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The value of prophylactic cranial irradiation in limited-stage small cell lung cancer: should it always be recommended?

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Purpose: Prophylactic cranial irradiation (PCI) is a standard treatment for limited-stage small cell lung cancer (LS-SCLC) showing a response to initial treatment, but many patients do not receive PCI due to comorbidities or refusal. This study aims to define the patient group for whom PCI can be omitted with minimal risk.

Materials and Methods: Patients with LS-SCLC who underwent radiotherapy with curative aim at our institution between January 2004 and December 2015 were retrospectively reviewed. Patients who did not receive PCI were evaluated for brain metastasis-free survival (BMFS), progression-free survival (PFS), overall survival (OS), and prognostic factors for survival, and treatment outcomes were compared with a patient cohort who received PCI.

Results: A total of 350 patients achieved a response following thoracic radiotherapy, and 190 of these patients did not receive PCI. Stage I–II and a complete response (CR) to initial therapy were good prognostic factors for BMFS and OS on univariate analysis. Patients with both stage I–II and a CR who declined PCI showed comparable 2-year BMFS to those who received PCI (92% vs. 89%). In patients who achieved CR, PCI did not significantly improve OS or PFS.

Conclusion: There should be less concern about omitting PCI in patients with comorbidities if they have stage I–II or a CR, with brain metastasis control being comparable to those patients who receive PCI.

Keywords: Small cell lung carcinoma, Radiotherapy, Prophylactic cranial irradiation, PCI, Brain, Complete remission

Introduction

Small cell lung cancer (SCLC) is an aggressive variant of lung cancer forming approximately 13% of lung cancer cases. Limited-stage SCLC (LS-SCLC), which is a candidate for definitive radiotherapy combined with chemotherapy, accounts for 37%–40% of SCLC cases at the time of diagnosis [1,2]. Although SCLC typically shows a good response to chemoradiotherapy, the prognosis for LS-SCLC remains dismal with a median survival time of around 13 months [1]. The central nervous system (CNS) is a common site of distant failure with the 2 year brain metastasis rate being above 50% for patients who do not receive prophylactic cranial irradiation (PCI) [3].

PCI for LS-SCLC patients showing a good response to initial therapy is known to reduce the risk of brain metastasis

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and improve overall survival (OS) [4,5]. The recent National Comprehensive Cancer Network (NCCN) guidelines, version 2.2018 for SCLC recommend PCI for LS-SCLC patients showing a complete response (CR) or partial response (PR), excluding those with poor performance status or impaired neurocognitive function [6]. Although consistent data on neurocognitive decline associated with the generally used PCI dose of 25 Gy is limited [7-9], the risk of neurocognitive dysfunction after PCI is a main concern associated with the decision of whether or not to apply PCI. Around 40% of patients with LS-SCLC are reported to decline PCI because of neurotoxicity concerns [10,11].

To our knowledge, only a few reports on the treatment outcomes of patients who did not receive PCI have been published according to current medical treatments [12,13]. An understanding of the treatment outcomes and prognostic factors may be helpful in deciding whether or not to apply PCI to patients with comorbidity, despite a good response to initial therapy. Therefore, we retrospectively analyzed the survival outcomes and prognostic factors in LS-SCLC patients who did not receive PCI in attempt to identify the patient group for whom not administering PCI would cause minimal concern.

Materials and Methods

1. Patient enrollment

We retrospectively reviewed patients with LS-SCLC who received radiotherapy with a curative aim at our institution between January 2004 and December 2015. All patients were diagnosed pathologically and underwent a standardized evaluation including routine laboratory tests, chest computed tomography (CT), and bone scan or positron emission tomography/computed tomography (PET/CT). Contrast-enhanced magnetic resonance imaging (MRI) or CT of the brain was performed before initiation of treatment to confirm the absence of brain metastasis. Staging was performed according to the tumor-node-metastasis (TNM) classification of the American Joint Committee on Cancer 7th edition, and a two-stage staging based on the NCCN guidelines, version 2.2018 [6]. Therapeutic response was evaluated with chest CT using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1. A total of 372 LS-SCLC patients received thoracic radiotherapy, and 94.1% (350/372) achieved a CR or PR following initial therapy. Of these patients, 57% (190/350) did not receive PCI despite a response following thoracic radiotherapy, and this patient group was evaluated to determine the prognostic factors for survival outcomes.

