Radiotherapy and Oncology 143 (2020) 81–87

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Risk stratification of symptomatic brain metastases by clinical and FDG PET parameters for selective use of prophylactic cranial irradiation in patients with extensive disease of small cell lung cancer

Joo-Hyun Chung [a,1], Seo Young Kang [b,h,1], Hong-Gyun Wu [a,d], Young Seok Seo [a], Dong-Wan Kim [c,f], Keon Wook Kang [b,e,g], Hak Jae Kim [a,d,g,*], Gi Jeong Cheon [b,e,g,*]

[a] Department of Radiation Oncology; [b] Department of Nuclear Medicine; [c] Department of Internal Medicine; [d] Department of Radiation Oncology; [e] Department of Nuclear Medicine; [f] Department of Internal Medicine, Seoul National University College of Medicine; [g] Cancer Research Institute, Seoul National University; and [h] Department of Molecular Medicine and Biopharmaceutical Science, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea

ARTICLE INFO

Article history:
Received 16 August 2019
Received in revised form 6 December 2019
Accepted 8 January 2020
Available online 7 February 2020

Keywords:
[18F]FDG PET
ED-SCLC
Symptomatic brain metastases
Prophylactic cranial irradiation

ABSTRACT

Purpose: To identify risk factors for developing symptomatic brain metastases and evaluate the impact of prophylactic cranial irradiation (PCI) on brain metastasis-free survival (BMFS) and overall survival (OS) in extensive disease small cell lung cancer (ED-SCLC).

Materials and methods: Among 190 patients diagnosed with ED-SCLC who underwent FDG PET/CT and brain Magnetic Resonance Imaging (MRI) prior to treatment, 53 (27.9%) received PCI while 137 (72.1%) did not. Prognostic index predicting a high risk of symptomatic brain metastases was calculated for the group without receiving PCI (observation group, n = 137) with Cox regression model.

Results: Median follow-up time was 10.6 months. Multivariate Cox regression showed that the following three factors were associated with a high risk of symptomatic brain metastases: the presence of extrathoracic metastases (p = 0.004), hypermetabolism of bone marrow or spleen on FDG PET (p < 0.001), and high neutrophil-to-lymphocyte ratio (p = 0.018). PCI significantly improved BMFS in high-risk patients (1-year rate: 94.7% vs. 62.1%, p = 0.001), but not in low-risk patients (1-year rate: 100.0% vs. 87.7%, p = 0.943). However, PCI did not improve OS in patients at high risk for symptomatic brain metastases (1-year rate: 65.2% vs. 50.0%, p = 0.123).

Conclusion: Three prognostic factors (the presence of extrathoracic metastases, hypermetabolism of bone marrow or spleen on FDG PET, and high neutrophil-to-lymphocyte ratio) were associated with a high risk of symptomatic brain metastases in ED-SCLC. PCI was beneficial for patients at a high risk of symptomatic brain metastases in terms of BMFS, but not OS. Thus, selective use of PCI in ED-SCLC according to the risk stratification is recommended.

Prophylactic cranial irradiation (PCI) has become the standard treatment for small cell lung cancer patients with complete remission after chemotherapy and radiotherapy since the publication of an individual-patient-data-based meta-analysis [1]. However, PCI for patients with extensive disease small cell lung cancer (ED-SCLC) is controversial in terms of survival benefit. In 2007, the European Organization for Research and Treatment of Cancer published results of a phase 3 study in which 286 patients with ED-SCLC were randomly assigned to receive PCI or observation [2]. Investigators of that study concluded that PCI could reduce the incidence of symptomatic brain metastases and increase the overall survival compared to observation. However, in 2017, Japanese groups published another phase 3 study and reported that PCI did not result in longer overall survival of ED-SCLC patients compared to observation [3]. They reported that PCI might be helpful for some patients. Thus, it is crucial to identify those patients and provide tailored therapy.

A few studies have suggested that [18F]fluoro-2-deoxy-d-glucose (FDG) positron emission tomography/computed tomography (PET/CT) might be useful in the initial-staging, treatment planning, and follow-up of patients with ED-SCLC as well as limited-disease (LD) [4–6]. Schumacher et al. [7] have reported that 27% of primary staging in SCLC patients are upstaged from

* Corresponding authors at: Department of Radiation Oncology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea (H.J. Kim). Department of Nuclear Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, South Korea (G.J. Cheon).

E-mail addresses: khjae@snu.ac.kr (H.J. Kim), larrycheon@snu.ac.kr (G.J. Cheon).

[1] Joo-Hyun Chung and Seo Young Kang contributed equally to this article.

https://doi.org/10.1016/j.radonc.2020.01.009
0167-8140/

LD by conventional imaging to ED by FDG PET. Several other studies have also suggested that FDG PET is significantly better than conventional imaging in the detection of extrathoracic lymph node and stage migration, thus correctly upstaging patients to ED or downstaging them to LD [8,9].

