC no difference in development of BM and in survival outcomes were found.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Olfred Hansen http://orcid.org/0000-0003-0396-1424
Stefan Starup Jeppesen http://orcid.org/0000-0003-2738-0069

References

[1] Danckert BF, Engholm G, Hansen HL, et al. NORDCAN: cancer incidence, mortality, prevalence and survival in the Nordic countries, Version 8.2. 2019.
[2] Spiro SG, Porter JC. Lung cancer-where are we today? Current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med. 2002;166(9):1166–1196.
[3] van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378(9804):1741–1755.
[4] Clouston PD, DeAngelis LM, Posner JB. The spectrum of neurological disease in patients with systemic cancer. Ann Neurol. 1992;31(3):268–273.
[5] Nieder C, Haukland E, Mannsåker B, et al. Presence of brain metastases at initial diagnosis of cancer: patient characteristics and outcome. Cureus. 2019;11(2):e4113.
[6] Hochstenbag MM, Twijnstra A, Wilmink JT, et al. Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. J Neurooncol. 2000;48(3):243–248.
[7] Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7):476–484.
[8] ASTRO. [cited 2020 Dec 9]. Available from: https://www.practicalradonc.org/article/S1879-8500(20)30053-9/fulltext.
[9] ESTRO. [cited 2020 Dec 30]. Available from: https://www.estro.org/Science/Guidelines.
[10] Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol. 2009;27(1):78–84.
[11] Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(5):663–671.
[12] Lee JS, Murphy WK, Glisson BS, et al. Primary chemotherapy of brain metastasis in small-cell lung cancer. J Clin Oncol. 1989;7(7):916–922.
[13] Grønberg BH, Killingberg KT, Fløtten Ø, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol. 2021;22(3):321–331.
[14] Ozawa Y, Omae M, Fujii M, et al. Management of brain metastasis with magnetic resonance imaging and stereotactic irradiation attenuated benefits of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. BMC Cancer. 2015;15:589.
[15] Mamesaya N, Wakuda K, Omae K, et al. Efficacy of prophylactic cranial irradiation in patients with limited-disease small-cell lung cancer who were confirmed to have no brain metastasis via magnetic resonance imaging after initial chemoradiotherapy. Oncotarget. 2018;9(25):17664–17674.
[16] Pezzi TA, Fang P, Gjyshi O, et al. Rates of overall survival and intracranial control in the magnetic resonance imaging era for patients with limited-stage small cell lung cancer with and without prophylactic cranial irradiation. JAMA Netw Open. 2020;3(4):e201929.
[17] Ghanta S, Keller A, Rodriguez-Lopez JL, et al. Utility of prophylactic cranial irradiation for limited stage small cell lung cancer in the modern era with magnetic resonance imaging surveillance. Clin Oncol (R Coll Radiol). 2021;33(8):e323–e30.
[18] Xu J, Yang H, Fu X, et al. Prophylactic cranial irradiation for patients with surgically resected small cell lung cancer. J Thorac Oncol. 2017;12(2):347–353.
[19] Zhu H, Guo H, Shi F, et al. Prophylactic cranial irradiation improved the overall survival of patients with surgically resected small cell lung cancer, but not for stage I disease. Lung Cancer. 2014;86(3):334–338.
[20] Moon HI, Nam JS, Leem MJ, et al. Periventricular white matter lesions as a prognostic factor of swallowing function in older patients with mild stroke. Dysphagia. 2017;32(4):480–486.
[21] ClinicalTrials.gov [Internet]. EORTC: National Library of Medicine (US). -. Identifier NCT04790253, PRophylactic Cerebral Irradiation or Active MAgnetic Resonance Imaging Surveillance in Small-cell Lung Cancer Patients (PRIMALung Study) (PRIMALung); 2021. March 10 [cited 2021 Aug 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT04790253?term=PCI%2C+EORTC&cond=SCLC&draw=2&rank=1.
[22] ClinicalTrials.gov [Internet]. C. Rusthoven: National Library of Medicine (US). -. Identifier NCT04155034, SWOG S1827 (MAVERICK) Testing Whether the Use of Brain Scans Alone Instead of Brain Scans Plus Preventive Brain Radiation Affects Lifespan in Patients With Small Cell Lung Cancer; 2019 November 7th [cited 2021 Aug 13]. Available from: https://clinicaltrials.gov/ct2/show/NCT04155034?term=PCI+SWOG&cond=SCLC&draw=2&rank=1.