Additionally, the survival was compared between patients who underwent PCI and those who did not. This study was approved by the Institutional Review Board of the Asan Medical Center (No. 2019-0772), and the requirement for informed consent was waived because of the retrospective nature of the study.

2. Treatment

Thoracic radiotherapy was planned using either three-dimensional conformal radiotherapy (3D-CRT; 183/190, 96.3%), intensity-modulated radiotherapy (3/190, 1.6%), or stereotactic body radiotherapy for the small primary tumor combined with 3D-CRT for mediastinal nodes (4/190, 2.1%). Treatment planning was performed using CT simulation, with the gross tumor volume (GTV) including the primary tumor and involved lymph nodes. A clinical target volume (CTV) was delineated in the case of clinically suspicious lesions, and the planning target volume included the GTV or CTV with a 5–10 mm margin. Conventional fractionated radiotherapy to a total of 50–66 Gy (median, 52.5 Gy) with 2.0–2.2 Gy per fraction (median, 2.1 Gy per fraction) was given within 5–7 weeks. Chemotherapy mainly consisted of an etoposide and cisplatin regimen, and was delivered every 3 weeks as a cycle. Dose adjustment or replacement of the anticancer agent by carboplatin or irinotecan was considered, depending on patients' medical or general condition. Chemotherapy and thoracic radiotherapy were conducted either concurrently or sequentially, and when initial chemotherapy administered with the thoracic radiotherapy it was considered as early concurrent chemoradiotherapy (CCRT). The therapeutic effect of the initial treatment was evaluated using contrast-enhanced chest CT before consideration of PCI, and routine blood tests and chest CTs were performed every 3–6 months. MRI or CT of the brain was not routinely performed during the follow-up period, unless the patients complained of symptoms suspicious of brain metastasis.

3. Statistical analysis

Progression-free survival (PFS) and brain metastasis-free survival (BMFS) were defined as the period between the start date of any anticancer treatment and the date of recurrence confirmed by radiographic study. OS was defined as the time from initiation of anticancer treatment to death. The Kaplan–Meier method was used to analyze survival, and differences in survival times were evaluated using the log-rank test. The t-test and chi-square test were used to evaluate differences in related factors between patients who underwent PCI and

Table 1. Patients' characteristics

	No PCI (57%, n = 190)	PCI (43%, n = 160)	All patients (n = 350)	p-value
Age (yr)	64 (41–83)	59 (35–75)	61 (32–83)	<0.001
Gender				0.313
Male	165 (86.8)	145 (90.6)	310 (88.6)	
Female	25 (13.2)	15 (9.4)	40 (11.4)	
ECOG performance status				0.197
0–1	178 (93.7)	154 (96.2)	332 (94.8)	
2	11 (5.8)	5 (3.1)	16 (4.6)	
3	1 (0.5)	1 (0.6)	2 (0.6)	
Smoking history				0.188
No	27 (14.2)	15 (9.4)	42 (12.0)	
Yes	163 (85.8)	145 (90.6)	308 (88.0)	
TNM stage				0.084
I	8 (4.2)	2 (1.3)	10 (2.9)	
II	18 (9.5)	24 (15.0)	42 (12.0)	
III	164 (86.3)	134 (83.8)	298 (85.1)	
Timing of thoracic RT				<0.001
Early CCRT	57 (30.0)	71 (44.4)	128 (36.6)	
Late CCRT	73 (38.4)	75 (46.9)	148 (42.3)	
Sequential RT	59 (31.1)	14 (8.8)	73 (20.9)	
RT alone	1 (0.5)	0 (0.0)	1 (0.3)	
Response to thoracic RT				<0.001
CR	53 (27.9)	101 (63.1)	154 (44.0)	
PR	137 (72.1)	59 (36.9)	196 (56.0)	

Values are presented as median (range) or number (%).
PCI, prophylactic cranial irradiation; ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CR, complete response; PR, partial response.

those who did not. Univariate analysis and multivariate Cox regression analysis were performed to evaluate the influence of risk factors on survival outcomes. A p-value less than 0.05 was considered statistically significant. All statistical analysis was conducted with SPSS version 22.0 for Windows (IBM, Armonk, NY, USA).