Recently, several articles have reported that bone marrow (BM) or spleen uptake of pretreatment FDG PET/CT is an independent prognostic factor for predicting recurrence [10,11]. Bang et al. have suggested that FDG uptakes by the spleen, BM, liver, and primary tumor are all significant prognostic factors for recurrence in univariate analysis. In addition, splenic FDG uptake was an independent, powerful poor prognostic factor for predicting disease-free survival. Based on previous studies, we expect that we may find metabolic parameters from spleen or BM as well as primary tumor on FDG PET/CT for predicting symptomatic brain metastases and use them to select patients who can benefit from PCI.

In this study, we aimed to find clinical and metabolic parameters on FDG PET/CT for predicting the development of symptomatic brain metastases in ED-SCLC patients without brain metastases on initial brain Magnetic Resonance Imaging (MRI) in order to select high-risk patients with symptomatic brain metastases who might obtain benefit from PCI.

Materials and methods

Patient characteristics

Patients diagnosed as ED-SCLC from June 2006 to December 2017 were enrolled in this retrospective study. Initial staging evaluation for selecting ED-SCLC patients was performed based on pretreatment FDG PET/CT and brain MRI. Patients without brain MRI nor FDG PET/CT workup were excluded from this study to reflect the current practice as realistically as possible. All patients were confirmed to be free of brain metastases. They received at least two cycles of platinum-based doublet chemotherapy. The median interval between FDG PET/CT and the start of chemotherapy was 5 days (range, 0–36 days). Imaging for evaluating response to the initial chemotherapy was performed around one month before and after the end of the initial chemotherapy cycle. Brain metastasis-free survival (BMFS) analysis was performed for the total set of patients (n = 190) (Fig. 1). Risk prediction model analysis was performed using a subset of observed patients (n = 137) to assess the predictability of brain metastasis in the absence of brain irradiation. Finally, overall survival (OS) analysis was performed after 1:1 propensity score matching (n = 96) to correct patient selection bias.

Treatment and follow-ups

Patients received a combination of cisplatin/etoposide, carboplatin/etoposide, or cisplatin/irinotecan. Radiotherapy was administered for PCI as well as consolidative thoracic radiation. While thoracic radiation was administered using either three-dimensional conformal radiotherapy or intensity-modulated radiotherapy, opposed lateral fields of two-field technique were used for PCI with dose/fractionation scheme of either 25 Gy/10 fx or 20 Gy/5 fx. Assessment of response to the initial chemotherapy was performed via chest/abdomen CT at 1 month before and after the end of the initial chemotherapy. Routine follow-ups were performed every three months. Brain imaging was reserved for patients with symptoms including headaches, nausea, neurologic symptoms, and so on suggestive of brain metastasis only. Routine surveillance brain imaging was not performed. Each patient was instructed to visit the emergency room as early as possible when any symptom occurred or aggravated.

Propensity score matching

To correct patient selection bias arisen from choosing whom to give PCI, propensity score (PS) matching was performed. Significantly different variables after Chi-square analysis between PCI and observation groups were selected for PS matching. PS matching was carried out using a ratio of 1:1 and a caliper distance of 0.025 without replacement. Since covariates considered for PS matching primarily included factors associated with OS, PS-matched cohort was used in OS analysis only.

Generating prognostic index for brain metastasis

Prognostic index predicting a high risk of symptomatic brain metastasis was calculated in the observation group (n = 137) using Cox regression model. Prognostic index was generated by summating significant factors weighted by hazard ratio of each. The patient group was dichotomized into two groups according to the calculated risk score, the prognostic index.

^{18}F-FDG PET/CT protocol

^{18}F-FDG PET/CT was performed for staging before the initiation of any treatment. Patients underwent ^{18}F-FDG PET/CT using a dedicated PET/CT scanner (Biograph 40 True-point, Siemens, Knoxville, TN, USA). After fasting for at least six hours, [^{18}F] FDG of 5.18 MBq/kg was administered intravenously. Image acquisition was started at 60 min after the injection. Serum glucose levels were less than 150 mg/dL at the time of FDG administration in all patients. PET images were corrected for attenuation and reconstructed onto a matrix of 128 × 128 using a three-dimensional ordered-subsets expectation maximization algorithm (2 iterations, 21 subsets).

Analysis of FDG PET/CT

FDG uptakes in spleen and BM were visually interpreted because not all patients had eligible data available for quantifying standardized uptake values (SUV) of BM or spleen. Visual analysis was done without any clinical information by consensus between two nuclear medicine physicians using a commercial software (Syngo.via, VA 30, Siemens Healthcare, Erlangen, Germany). Maximum-intensity projection (MIP) images were preferentially used for assessing FDG uptake of the spleen and BM (Supplementary Fig. 1). If it was difficult to judge FDG uptake from MIP images, transaxial and coronal fusion images were used together. When either BM or spleen showed FDG uptake, we annotated such case as "SBM uptake". When comparing visual examination and quantification analysis in quantifiable FDG PET/CT subgroups, no significant difference was observed between the two methodologies. Therefore, we concluded that visual analysis was an acceptable method for assessing FDG uptakes in both BM and spleen (Supplementary Table 1).