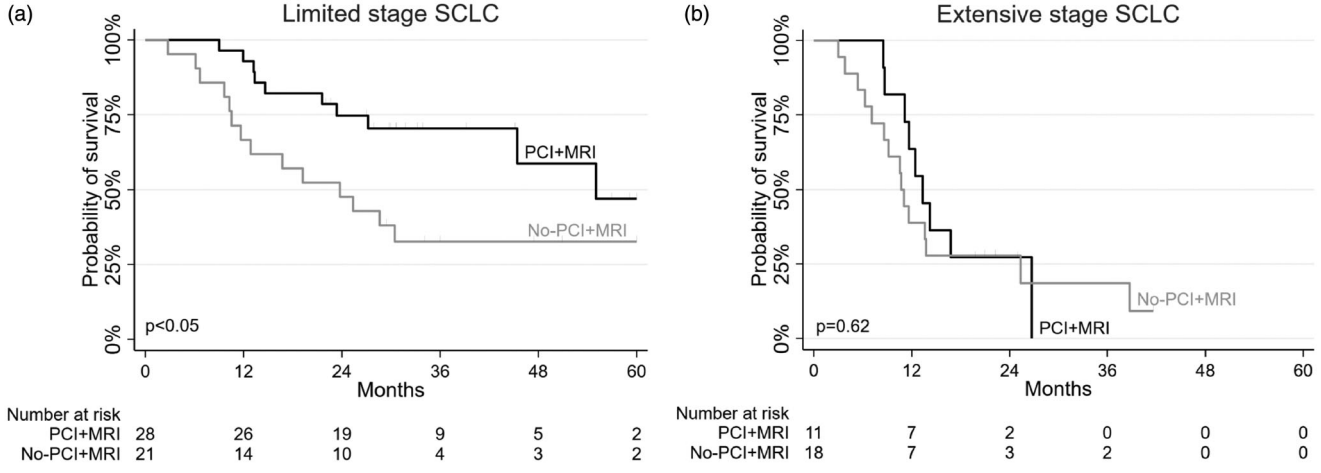
Appendix 1

	LS-SCLC (*N* = 62) PCI-MRI (*N* = 35)	No-PCI-MRI (*N* = 27)	*p*-Value	ES-SCLC (*N* = 105) PCI-MRI (*N* = 43)	No-PCI-MRI (*N* = 62)	*p*-Value
Age (years)			N/S			N/S
Median	62.8	64.5		62.4	63.5	
Range	47.5–70.6	56.3–70.9		47.7–70.8	43.3–70.7	
Sex			N/S			N/S
Female	19 (54%)	16 (59%)		27 (63%)	35 (56%)	
Male	16 (46%)	11 (41%)		16 (37%)	27 (63%)	
WHO performance score			$p < 0.05$			<0.05
0–1	33 (94%)	18 (67%)		34 (79%)	28 (45%)	
2	1 (3%)	3 (11%)		6 (14%)	22 (35%)	
3–4	1 (3%)	6 (22%)		3 (7%)	12 (19%)	
PET-CT baseline	35 (100%)	26 (96%)	N/S	41 (95%)	56 (90%)	N/S
Use of tobacco at inclusion			N/S			N/S
Currently smoker or stopped within 10 years	32 (91%)	27 (100%)		41 (95%)	55 (89%)	
Stopped smoking > 10 years ago or never smoked	3 (9%)	0 (0%)		2 (5%)	7 (11%)	
Initial systemic regime			N/S			N/S
Carboplatin/Cisplatin & Etoposide	34 (100%)	24 (89%)		39 (93%)	54 (89%)	
Mono Etoposide	0 (0%)	1 (4%)		0 (0%)	4 (7%)	
Other regimens	0 (0%)	2 (7%)		3 (7%)	3 (5%)	
Thoracic radiation			$p = 0.08$			N/S
45 GY/30 F*	21 (60%)	10 (37%)		2 (5%)	1 (2%)	
60 GY/40 F*	2 (6%)	0 (0%)		0 (0%)	0 (0%)	
45 GY/25 F	6 (17%)	5 (19%)		0 (0%)	1 (2%)	
Other regimens	5 (14%)	8 (29%)		16 (37%)	27 (43%)	
No radiation	1 (3%)	2 (7%)		25 (58%)	33 (52%)	
Time from diagnose to PCI (days)						
Median	98			130		
Range	35–194			75–174		
Follow-up time (months)			N/S			N/S
Median	37	27		20	15	
Range	11–104	4–108		4–105	2–112	
Histologi			N/S			N/S
SCLC	35 (100%)	26 (96%)		43 (100%)	61 (98%)	
Mixed NSCLC-SCLC	0 (0%)	1 (4%)		0 (0%)	1 (2%)	

*10 fractions weekly.
Baseline characteristics of the study population staged without brain MRI.

Appendix 2

Kaplan-Meier plot of probability of progression-free survival when treated with and without PCI, in patients staged with brain MRI with limited and extensive stage small cell lung cancer.



Appendix 3

	Limited stage SCLC						Extensive stage SCLC					
	Univariate model			Multivariate model			Univariate model			Multivariate model		
	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI	HR	*p*-Value	95% CI
PCI	0.40	<0.05	0.18–0.91	0.51	0.15	0.21–1.28	0.81	0.62	0.35–1.88	—	—	—
Performance status 2+	2.39	<0.05	1.06–5.35	1.74	0.23	0.70–4.33	3.16	<0.05	1.35–7.41	3.33	<0.05	1.41–7.89
Age (per year)	1.02	0.76	0.94–1.09	—	—	—	1.02	0.54	0.96–1.08	—	—	—
Male	1.13	0.77	0.51–2.51	—	—	—	0.71	0.40	0.31–1.58	—	—	—
Ex-smoker/never smoker	0.85	0.77	0.29–2.50	—	—	—	0.36	0.18	0.79–1.60	0.29	0.11	0.06–1.35

Uni- and multivariate cox regression of overall survival over time for patients staged with brain MRI with limited and extensive stage small cell lung cancer.