Results

Three-hundred and fifty patients achieved either a PR or CR after radiotherapy for LS-SCLC. Among these patients, 190 (165 men, 25 women) did not receive PCI and were followed-up for a median period of 15 months (range, 2 to 129 months). The clinical characteristics of these patients are summarized in Table 1. Compared with the patients who received PCI, those who did not receive PCI were significantly older, older underwentless CCRT, and showed less response after initial thoracic radiotherapy. All patients received chemotherapy

concurrently or sequentially, except one patient who was treated with radiotherapy alone because of underlying end-stage renal disease. The median number of chemotherapy cycles was 4 (range, 1 to 13 cycles). Fifty-nine of the patients who did not undergo PCI (31.1%) received sequential radiotherapy compared with 14 patients (8.8%) with PCI (p < 0.01). Most of the patients (164/190, 86.3%) were clinical stage III with there being no significant difference in the distribution of clinical stages between those who received PCI and those who did not.

The 2-year OS, PFS, and BMFS rates of the patients without PCI were 38.2%, 25.2%, and 65.2%, respectively. Table 2 shows the prognostic factors for survival according to the univariate analysis. Stage I–II (p = 0.025) and achievement of a CR (p < 0.01) were good prognostic factors for OS. The BMFS rate was also significantly related to TNM stage (p = 0.034) and response to thoracic radiotherapy (p = 0.038). The 2-year BMFS rates of the patients with stage I–II and a CR

Table 2. Prognostic factors for survival in patients without PCI (univariate analysis)

	No. of patients	2-yr OS (%)	p-value	2-yr PFS (%)	p-value	2-yr BMFS (%)	p-value
Age (yr)			0.082		0.782		0.581
<65	105	41.6		24.9		63.9	
≥65	85	41.6		25.6		67.1	
Gender			0.831		0.345		0.722
Male	165	40.5		26.5		63.7	
Female	25	36.0		13.5		74.5	
ECOG performance status			0.255		0.289		0.264
0–1	178	38.5		26.2		65.3	
2–3	12	33.3		10.4		63.6	
Smoking			0.872		0.398		0.837
No	27	33.3		20.5		78.9	
Yes	163	39.0		25.9		62.9	
TNM stage			0.025		0.090		0.034
I-II	26	57.7		42.6		79.7	
III	164	35.1		22.3		62.6	
Timing of thoracic RT			0.070		0.374		0.939
Early CCRT	57	41.6		29.2		60.4	
Late CCRT	73	42.3		27.9		68.9	
Sequential RT	59	30.5		18.2		63.8	
Response to thoracic RT			<0.001		<0.001		0.038
CR	53	66.0		48.8		72.4	
PR	137	27.3		13.4		60.3	

PCI, prophylactic cranial irradiation; OS, overall survival; BMFS, brain metastasis-free survival; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CR, complete response; PR, partial response.
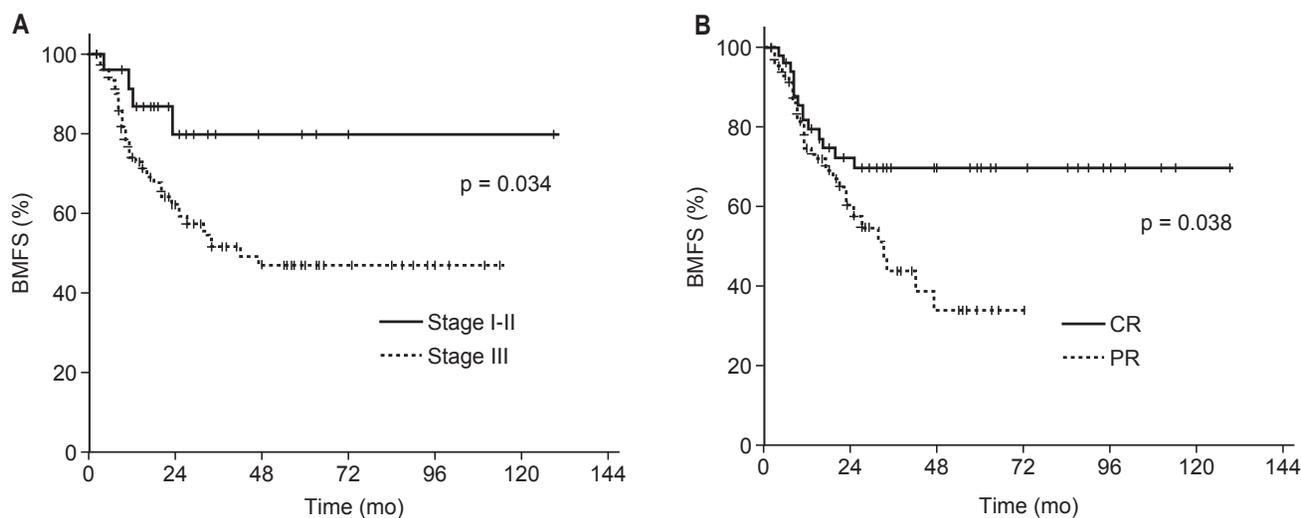

