

Prophylactic Cranial Irradiation for Extensive-Stage Small-Cell Lung Cancer: A Retrospective Analysis

abstract

Purpose Extensive-stage small-cell lung cancer (esSCLC) is an incurable disease and represents a therapeutic challenge because of its poor prognosis. Studies in prophylactic cranial irradiation (PCI) in esSCLC have shown a decreased incidence of symptomatic brain metastases in patients who respond to systemic chemotherapy. However, its effect on overall survival is debatable. We evaluated the benefit of PCI in patients with esSCLC in terms of overall survival, progression-free survival, incidence of brain metastases, recurrence rate, and exposure to postrecurrence therapies.

Materials and Methods We retrospectively reviewed electronic charts from patients diagnosed with esSCLC from 2008 to 2014 at our institution. All patients had negative baseline brain imaging before chemotherapy and PCI and received at least 4 cycles of platinum-based chemotherapy in the first-line setting without progressive disease on follow-up. PCI was performed at the discretion of the treating physician. Analyses were based on descriptive statistics. Survival curves were calculated by Kaplan-Meier method.

Results Among 46 eligible patients, 16 (35%) received PCI and 30 (65%) did not. Compared with no PCI, PCI led to improved progression-free survival (median, 10.32 v 7.66 months; hazard ratio, 0.4521; 95% CI, 0.2481 to 0.8237; $P < .001$) and overall survival (median, 20.94 v 11.05 months; hazard ratio, 0.2655; 95% CI, 0.1420 to 0.4964; $P < .001$) as well as lower incidence of brain metastases (19% v 53%; $P = .0273$) and higher exposure to second-line chemotherapy (87% v 57%; $P = .0479$).

Conclusion Careful patient selection for PCI can improve not only brain metastases control and higher second-line chemotherapy exposure but also patient survival.

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INTRODUCTION

Small-cell lung cancer (SCLC) is an aggressive malignancy most commonly staged as limited versus extensive disease.¹ The use of combined chemotherapy is still the single most important component of SCLC treatment since the 1980s, with small but existent benefit in overall survival (OS).² Thoracic radiation therapy (RT) is also important to control local tumor progression, with an improvement in absolute survival of approximately 5.4% at 3 years after induction chemotherapy in limited disease compared with chemotherapy alone.³ Current studies of this approach in patients with extensive-stage SCLC (esSCLC) have shown that thoracic RT also improves local symptomatic control regardless of the metastatic spread of the disease.⁴ However, in both stages, SCLC has a very poor prognosis even after treatment, with the median OS ranging from 15 to 20 months and 8 to 13 months in limited and extensive disease, respectively.²

Because of the SCLC nature of rapid spread, a significant rate of brain metastases is found at diagnosis or at later stages after initial treatment, despite good systemic disease control.⁵ Prophylactic cranial irradiation (PCI) has been extensively studied as an attempt to decrease the incidence of brain metastases after chemotherapy in patients with limited and extensive disease and prevents associated morbidity and mortality.⁶ This was initially established in a meta-analysis of seven randomized trials that compared PCI with no PCI in a total of 987 patients who experienced a complete remission with chemotherapy.⁶ In the meta-analysis, most patients had limited-stage disease, but 12% in the PCI group and 17% in the control group had extensive-stage disease. The addition of PCI significantly decreased both the incidence of brain metastases (risk ratio, 0.46; 95% CI, 0.38 to 0.57) and the mortality rate (risk ratio, 0.84; 95% CI, 0.73 to 0.97), which corresponds to an increase of the survival rate from 15.3% to 20.7% at 3 years.⁶

However, when it comes to esSCLC only, the extent of the benefit of PCI is still not clear. PCI is known to decrease the incidence of symptomatic brain metastases in patients with esSCLC who respond to systemic chemotherapy, but its effect on OS is controversial.⁷⁻⁹ Two multicenter randomized trials evaluated this matter. In a phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), 286 patients with SCLC who responded to chemotherapy were randomly assigned to either PCI or observation. No CNS imaging was required before enrollment. Patients treated with PCI had a significantly decreased 1-year incidence of symptomatic brain metastases (14.6% v 40.4% without PCI; hazard ratio [HR], 0.27; 95% CI, 0.16 to 0.44). Both disease-free survival (14.7 v 12 weeks; HR, 0.76; 95% CI, 0.59 to 0.96) and median OS (6.7 v 5.4 months; HR, 0.68; 95% CI, 0.52 to 0.88) were also in favor of patients treated with PCI versus observation.⁷ However, OS results differed in a second trial conducted in Japan in 224 patients who responded to initial chemotherapy. Contrary to the EORTC trial, CNS staging was mandatory for all patients before random assignment. Patients were randomly assigned to either PCI or observation, but preliminary results presented at the 2014 ASCO annual meeting and confirmed in the study's final publication showed that the trial was stopped prematurely for futility after 111 deaths. OS was shorter in the PCI treatment group than in the observation group (10.1 v 15.1 months, respectively; HR, 1.38; 95% CI, 0.95 to 2.02), although these results were not statistically significant. In accordance with the EORTC trial results, the Japanese trial also showed a significant decrease in the 1-year incidence of brain metastases with PCI versus observation (32% v 58%; $P < .001$), and fewer patients required RT for symptomatic control of brain metastases (31% v 80%).^{8,9}