Statistical analysis

BMFS was defined as the time from the date of initial diagnosis to the date of brain metastases. OS was calculated from the time from the date of initial diagnosis to the date of death or the last follow-up. BMFS and OS curves were calculated using the Kaplan–Meier method. Differences between curves were assessed with the log-rank test. P-value <0.050 was considered statistically significant. Factors initially significant on univariate analyses and factors found to be clinically significant determined by researchers were incorporated into multivariate models. Backward stepwise elimination with a threshold of p = 0.050 was used to select factors in the final model.

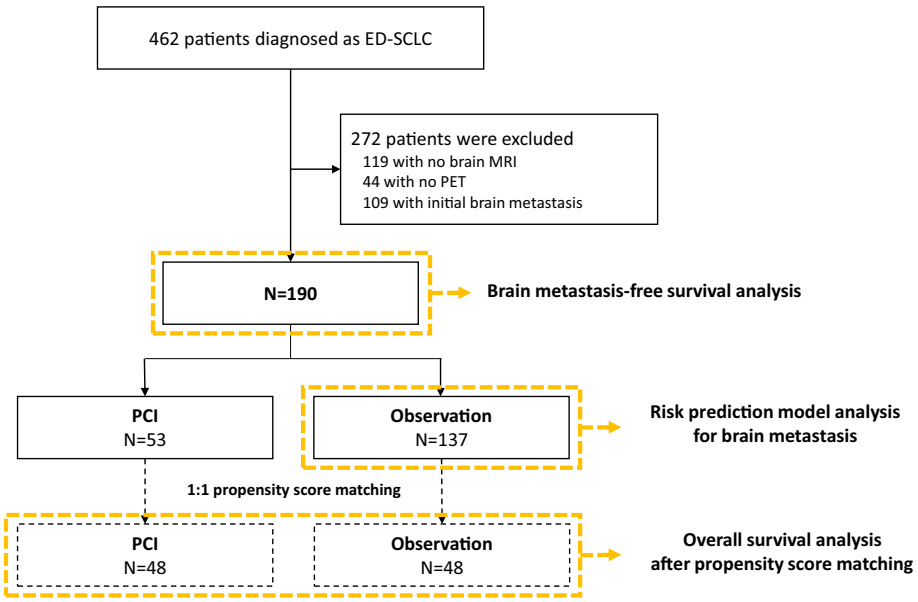


Fig. 1. Patient enrollment and analysis subgroups. Among 462 patients with ED-SCLC, only 190 were enrolled for this study. A total of 190 patients were eligible for brain metastasis-free survival analysis. Patients who did not receive PCI were eligible for risk prediction model analysis for brain metastases. Overall survival analysis was performed after 1:1 propensity score matching.

The predictive performance of SBM uptake was investigated by time-dependent receiver operating characteristic (ROC) analysis for BMFS and OS. All continuous variables were dichotomized as yes or no, or high or low, with a different cut-off value that maximized the area under the ROC curve (AUROC). AUROC was calculated using the cutoff finder [12], a freely available program on the internet (http://molpath.charite.de/cutoff). All statistical analyses were performed using STATA software version 14.0 (Stata Co., College Station, TX, USA).

Results

Patients characteristics

Clinical features of 190 patients who met our inclusion and exclusion criteria are summarized in Table 1. Fifty-three patients (27.9%) received PCI while 137 (72.1%) patients did not. The median follow-up duration was 10.6 months (range, 1.5–56.2 months). The median age was 66 years (range, 47–87 years) in the PCI group and 70 years (range, 42–89 years) in the observation group (p = 0.100). Percentages of patients with the Eastern Cooperative Oncology Group (ECOG) performance status score higher than 2 (5.7% vs. 23.4%, p = 0.005), stable or progressive disease after initial chemotherapy (15.1% vs. 38.6%, p < 0.001), and less than four cycles of initial chemotherapy (0% vs. 19.0%, p = 0.001) were lower in the PCI group. There was also an unbalanced use of initial chemotherapy regimens between PCI and observation groups (p = 0.041). Thoracic radiation was administered to 5 (9.4%) patients in the PCI group and 12 (8.8%) patients in the observation group, respectively (p = 0.884). Forty-seven (88.7%) and six (11.3%) patients received PCI at dose of 25 Gy/10fx and 20 Gy/5fx, respectively.

Survival outcome

Brain metastasis-free survival & overall survival

Univariate and multivariate analyses according to risk factors were evaluated for BMFS and OS (Supplementary Table 2). In multivariate analysis, progressive disease after initial chemotherapy (HR: 4.175; 95% CI: 1.380–12.630; p = 0.011) and the presence of extrathoracic metastases (HR: 3.762; 95% CI: 1.546–9.155;

Table 1
Patient characteristics.