Fig. 1. Brain metastasis-free survival (BMFS) of no prophylactic cranial irradiation patients according to (A) TNM stage and (B) response to thoracic radiotherapy. CR, complete response; PR, partial response.

were 79.7% and 72.4%, respectively (Fig. 1). The patients' age at the time of diagnosis showed a marginal relationship with OS (p = 0.082), as did the timing of thoracic radiotherapy (p = 0.070). Response to thoracic radiotherapy was a statistically

Table 3. Prognostic factors for survival in patients without PCI (multivariate analysis)

	No. of patients	OS		PFS		BMFS	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (yr)			0.061		0.643		0.883
<65	105	1		1		1	
≥65	85	1.389 (0.985–1.957)		0.916 (0.632–1.328)		0.958 (0.539–1.702)	
TNM stage			0.086		0.295		0.070
I–II	26	1		1		1	
III	164	1.609 (0.935–2.770)		1.333 (0.779–2.282)		2.603 (0.924–7.334)	
Timing of thoracic RT			0.164		0.193		0.954
CCRT	130	1		1		1	
Sequential RT	59	1.285 (0.902–1.829)		1.289 (0.880–1.887)		0.983 (0.543–1.778)	
Response to thoracic RT			<0.001		<0.001		0.069
CR	53	1		1		1	
PR	137	3.419 (2.193–5.330)		2.702 (1.755–4.160)		1.781 (0.957–3.318)	

PCI, prophylactic cranial irradiation; OS, overall survival; BMFS, brain metastasis-free survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; CR, complete response; PR, partial response.
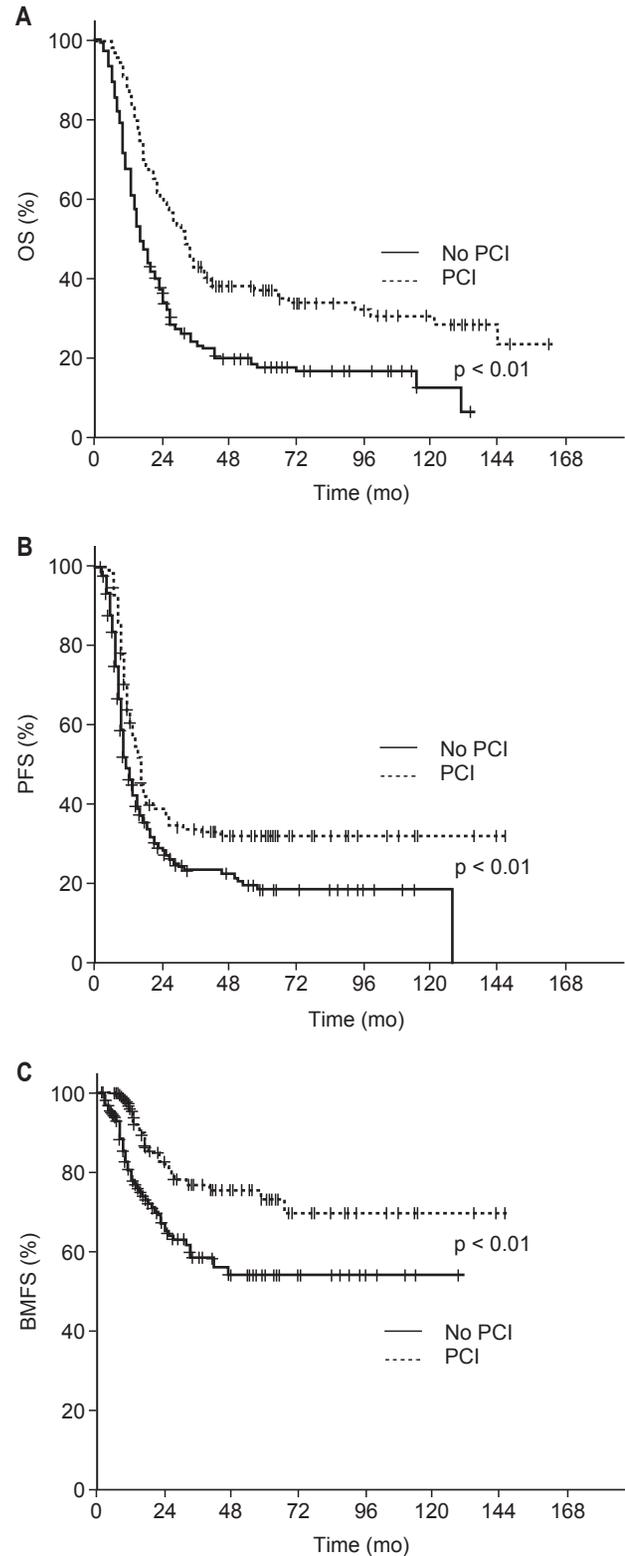