The results of those trials provide strong evidence that PCI in esSCLC can decrease the incidence of symptomatic brain metastases but leads to a conflicting interpretation about OS.⁷⁻⁹ To better understand the effect of PCI given to patients with esSCLC after systemic platinum-based chemotherapy and initial response, we performed a retrospective analysis that evaluated the incidence of brain metastases, recurrence rate, exposure to postrecurrence therapies, progression-free survival (PFS), and OS at our institution.

MATERIALS AND METHODS

Electronic charts from patients with histologically proven esSCLC from 2008 to 2014 at Instituto do

Câncer do Estado de São Paulo were retrospectively reviewed. The primary end point was the OS effect of PCI in a nonselected population outside controlled clinical trials. Secondary end points were PFS, incidence of brain metastases, recurrence rate, and exposure postrecurrence therapies.

esSCLC was defined as tumor beyond the boundaries of limited disease (tumor confined to the ipsilateral hemithorax and regional nodes able to be included in a single tolerable RT port), including distant metastases, malignant pericardial or pleural effusions, and contralateral supraclavicular and contralateral hilar involvement.¹⁰ All patients had a baseline negative CNS evaluation with contrasted computed tomography scans and/or magnetic resonance imaging before chemotherapy and computed tomography scans before PCI. To be included in the analysis, all patients had to reach stable disease, partial response, or complete response after initial chemotherapy. Patients with early interruption of treatment with fewer than 4 cycles of platinum-based chemotherapy in the first-line setting were excluded as were those with progressive disease at follow-up assessment. PCI was performed with no prespecified criteria to indicate or refuse the procedure other than the treating physician's discretion.

Analyses were based on descriptive statistics. Categorical data were compared by χ^2 test, and continuous data were compared by Mann-Whitney U test. Survival curves were estimated by using the Kaplan-Meier method and compared statistically by using the log-rank test. MedCalc software, version 17.1 (MedCalc Software, Ostend, Belgium) was used for the statistical analyses. This study was reviewed and approved by the local ethics committee.

RESULTS

Forty-six patients with esSCLC who were previously scanned for CNS metastases from 2008 to 2014 were included in the analyses. Demographic characteristics are listed in Table 1. Among all patients, 16 received PCI (PCI group, 35%), whereas 30 did not (no PCI group, 65%). Most patients were male, were current or former smokers, and presented with extrathoracic metastatic spread of the disease.

Treatment characteristics are listed in Table 2. After initial staging work-up, all patients underwent our institutional treatment protocols for SCLC with platinum-based systemic chemotherapy alone (96% of all patients), whereas a few received systemic chemotherapy followed by thoracic RT

Table 1. Demographic Characteristics of All Patients With Extensive-Stage SCLC

Characteristic	Patient Group, No. (%)			P
	PCI	No PCI	Total	
No. of patients	16 (35)	30 (65)	46 (100)	
Median age, years (range)	65 (42-73)	65 (45-81)	65 (42-81)	.8176
Sex				
Male	9 (56)	18 (60)	27 (59)	.7953
Female	7 (44)	12 (40)	19 (41)	.7953
Smoking status				
Current or former	16 (100)	26 (87)	42 (91)	.1359
Never	0	1 (3)	1 (2)	.4889
Unknown	0	3 (10)	3 (7)	.1957
Median pack-years (range)	50 (20-120)	50 (32-180)	50 (20-180)	.4504
ECOG performance status				
0 to 1	10 (63)	14 (47)	24 (52)	.3060
2 to 3	6 (38)	14 (47)	20 (43)	.5623
Unknown	0 (0)	2 (7)	2 (4)	.2840
Site of extensive disease				
Visceral (liver, adrenal gland, thorax)	12 (75)	20 (67)	32 (70)	.5778
Nonvisceral (bones)	3 (19)	12 (40)	15 (33)	.1526

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PCI, prophylactic cranial irradiation, SCLC, small-cell lung cancer.