Variables	PCI (%) (n = 53)	Observation (%) (n = 137)	p-value
Age, years (range)	66 (47–87)	70 (42–89)	0.100
>70	33 (62.3)	66 (48.2)	0.081
≤70	20 (37.7)	71 (51.8)	
Sex			
Male	45 (84.9)	117 (85.4)	0.931
Female	8 (15.1)	20 (14.6)	
ECOG			
0–1	50 (94.3)	105 (76.6)	0.005
≥2	3 (5.7)	32 (23.4)	
Response to initial chemotherapy			
Complete	6 (11.3)	2 (1.5)	<0.001
Partial	39 (73.6)	82 (59.9)	
Stable, progressive	8 (15.1)	53 (38.6)	
Total number of initial chemotherapy			
<4	0 (0.0)	26 (19.0)	0.001
≥4	53 (100.0)	111 (81.0)	
Regimen of initial chemotherapy			
Carboplatin/Etoposide	18 (34.0)	73 (53.3)	0.041
Cisplatin/Etoposide	31 (58.5)	53 (38.7)	
Cisplatin/Irinotecan	4 (7.5)	11 (8.0)	
Number of metastatic lesions			
1	31 (58.5)	76 (55.5)	0.707
≥2	22 (41.5)	61 (44.5)	
Presence of extrathoracic metastases			
Yes	39 (73.6)	98 (71.5)	0.777
No	14 (26.4)	39 (28.5)	
Smoking			
Yes	40 (75.5)	113 (82.5)	0.274
No	13 (24.5)	24 (17.5)	
Radiotherapy			
Thoracic radiation	5 (9.4)	12 (8.8)	0.884
PCI dose/fractionation			
25 Gy/10 fx	47 (88.7)	–	
20 Gy/5 fx	6 (11.3)	–	

$p = 0.004$) were independently associated with worse BMFS. However, receipt of PCI did not improve BMFS (HR: 1.777; 95% CI: 0.879–3.592; $p = 0.110$). As for OS, multivariate analysis showed that ECOG score higher than 2 (HR: 2.176; 95% CI: 1.446–3.275; $p < 0.001$), less than four cycles of initial chemotherapy (HR: 2.223; 95% CI: 1.335–3.702; $p = 0.002$), progressive disease after initial chemotherapy (HR: 2.117; 95% CI: 1.279–3.503; $p = 0.004$), presence of extrathoracic metastases (HR: 1.881; 95% CI: 1.286–2.751; $p = 0.001$), and omitting PCI (HR: 1.443; 95% CI: 1.001–2.052; $p = 0.049$) were associated with worse OS. With the assumption that there might have been a selection bias in the PCI group with better survival prognosis, we used PS matching analysis to control for differences in baseline characteristics between PCI and observation groups.

Overall survival with propensity score matching

Patient characteristics were the same between the two groups after 1:1 PS matching was performed with a total number of 96 patients (Supplementary Table 3). In a PS-matched cohort, multivariate analysis showed that only the presence of extrathoracic metastases (HR: 1.769; 95% CI: 1.021–3.067; $p = 0.042$) was associated with worse OS (Table 2). PCI (HR: 1.324; 95% CI: 0.870–2.014; $p = 0.190$) was not associated with OS after PS matching.

Risk prediction model for brain metastasis and the impact of PCI

Risk prediction model for brain metastasis

In the observation group ($n = 137$), multivariate analysis showed that the following three risk factors were associated with worse BMFS: presence of extrathoracic metastases (HR: 8.674; 95% CI: 1.998–37.654; $p = 0.004$), hypermetabolism of BM or spleen from FDG PET (HR: 4.229; 95% CI: 1.891–9.458; $p < 0.001$), and high neutrophil to lymphocyte ratio (NLR) (HR: 2.674, 95% CI: 1.181–6.054; $p = 0.018$) (Table 3). The prognostic index for predicting brain metastasis was generated by multiplying weighting factor (β coefficient) to each variable (Fig. 2). A median prognostic index was 2.16 (range, 0–4.59). Patients were divided into two groups. Patients with a prognostic index higher than 3.0 were classified as high-risk ($n = 42$) while those with a prognostic index lower than 3.0 were classified as low-risk ($n = 95$). Prognostic index significantly divided patients into two subgroups of high- and low-risk of symptomatic brain metastases ($p < 0.001$) (Fig. 3A).

Impact of PCI according to risk groups

The prognostic index was applied to the total set of patients ($n = 190$, 61 with high-risk and 129 with low-risk) (Fig. 3B). Among low-risk patients, PCI did not improve BMFS ($p = 0.943$). However, PCI improved BMFS in high-risk patients ($p = 0.001$). The prognostic index was then applied to PS-matched cohort ($n = 96$, 32 with high-risk and 64 with low-risk) (Fig. 3C). PCI did not improve OS in either the high- or the low-risk group ($p = 0.123$, $p = 0.398$, respectively).

Discussion

PCI was beneficial for patients with a high-risk of symptomatic brain metastases in terms of BMFS in our study. We also found that BM or spleen uptake in FDG PET was associated with symptomatic brain metastases. In addition, BM or spleen uptake in FDG PET was found to be an independent prognostic factor for BMFS. These findings suggest that in addition to clinical features of patients with ED-SCLC, metabolic features of spleen and BM shown on FDG PET can predict symptomatic brain metastases.

Some previous studies have assessed the clinical implication of FDG uptake by BM or spleen [13–17]. They reported that FDG uptakes in BM and spleen were independent prognostic factors. In addition, the metabolic activity of BM and spleen could be related to systemic inflammation [18–20]. Inflammatory responses are known to play decisive roles in different stages of tumor development as well as in immune surveillance and responses to therapy [21,22]. In our data, BM or spleen uptake in FDG PET was an independent prognostic factor associated with worse BMFS in multivariate analysis. In addition, systemic inflammatory markers such as NLR and platelet to lymphocyte ratio (PLR) in the SBM uptake group were higher than those in the non-SBM uptake group (Supplementary Table 4). Therefore, the correlation between SBM uptake on FDG PET and symptomatic brain metastases might be considered as a correlation between systemic inflammation and symptomatic brain metastases.