Fig. 2. Survival and recurrence in patients who received prophylactic cranial irradiation (PCI) and those who did not: (A) overall survival (OS), (B) progression-free survival (PFS), and (C) brain metastasis-free survival (BMFS).
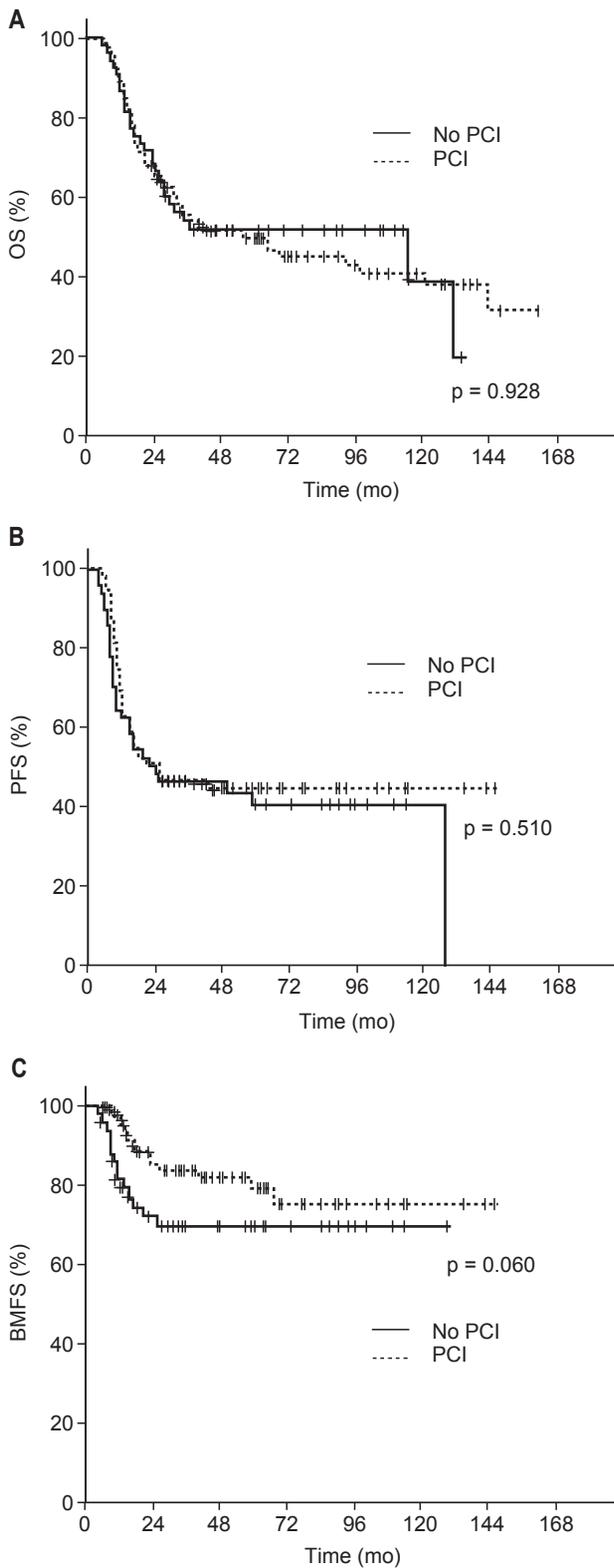
Fig. 3. Survival and recurrence in patients showing a complete response according to whether they received prophylactic cranial irradiation (PCI) or not: (A) overall survival (OS), (B) progression-free survival (PFS), and (C) brain metastasis-free survival (BMFS).
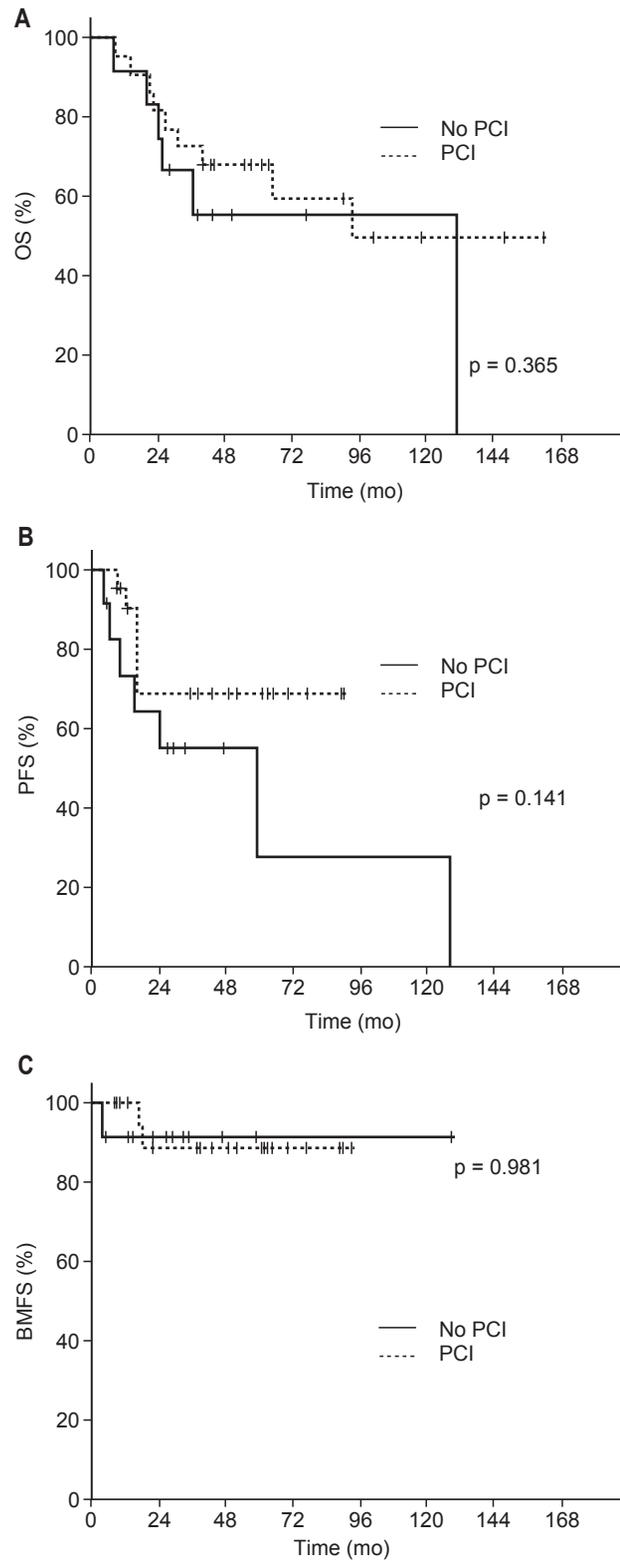
Fig. 4. Survival and recurrence in patients showing both complete response and stage I–II according to whether they received prophylactic cranial irradiation (PCI) or not: (A) overall survival (OS), (B) progression-free survival (PFS), and (C) brain metastasis-free survival (BMFS).