(4% of all patients, all from the PCI group). The most frequent regimen included etoposide in combination with a platinum agent (96% of all patients), and patients received cisplatin more commonly than carboplatin (63% v 37%, respectively).

Table 2. Treatment Characteristics of All Patients With Extensive-Stage SCLC

Treatment Characteristic	Patient Group, No. (%)			P
	PCI	No PCI	Total	
Treatment choice				
Chemotherapy alone	14 (88)	30 (100)	44 (96)	.0552
Chemotherapy followed by thoracic radiation therapy	2 (12)	0 (0)	2 (4)	.0552
First-line chemotherapy scheme				
Carboplatin + etoposide	6 (38)	11 (37)	17 (37)	.9473
Cisplatin + etoposide	10 (62)	17 (57)	27 (59)	.7456
Other (cisplatin + paclitaxel, cisplatin + irinotecan)	0 (0)	2 (6)	2 (4)	.3228
Median received cycles of chemotherapy (range)	6 (4-6)	6 (4-7)	6 (4-7)	.8514
Toxicity grade \geq 3 with chemotherapy	5 (31)	10 (33)	15 (31)	.8913
RT dosing in PCI				
20 Gy in 10 fractions	1 (6)	—	1 (6)	—
25 Gy in 10 fractions	10 (63)	—	10 (63)	—
30 Gy in 10 fractions	5 (31)	—	5 (31)	—

Abbreviations: PCI, prophylactic cranial irradiation; RT, radiation therapy; SCLC, small-cell lung cancer.

Grade \geq 3 adverse events attributable to chemotherapy occurred in 31% of all patients. The most frequent adverse event was neutropenia (11 patients in both groups, which corresponded to 73% of all adverse events, with four patients needing dosing adjustments because of neutropenia and three experiencing febrile neutropenia). In total, five patients had their treatment suspended before the sixth cycle of chemotherapy (two as a result of refractory neutropenia, two as a result of febrile neutropenia, and one as a result of grade 4 asthenia). No deaths occurred as a result of chemotherapy adverse events. Median radiation dose was 25 Gy (range, 20 to 30 Gy) given in 10 fractions (100% of the PCI group). Although patients were not systematically evaluated for PCI adverse events because of the retrospective nature of this analysis, PCI was well tolerated, with no acute toxicities reported and excellent compliance with the prescribed dose. Furthermore, in our follow-up, no significant decline in cognitive function was reported in patients' charts.

With a median follow-up of 12.6 months, the OS of patients with esSCLC who received PCI was significantly better than those in the no PCI group, with a survival benefit median of 20.94 months versus 11.05 months, respectively (HR, 0.2655; 95% CI, 0.1420 to 0.4964; $P < .001$; Fig 1). PFS was also statistically superior in favor of PCI

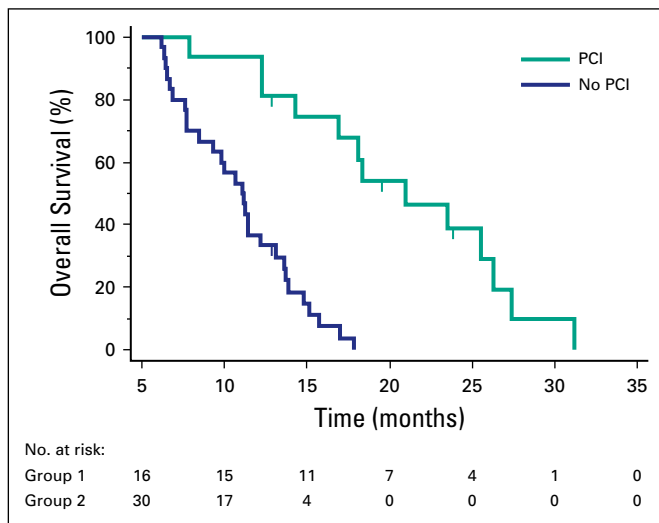


Fig 1. Kaplan-Meier curves of overall survival in patients with extensive-stage small-cell lung cancer by prophylactic cranial irradiation (PCI) versus no PCI. The survival benefit is in favor of the PCI group (median, 20.94 months v 11.05 months; hazard ratio, 0.2655; 95% CI, 0.1420 to 0.4964; $P < .001$).