Blood components or related factors such as platelets and NLR have been demonstrated to promote cancer progression [27,28]. In addition, high NLR is known to be related to worse survival outcome in SCLC [29–31]. Furthermore, a previous study has reported that NLR higher than 2.55 is associated with brain metastasis in patients with LD-SCLC without PCI [32]. Although the biological

Table 2
Overall survival with propensity score matched.

Variables		*N* (%)	Univariate analysis			Multivariate analysis		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	>70	39 (40.6)	1					
	≤70	57 (59.4)	1.057	0.691–1.619	0.798	–	–	–
Sex	Male	83 (86.5)	1.845	0.964–3.529	0.030	1.243	0.786–1.965	0.352
	Female	13 (13.5)	1					
ECOG	0–1	90 (93.8)	1.213	0.487–3.023	0.677	–	–	–
	≥2	6 (6.2)	1					
Total number of initial chemotherapy	<4	0 (0.0)	–	–	–	–	–	–
	≥4	96 (100.0)						
Response to initial chemotherapy	CR, PR, SD	92 (95.8)	1					
	PD	4 (4.2)	3.978	1.385–11.428	0.006	2.944	0.984–8.802	0.053
Number of metastatic lesions	1	55 (57.3)	1					
	≥2	41 (42.7)	1.651	1.084–2.514	0.018	1.357	0.866–2.126	0.183
Extrathoracic metastases	Yes	71 (74.0)	1.903	1.157–3.129	0.010	1.769	1.021–3.067	0.042
	No	25 (26.0)	1					
PCI	Yes	48 (50.0)	1					
	No	48 (50.0)	1.336	0.880–2.029	0.172	1.324	0.870–2.014	0.190

HR, hazard ratio; 95% CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3
Brain metastasis-free survival in observation group.

Variables		*N* (%)	Univariate analysis			Multivariate analysis		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (years)	>70	66 (48.2)	1					
	≤70	71 (51.8)	1.860	0.807–4.286	0.139	–	–	–
Sex	Male	117 (85.4)	1.171	0.403–3.403	0.771	–	–	–
	Female	20 (14.6)	1					
ECOG	0–1	105 (76.6)	1					
	≥2	32 (23.4)	2.480	0.885–6.952	0.074	–	–	–
Total number of initial chemotherapy	<4	26 (19.0)	1					
	≥4	111 (81.0)	1.427	0.337–6.052	0.628	–	–	–
Response to initial chemotherapy	CR, PR, SD	107 (78.1)	1					
	PD	30 (21.9)	3.738	1.242–11.253	0.012	–	–	–[†]
Number of metastatic lesions	1	76 (55.5)	1					
	≥2	61 (44.5)	1.915	0.877–4.179	0.097	–	–	–
Extrathoracic metastases	Yes	98 (71.5)	7.500	1.753–32.093	0.002	8.674	1.998–37.654	0.004
	No	39 (28.5)	1					
Smoking	Yes	113 (82.5)	1.849	0.433–7.900	0.400	–	–	–
	No	24 (17.5)	1					
Spleen or BM uptake in PET	Yes	18 (13.1)	4.481	2.017–9.956	<0.001	4.229	1.891–9.458	<0.001
	No	119 (86.9)	1					
NLR	<3.7	89 (65.5)	1					
	≥3.7	48 (35.0)	2.423	1.118–5.271	0.021	2.674	1.181–6.054	0.018
PLR	<151.2	66 (48.2)	1.122	0.518–2.428	0.770	–	–	-
	≥151.2	71 (51.8)	1					
SII	<0.88	83 (60.6)	1					
	≥0.88	54 (39.4)	2.822	1.288–6.183	0.007	–	–	–[†]

HR, hazard ratio; 95% CI, 95% confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; BM, bone marrow; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.
[†] Variables are excluded from multivariate analysis.

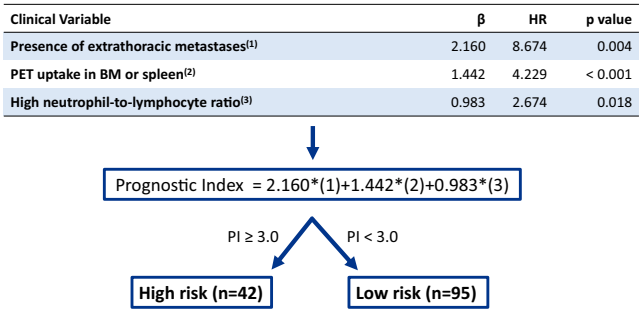


Fig. 2. Risk prediction model for brain metastases. The prognostic index was calculated based on three statistically significant variables for predicting worse brain metastasis-free survival. Each factor (one for existence or zero for absence) is multiplied by a β coefficient. The calculated prognostic index is dichotomized by 3.0 to obtain 42 high risk and 95 low-risk subsets.