Table 4. Survival outcomes in the No-PCI group with stage I–II and a CR in comparison with the PCI group

	No. of patients	2-yr OS (%)	2-yr PFS (%)	2-yr BMFS (%)
No PCI	190	36.1	28.9	67.1
Stage I–II	26	57.7	42.6	79.7
CR	53	66.0	48.8	72.4
Both stage I–II and CR	12	75.0	55.0	91.7
PCI	160	59.3	39.0	82.4

PCI, prophylactic cranial irradiation; CR, complete response; OS, overall survival; BMFS, brain metastasis-free survival; PFS, progression-free survival.

significant prognostic factor (p < 0.01) for PFS, while the TNM stage showed a marginal relationship (p = 0.090). The results of the multivariate analysis are described in Table 3. Achievement of a CR was a positive prognostic factor for OS and PFS (p < 0.01), and showed a marginal relationship with BMFS (p = 0.069). Stage I or II disease, rather than stage III, showed a tendency toward improved BMFS, although this was not statistically significant (p = 0.070).

Fig. 2 depicts the survival outcomes of those who did not receive PCI in comparison with those who did. The OS, PFS, and BMFS rates were significantly lower in those who did not receive PCI (p < 0.01). Additionally, a subgroup analysis conducted on the patient group who achieved a CR (n = 154) following thoracic radiotherapy (Fig. 3) showed that PCI marginally improved BMFS in this patient group (p=0.060), but had no significant benefit on OS or PFS. A subgroup of the patient with both CR and stage I–II (n = 34) was analyzed, and there was no significant difference on OS, PFS, and BMFS (Fig. 4).

The survival rate of the patient group with stage I–II, CR, and both stage I–II and a CR who did not receive PCI is described in Table 4 in comparison with that of the group who did receive PCI. The 2-year BMFS rates of 72%–80% in the patient group with stage I–II or a CR who did not receive PCI were little different to those of the patient groups who did receive PCI (2-year BMFS, 82.4%). The 2-year OS and PFS rates of the no-PCI group with favorable prognostic factors were also comparable to the outcomes of the patients who received PCI. Although the number of the patients in the analysis was relatively small, the BMFS, OS, and PFS rates of the no-PCI group with both stage I–II and a CR were favorable compared to the outcomes of the patients who did receive PCI.

Discussion and Conclusion

For LS-SCLC patients, chemotherapy with etoposide and cisplatin together with thoracic radiotherapy is the standard treatment, which is then followed by PCI for patients with a response, irrespective of other indications except those of poor performance status and neurocognitive dysfunction [6]. The positive role of PCI has been identified in several randomized trials. A meta-analysis of seven randomized trials with a total of 987 mainly LS-SCLC patients (847/987, 85%) reported improvements in OS and disease-free survival in those who gained a CR [5]. However, in real clinical practice, PCI is not administered to all eligible patients due to concerns over neurocognitive toxicity or combined comorbidity. A retrospective study on PCI utilization reported that 39% of patients did not receive PCI, 38% of whom declined it mainly because of concerns about its toxicity [10]. Another retrospective study on 208 eligible patients reported a comparable result, showing that 45% of the patients declined PCI, with the major reasons for omission being patient refusal due to concern about its toxicity (38%) and oncologists' decisions that patients were medically unfit to receive PCI (33%) [11]. In our institution, 57% of the LS-SCLC patients with a response did not receive PCI, although there were insufficient records to allow us to report on the reasons for PCI omission. Understanding the clinical outcomes of patients who do not receive PCI despite a good response to initial therapy would be helpful for clinicians making decisions on PCI utilization in patients with comorbidities.

There is little published information available on the survival outcomes and prognostic factors of patients who decline PCI, in the recent clinical situations in which PCI is accepted as a standard treatment for LS-SCLC. A retrospective study that reported treatment outcomes of 60 LS-SCLC patients who did not receive PCI after a CR or near-CR showed that brain metastasis, performance status, and T-stage were significantly related to OS [13]. Another recent study that performed a multivariate analysis with 153 patients reported that high T-stage, high neutrophil-to-lymphocyte ratio, early thoracic

radiotherapy, and fewer chemotherapy cycles were risk factors for brain metastasis [12]. In our patient cohort, a lower stage and better response were associated with improved BMFS and OS in the univariate analysis, although only the relationship between response to thoracic radiotherapy and OS was significant in the multivariate analysis, with the other relationships showing only non-significant tendencies.