(median 10.32 v 7.66 months, respectively; HR, 0.4521; 95% CI, 0.2481 to 0.8237; $P < .001$; Fig 2). Other secondary end point results are listed in Table 3. PCI did not decrease the total rate of disease recurrence (94% v 90% for the PCI and no PCI groups, respectively; $P = .6487$), but it was associated with higher exposure to second-line chemotherapy (87% v 57%, respectively; $P = .0479$) and lower CNS metastatic spread (19% v 53%, respectively; $P = .0273$). All patients who developed CNS recurrence in the no PCI group (16 [53%]) had brain metastases diagnosed at the first moment of disease recurrence. Among those, 11 (69%) received therapeutic doses of RT to the brain, four (25%) could not receive therapeutic RT to the brain and were ultimately treated with best supportive care because of poor Eastern Cooperative Oncology Group performance status upon recurrence, and one (6%) received second-line chemotherapy followed by best supportive care. Among all patients in the PCI group whose disease recurred in the CNS (three [19%]), one (33%) underwent additional RT upon CNS recurrence after second-line chemotherapy because of prior systemic recurrence, whereas the other two (67%) had disease recurrence in the CNS at the first moment of disease recurrence and were treated with second-line chemotherapy followed by best supportive care. All diagnoses of brain metastases were based on the onset of suspicious neurologic symptoms. Patients were not routinely screened for the development of brain metastases.

DISCUSSION

Data from two large randomized trials are clear on the benefit of PCI in esSCLC in terms of decreasing the incidence of symptomatic brain metastases.⁷⁻⁹

However, OS outcomes are conflicting. In the EORTC study, which showed an OS benefit with PCI, patients were not routinely screened for brain metastasis before random assignment.⁷ This might have allowed the inclusion of patients with CNS metastases into the group that received cranial irradiation with a therapeutic role instead of with a prophylactic approach as the study intended. This bias could have compromised the interpretation of the study's results and outcomes and may have led to conflicting results in the Japanese trial where patients were routinely screened with brain imaging before random assignment.^{8,9} In the current study, all included patients had negative baseline CNS results with contrasted computed tomography scans and/or magnetic resonance imaging before chemotherapy and computed tomography scans before PCI. Patients with newly diagnosed brain metastases before PCI were not included in this trial because they did not meet the inclusion criteria of stable disease, or partial or complete response to chemotherapy.

Our study showed a benefit of PCI for patients with esSCLC in lowering the incidence of brain metastasis, as previously expected, but also in higher exposure to second-line chemotherapy and improvement of PFS and OS. These findings are important considering that patients who did not receive PCI had a lower expected survival but still with enough lifetime to develop CNS metastases. These results need to be interpreted cautiously because of the retrospective nature of this study, which included patients who were not randomly assigned, a small sample size from a single center, and data extracted from nonstandardized electronic charts, all of which lead to a selection bias. Patient selection for PCI was possibly based on the presence of better prognostic factors associated with better treatment response. Despite the non-significant difference, in the PCI group versus the no PCI group, more patients had an Eastern Cooperative Oncology Group performance status of 0 or 1 (63% v 47%, respectively; $P = .3060$; Table 1); received thoracic RT (12% v 0%, respectively; $P = .0552$; Table 2); and had a better response rate (100% v 87%, respectively; $P = .1359$; Table 3). In addition, the median OS of 20.94 months seen in this study does not match the median OS for patients who received PCI in the EORTC and Japanese trials (6.7 months and 10.1 months, respectively), which can all be a result of patient selection bias in the current study.

The effect of radiation dose has been evaluated, and no advantage for doses > 25 Gy in 10 fractions was demonstrated.^{11,12} A multinational phase III

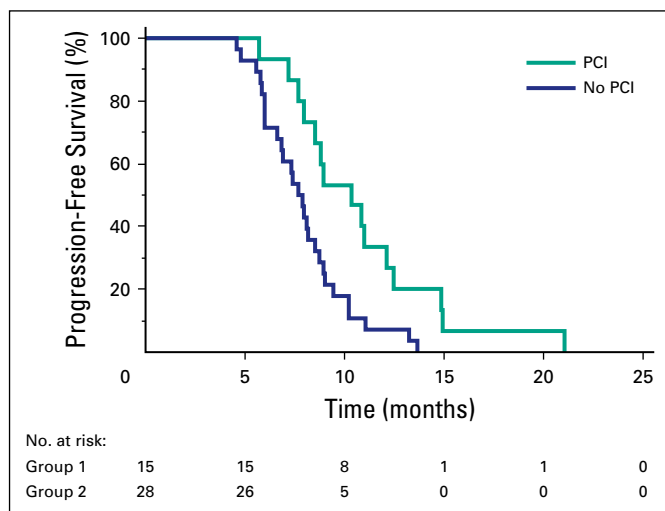


Fig 2. Kaplan-Meier curves of progression-free survival of patients with extensive-stage small-cell lung cancer by prophylactic cranial irradiation (PCI) versus no PCI. The survival benefit is in favor of the PCI group (median, 10.32 months v 7.66 months; hazard ratio, 0.4521; 95% CI, 0.2481 to 0.8237; $P < .001$).