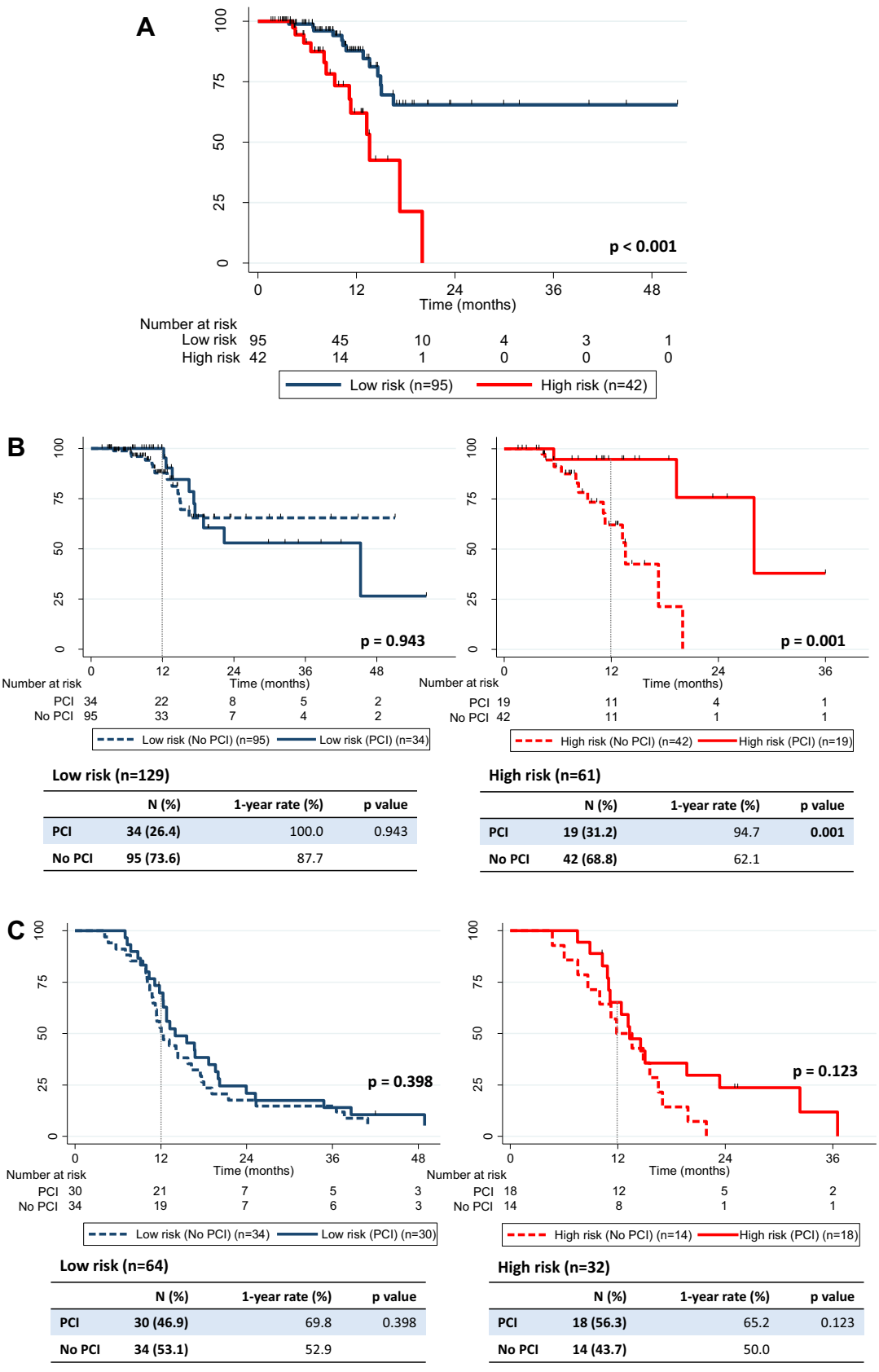
mechanism behind the association between high NLR and brain metastases remains unclear, increased neutrophil-dependent inflammation and reduced lymphocyte mediated tumor response might play a role [33,34]. In this study, neither SBM uptake nor high NLR was associated with progression-free survival, although they were independent prognostic factors for predicting brain metastases.

A series of studies have consistently asserted that extensive tumor burden, especially extrathoracic metastases, are a critical risk factor that can increase the chance of brain metastases [23]. Zeng et al. [24] have also insisted that stage IIIB-IV is an independent risk factor for brain metastases. Since the Japanese study, the dominant opinion is that PCI is not necessary for patients who achieve CR after initial chemotherapy [3,25,26]. The current study showed that PD at the initial disease site after the initial chemotherapy was a risk factor for brain metastases, suggesting that PCI might prolong BMFS in PD subsets.

The current study concludes that PCI does not prolong OS in either risk group. The specific cause of death could not be clarified because most patients were sent to hospice care when the disease had severely progressed. Since routine use of regular brain MRI was not performed, it was impossible to specify whether the cause of death was due to brain progression or else. We could not assess adverse events either due to the nature of the retrospective study. While no significant decline in the mini-mental status exam was observed in the Japanese study [3], several other studies have reported detrimental effects of PCI [35,36]. Therefore, selective use of PCI in selected patients with maximum potential benefit is justified.