High TNM stage is known to be a risk factor for brain metastasis and OS in LS-SCLC. Wu et al. [14] report that stage I–II patients show a lower incidence of brain metastasis than stage III patients (12% vs. 26% at 5 years; p = 0.020), suggesting that PCI may play a relatively limited role in early-stage patients. Favorable survival outcomes and a low rate of brain metastasis in early-stage patients after surgical resection have been reported in several studies [15,16]. This relationship was also identified in our cohort of LS-SCLC patients for whom PCI was omitted after thoracic radiotherapy, although we found that early-stage disease had only a marginally significant influence on OS and BMFS in the multivariate analysis. However, patients with stage I or II made up only 14% of the cases in our analysis. Stage I is rarely diagnosed and is usually treated with a surgical approach. As we analyzed only those patients who received thoracic radiotherapy, only a small number of stage I patients were included in this study. As the number of patients with early-stage disease is relatively small, caution is required in the interpretation of our results, and further analysis to determine the prognostic factors of this patient group is warranted. Nevertheless, the results of this study suggest that the use of TNM staging in addition to the two-stage system may be helpful for clinical decision-making.

Attainment of a CR correlated with OS, BMFS, and PFS in patients who did not receive PCI. A phase III study demonstrated that complete responders after CCRT had a more favorable prognosis [17], while a retrospective study with a heterogeneous patient cohort also reported that a CR was associated with better OS and PFS [18]. This relationship was observed in our patient cohort without PCI, although we did not find a significant relationship between the timing of thoracic radiotherapy and survival rates, except for a tendency toward lower OS in patients treated with sequential radiotherapy rather than CCRT, which is in agreement with previous reports [19,20]. Advanced age is a critical factor when deciding on PCI, and the patients who did not receive PCI were significantly older than those who did. Patients aged over 65 showed lower OS, although age did not independently affect BMFS or PFS in this study. On the basis of the results of this study, various factors should be considered when evaluating the prognosis of patients who decline PCI.

The appropriateness of prescribing PCI to all patients with a response to initial treatment has been continuously challenged. Although previous randomized studies investigating the efficacy of PCI have shown a clear reduction in brain metastasis, there was relatively low improvement in OS, which was reported to improve by only about 5% [5]. A meta-analysis by Meert et al. [4] shows that with the introduction of brain imaging assessment before PCI, there is a lack of data supporting the general use of PCI in all CR situations. It should be noted that most of the studies that randomly assigned patients to undergo PCI or not were performed before the modern era of MRI. A recent randomized trial with active brain MRI surveillance found the role of PCI for extensive-stage SCLC to be not essential [21], which is contrary to the result of European Organisation for Research and Treatment of Cancer (EORTC) trial, which did not include CNS imaging either before randomization or during the follow-up period [22]. A recent retrospective analysis of LS-SCLC reported no significant survival benefit from PCI in those patients who were confirmed on brain MRI to have no brain metastasis after initial treatment [23]. In this context, PCI may not improve survival in all LS-SCLC patients with a response, although there is not enough data to fully support this suggestion. Defining the patient group that may show no benefit from PCI is important, but prognostic factors other than the application of brain MRI have rarely been reported. On the basis of this study, omission of PCI in patients with stage I–II or a CR may be considered with reduced concern about the increased risk of brain metastasis, especially in the era of easily accessible brain MRI.

This study has several limitations, including its retrospective nature. There may be a considerable amount of selection bias because the patients who did not receive PCI were selected without consistent criteria being applied, and there was a lack of information in the medical records on the reasons for omission of PCI. We briefly compared the outcomes of treatment with or without PCI, but the findings should be interpreted cautiously because of the heterogeneity in the characteristics between the patient groups. Conducting a prospective study to identify prognostic factors in patients without PCI is difficult because PCI is generally accepted as a standard treatment for LS-SCLC showing a response. Despite these drawbacks, to the best of our knowledge, this study is the largest retrospective single-institution study to describe the outcomes and prognostic factors of patients who did not

receive PCI following a response to thoracic radiotherapy.

In conclusion, stage I–II and a CR were good prognostic factors for BMFS and OS in the patient cohort who did not receive PCI, with such patients showing comparable survival outcomes with those who did receive PCI. In complicated clinical situations where application of PCI is associated with concerns over comorbidities or neurotoxicity, PCI omission may be considered with reduced concerns about CNS failure in patients with stage I–II and a CR.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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