trial randomly assigned 720 patients with limited-stage SCLC and a complete response to initial treatment to PCI at a dose of either 25 Gy in 10 fractions, 36 Gy in 15 or 18 fractions, or twice daily 1.5 Gy in 24 fractions. The 2-year incidence rates of brain metastases were not statistically significant (23% v 29% for the higher and lower radiation doses, respectively; HR, 0.80; 95% CI, 0.57 to 1.11); the higher dose group trended toward a significantly lower 2-year survival rate (37% v 42%; HR, 1.20; 95% CI, 1.00 to 1.44).^{11,12} Our institutional RT protocol for PCI is based on those findings, and our median dose of 25 Gy in 10 fractions is considered as adequate for this purpose.

Cranial irradiation can be related to both acute and long-term toxicity.^{7,13} Acute adverse effects associated with PCI are fatigue, alopecia, scalp erythema, headaches, and low-grade nausea, all of which usually are self-limited, whereas long-term toxicity, especially neurocognitive impairment, is a potential concern.^{7,13} In the current study, no acute or long-term adverse events as a result of

PCI were reported in the charts, possibly because of the small sample size and the retrospective study design. Long-term toxicities are difficult to assess and quantify, with limited data available in a population with a low long-term survival expectancy. Potentially severe neurologic and cognitive disabilities are seen with earlier treatment techniques that used concurrent chemotherapy, large fraction sizes (3.0 to 4.0 Gy), and/or a high total dose.¹⁴⁻¹⁷ However, the risk of severe deficits appears to be less frequent with the current protocols for PCI. The Radiation Therapy Oncology Group 0212 trial performed detailed neurocognitive and quality-of-life assessments, and chronic neurotoxicity was significantly less frequent in patients treated with 25 Gy than in those treated with 36 Gy (60% v 85% and 89%, respectively; $P = .02$), which reinforces the lesser extent of toxicities with a lower dose.¹² Cognitive functioning and quality of life were also assessed both before and after treatment with PCI in a trial from the United Kingdom and the EORTC, with no adverse events attributable to PCI.¹⁸ In addition, chemotherapy itself can lead to cognitive function impairment that can be potentialized by PCI.¹⁹ Long-term potential neurotoxicity as a result of PCI in patients with esSCLC might become more noticeable as patients present improvement in OS. Therefore, research efforts to minimize the neurotoxicity of PCI are either concluded^{20,21} or ongoing (ClinicalTrials.gov identifiers: NCT02635009, NCT02504788, NCT01486459, and NCT00006349) and have included twice-daily fractionation, hippocampal-sparing whole-brain RT, and the use of potentially neuroprotective systemic agents. Of note, among patients who did not receive initial PCI, more than one half experienced recurrence in the CNS (53%), and among them, the majority underwent therapeutic CNS RT (69%), which led to an

Table 3. Outcomes on the Basis of PCI Versus No PCI

Outcome	Patient Group, No. (%)			P
	PCI (n = 16)	No PCI (n = 30)	Total (n = 46)	
Response rate to chemotherapy (complete and partial response) before PCI	16 (100)	26 (87)	42 (91)	.1359
Recurrence/progression of disease	15 (94)	28 (90)	42 (91)	.6595
CNS recurrence rate	3 (19)	16 (53)	19 (41)	.0273
Second-line chemotherapy among those who progressed	13 of 15 (87)	16 of 28 (57)	29 of 43 (67)	.0479
CNS RT among those who developed brain metastases	1 of 3 (33)	11 of 16 (69)	12 of 19 (63)	.2478

Abbreviations: PCI, prophylactic cranial irradiation; RT, radiation therapy.

ultimately unavoidable exposure to CNS RT whether with a prophylactic or therapeutic intent.

In conclusion, our findings suggest that PCI in patients with esSCLC improves results on the basis of an exploratory analysis of selected patients with tumor response after initial chemotherapy. However, a definitive answer about the role of PCI can only be achieved with randomized prospective studies with careful patient selection and consideration of clinical features,

such as performance status, neurocognitive basal status, disease burden, and response to prior therapy, to minimize the potential biases of this retrospective analysis. Continuous efforts in SCLC research hopefully will bring a clearer benefit not only from PCI but also from newer treatment options to promote more comprehensive and efficient patient care.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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