A fundamental limitation of this study was that it was retrospectively investigated. In addition, a relatively small number of patients were enrolled in this study. Further validation with a large number of cohort patients is required. Brain MRI was performed only at the initial staging, not right before PCI. Routine brain MRI for follow-up was not guaranteed. Only when symptoms occurred, brain MRI was performed. Thus, it was inevitable for symptomatic brain metastases to become the endpoint of this study. Nevertheless, the current study included patients only if the initial brain MRI and whole body FDG PET/CT workup were completed. Such inclusion criteria reflected the standard practice of ED-SCLC currently performed in clinical settings. They have a significant advantage over the study of Slotman study [2].

In conclusion, we found that three prognostic factors (the presence of extrathoracic metastases, hypermetabolism of BM or spleen, and high NLR) were associated with a high risk of symptomatic brain metastases in ED-SCLC. According to the risk stratification model, PCI was beneficial for patients at high risk of symptomatic brain metastases in terms of BMFS, but not OS. Thus,



Low risk (n=129)

	N (%)	1-year rate (%)	p value
PCI	**34 (26.4)**	100.0	0.943
No PCI	**95 (73.6)**	87.7	

High risk (n=61)

	N (%)	1-year rate (%)	p value
PCI	**19 (31.2)**	94.7	**0.001**
No PCI	**42 (68.8)**	62.1	

Low risk (n=64)

	N (%)	1-year rate (%)	p value
PCI	**30 (46.9)**	69.8	0.398
No PCI	**34 (53.1)**	52.9	

High risk (n=32)

	N (%)	1-year rate (%)	p value
PCI	**18 (56.3)**	65.2	0.123
No PCI	**14 (43.7)**	50.0	

Fig. 3. Risk stratification for BMFS and impact of PCI on BMFS and OS according to risk groups. (A) Risk stratification for BMFS. Brain metastasis-free survival in the observation group was divided into two risk-groups based on the prognostic index. The high-risk group had worse brain metastasis-free survival than the low-risk group ($p < 0.001$). (B) Impact of PCI on BMFS according to risk groups. PCI significantly improved BMFS in high-risk patients ($p = 0.001$), whereas PCI did not improve BMFS in low-risk patients ($p = 0.943$). (C) Impact of PCI on OS according to risk groups. PCI did not improve OS in either high- or low-risk group ($p = 0.398$, $p = 0.123$, respectively).

selective use of PCI in ED-SCLC according to the risk stratification is recommended. However, prospective trials with a larger population are needed to validate the use of prognostic index for predicting brain metastases.

Declaration of competing interest

The authors declare no potential conflicts of interest.

Funding

This research was supported by an intramural research fund of Seoul National University (No. 800-20180367) and grants (HI14C1072 & H18C1916 to Dr. Gi Jeong Cheon) of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea. This research was also supported by grants (NRF2017M2A2A7A01070925 and 2016R1D1A1B03934691 to Hak Jae Kim) funded by the Ministry of Science, ICT, and Future Planning, Republic of Korea.

Ethical approval

The study protocol was reviewed and approved by our Institutional Review Board (approval no. H-1307-132-508). This study was conducted in accordance with the Principles of the Declaration of Helsinki.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.01.009.

References

[1] Aupérin A, Arriagada R, Pignon J-P, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med 1999;341:476–84.
[2] Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664–72.
[3] Takahashi T, Yamanaka T, Seto T, Harada H, Nokihara H, Saka H, 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;18:663–71.
[4] Bradley JD, Dehdashti F, Mintun MA, Govindan R, Trinkaus K, Siegel BA. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol 2004;22:3248–54.
[5] Kut V, Spies W, Spies S, Gooding W, Argiris A. Staging and monitoring of small cell lung cancer using [18F]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). Am J Clin Oncol 2007;30:45–50.
[6] Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med 2003;44:1911–7.
[7] Schumacher T, Brink I, Mix M, Reinhardt M, Herget G, Digel W, et al. FDG-PET imaging for the staging and follow-up of small cell lung cancer. Eur J Nucl Med 2001;28:483–8.
[8] Azad A, Chionh F, Scott AM, Lee ST, Berlangieri SU, White S, et al. High impact of 18F-FDG-PET on management and prognostic stratification of newly diagnosed small cell lung cancer. Mol Imag Biol 2010;12:443–51.
[9] Fischer BM, Mortensen J, Langer SW, Loft A, Berthelsen AK, Petersen BI, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol 2007;18:338–45.
[10] Bang JI, Yoon HJ, Kim BS. Clinical utility of FDG uptake within reticuloendothelial system on F-18 FDG PET/CT for prediction of tumor recurrence in breast cancer. PLoS ONE 2018;13:e0208861.
[11] Lee JW, Baek MJ, Ahn TS, Lee SM. Fluorine-18-fluorodeoxyglucose uptake of bone marrow on PET/CT can predict prognosis in patients with colorectal cancer after curative surgical resection. Eur J Gastroenterol Hepatol 2018;30:187–94.
[12] Budczies J, Klauschen F, Sinn BV, Gyorffy B, Schmitt WD, Darb-Esfahani S, et al. Cutoff Finder: a comprehensive and straightforward Web application enabling rapid biomarker cutoff optimization. PLoS ONE 2012;7:e51862.
[13] Lee JW, Seo KH, Kim ES, Lee SM. The role of (18)F-fluorodeoxyglucose uptake of bone marrow on PET/CT in predicting clinical outcomes in non-small cell lung cancer patients treated with chemoradiotherapy. Eur Radiol 2017;27:1912–21.
[14] Bural GG, Torigian DA, Chen W, Houseni M, Basu S, Alavi A. Increased 18F-FDG uptake within the reticuloendothelial system in patients with active lung cancer on PET imaging may indicate activation of the systemic immune response. Hellenic J Nucl Med 2010;13:23–5.
[15] Van de Wiele C, VandeVyver F, Debruyne C, Philippe J, van Meerbeeck JP. FDG uptake by the bone marrow in NSCLC patients is related to TGF-beta but not to VEGF or G-CSF serum levels. Eur J Nucl Med Mol Imaging 2008;35:519–22.
[16] Prevost S, Boucher L, Larivee P, Boileau R, Benard F. Bone marrow hypermetabolism on 18F-FDG PET as a survival prognostic factor in non-small cell lung cancer. J Nucl Med 2006;47:559–65.
[17] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76.
[18] Nunez R, Rini JN, Tronco GG, Tomas MB, Nichols K, Palestro CJ. Correlation of hematologic parameters with bone marrow and spleen uptake in FDG PET. Revista espanola de medicina nuclear 2005;24:107–12.
[19] Murata Y, Kubota K, Yukihiro M, Ito K, Watanabe H, Shibuya H. Correlations between 18F-FDG uptake by bone marrow and hematological parameters: measurements by PET/CT. Nucl Med Biol 2006;33:999–1004.
[20] Inoue K, Goto R, Okada K, Kinomura S, Fukuda H. A bone marrow F-18 FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. Ann Nucl Med 2009;23:643–9.
[21] Mittal V, El Rayes T, Narula N, McGraw TE, Altorki NK, Barcellos-Hoff MH. The microenvironment of lung cancer and therapeutic implications. Adv Exp Med Biol 2016;890:75–110.
[22] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature 2008;454:436–44.
[23] Macrae RM. Prophylactic cranial irradiation in extensive stage small cell lung cancer: outcomes at a comprehensive cancer centre. Int J Radiat Oncol Biol Phys 2018;101:1133–40.
[24] Zeng H, Xie P, Meng X, Yuan S, Sun X, Li W, et al. Risk factors for brain metastases after prophylactic cranial irradiation in small cell lung cancer. Sci Rep 2017;7:1–6.
[25] Nosaki K, Seto T, Shimokawa M, Takahashi T, Yamamoto N. Is prophylactic cranial irradiation (PCI) needed in patients with extensive-stage small cell lung cancer showing complete response to first-line chemotherapy?. Radiother Oncol 2018;127:344–8.
[26] Suzuki R, Komaki R. Is prophylactic cranial irradiation indicated for patients with extensive-stage small cell lung cancer with a complete response to first-line treatment?. Radiother Oncol 2018;127:339–43.
[27] Placke T, Orgel M, Schaller M, Jung G, Rammensee HG, Kopp HG, et al. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. Cancer Res 2012;72:440–8.
[28] Sitia G, Aiolfi R, Di Lucia P, Mainetti M, Fiocchi A, Mingozzi F, et al. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. PNAS 2012;109:E2165–72.
[29] Kang MH, Go SI, Song HN, Lee A, Kim SH, Kang JH, et al. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br J Cancer 2014;111:452–60.
[30] Kasmann L, Bolm L, Schild SE, Janssen S, Rades D. Neutrophil-to-lymphocyte ratio predicts outcome in limited disease small-cell lung cancer. Lung 2017;195:217–24.
[31] Liu D, Huang Y, Li L, Song J, Zhang L, Li W. High neutrophil-to-lymphocyte ratios confer poor prognoses in patients with small cell lung cancer. BMC Cancer 2017;17:882.
[32] Zheng Y, Wang L, Zhao W, Dou Y, Lv W, Yang H, et al. Risk factors for brain metastasis in patients with small cell lung cancer without prophylactic cranial irradiation. Strahlenther Onkol 2018;194:1152–62.
[33] Brandau S, Dumitru CA, Lang S. Protumor and antitumor functions of neutrophil granulocytes. Semin Immunopathol 2013;35:163–76.
[34] Coffelt SB, Kersten K, Doornebal CW, Weiden J, Vrijland K, Hau CS, et al. IL-17-producing gammadelta T cells and neutrophils conspire to promote breast cancer metastasis. Nature 2015;522:345–8.
[35] Le Pechoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99–01, EORTC 22003–08004, RTOG 0212, and IFCT 99–01): a randomised clinical trial. Lancet Oncol 2009;10:467–74.
[36] Gore EM, Bae K, Wong SJ, Sun A, Bonner JA, Schild SE, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol 2011;29:272–8.