Original Study

Prophylactic Cranial Irradiation for Patients With Limited-Stage Small-Cell Lung Cancer With Response to Chemoradiation

Patricia Tai,[1] Avi Assouline,[2] Kurian Joseph,[3] Larry Stitt,[4] Edward Yu[5]

Abstract

For patients with limited-stage small-cell lung cancer (SCLC) with an incomplete response (IR) to chemotherapy and chest radiotherapy, the benefit of prophylactic cranial irradiation (PCI) is not clear in the literature. This report was based on 289 patients treated with curative intent, 93 of whom had incomplete response (IR). These patients benefited from PCI, with a reduced rate of and a delayed time for the development of brain metastases, although without significant overall or cause-specific survival (CSS) benefit. PCI could be considered for both complete and incomplete responders.

Background: Previous clinical studies have generally reported that prophylactic cranial irradiation (PCI) was given to patients with a complete response (CR) to chemotherapy and chest radiotherapy in limited-stage small-cell lung cancer (SCLC). It is not clear if those with incomplete response (IR) would benefit from PCI. **Patients and Methods:** The Saskatchewan experience from 1981 through 2007 was reviewed. Patients were treated with chest radiotherapy and chemotherapy with or without PCI (typical doses: 2500 cGy in 10 fractions over 2 weeks, 3000 cGy in 15 fractions over 3 weeks, or 3000 cGy in 10 fractions over 2 weeks). **Results:** There were 289 patients treated for curative intent, 177/289 (61.2%) of whom received PCI. For the whole group of 289 patients, PCI resulted in significant overall survival (OS) and cause-specific survival (CSS) benefit ($P = .0011$ and 0.0005, respectively). The time to symptoms of first recurrence at any site with or without PCI was significantly different: 16.9 vs. 13.2 months ($P = .0006$). PCI significantly delayed the time to symptoms of first recurrence in the brain: 20.7 vs. 10.6 months ($P < .0001$). The first site of metastasis was the brain for 12.5% and 45.5% patients with CR with and without PCI, respectively ($P = .02$) and in 6.1% and 27.6% of patients with IR with and without PCI, respectively ($P = .05$). For the 93 patients with IR, PCI did not confer OS or CSS benefit ($P = .32$ and 0.39, respectively). **Conclusions:** Patients with IR benefited from PCI, with a reduced rate of and a delayed time for the development of brain metastases, although without significant OS or CSS benefit. PCI could be considered for all patients with limited-stage SCLC responding to chemoradiation.

Clinical Lung Cancer, Vol. 14, No. 1, 40-4
Keywords: Brain, Lung cancer, Metastasis, Radiotherapy, Survival

Introduction

The brain is a common site of metastasis for small-cell lung cancer (SCLC). Unfortunately, because of the blood-brain barrier, chemotherapy cannot achieve a sufficient tumoricidal dose. Some patients achieve a complete response (CR) in the chest, only to have brain metastases develop later. The literature shows that researchers have tested the efficacy of prophylactic cranial irradiation (PCI) in patients with limited-stage SCLC who achieved CR after combined chemotherapy and thoracic irradiation. They showed a trend toward improved survival.[1-4] Rosen et al published a study in 1983 that suggested that any prolongation of survival would be restricted to patients with CR, because those with residual extracranial cancer die of systemic metastases.[1] Subsequent to this, PCI was offered or recommended only to patients with CR in the vast majority of clinical trials and guidelines.[5-7] In the modern era, we revisit the benefit of PCI in patients who have an incomplete response (IR) to chemotherapy.

Limitations of past research are often due to the heterogeneous nature of the studies: these include trials that mixed limited and

[1]Department of Radiation Oncology, Allan Blair Cancer Center, Regina, Canada
[2]Department of Radiation Oncology, Centre Clinique de la Porte de Saint Cloud, Boulogne, France
[3]Department of Radiation Oncology, Cross Cancer Institute, University of Alberta, Alberta, Canada
[4]Clinical Research Unit, London Regional Cancer Program, London, Canada
[5]Department of Radiation Oncology, London Regional Cancer Program, University of Western Ontario, London, Canada

Submitted: Mar 4, 2012; Revised: Apr 19, 2012; Accepted: Apr 23, 2012; Epub: June 5, 2012

Address for correspondence: Patricia Tai, MD, Radiation Oncology Department, Allan Blair Cancer Center, Saskatchewan Cancer Agency, Regina, Saskatchewan S4T 7T1 Canada
Fax: 306-766-2845; e-mail contact: ptai2@yahoo.com

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.cllc.2012.04.005

Table 1 Overall Survival in Months for Patients With CR and IR

Variable	Median Survival (mo)	Range (mo)	No. Alive at 1 Year	No. Alive at 2 Years
All Patients (N = 289)	19.7	4.0-248.2	225/289 (77.9%)	108/289 (37.3%)
Patients With CR (n = 185)	21.6	5.0-256.0	160/185 (86.5%)	83/185 (44.9%)
Patients With IR (n = 93)	14.3	4.0-102.6	79/93 (84.9%)	18/93 (23.7%)

Abbreviations: CR = complete response; IR = incomplete response.

extensive stage together for analysis, patients treated with inadequate doses of PCI, and PCI given only to patients with CR in some studies,[5-7] whereas in others PCI was given to both patients with CR and patients with partial response (PR).[8] Separate analysis of CR vs. IR was seldom performed.[9-11] Our group undertook this population-based study, which is unique to our knowledge, because it reports the patterns of recurrence in patients with CR and patients with IR treated with and without PCI. We hope to answer the question of whether PCI in patients with IR is worthwhile or not in the modern era and describe the detailed outcome of patients with IR.

Patients and Methods

After institutional review board approval, a chart review was undertaken for limited-stage SCLC in the Saskatchewan provincial database from 1981 to 2007. We collected data on age, sex, performance status, lactic dehydrogenase and hemoglobin levels, total number of chemotherapy cycles, radiotherapy dose for chest and PCI, timing of chest radiotherapy and PCI, treatment interruptions, toxicities, development of local recurrence, nodal recurrence, distant metastases in different organs, time to disease relapse, and survival status.

Patients had chest radiographs, bone scans, computed tomographic scans, and other nuclear medicine scans if necessary for staging and monitoring of response or recurrence during and after chemotherapy.

Patients were treated with systemic chemotherapy and chest radiotherapy. Typical dose fractionation of locoregional radiotherapy to the chest was 4500 cGy in 25 fractions over 5 weeks, 5000 cGy in 25 fractions over 5 weeks, or 4000 cGy in 15 fractions over 3 weeks (a commonly used Canadian regimen during the time in question).[12] Typical PCI dose fractionation was 2500 cGy in 10 fractions over 2 weeks, 3000 cGy in 15 fractions over 3 weeks, or 3000 cGy in 10 fractions over 2 weeks. The decision to give PCI or not was made by the treating oncologist after discussion with the patient and family.

For the purpose of this study, CR was defined as complete disappearance of all clinical evidence of tumor radiologically. PR was defined as the decrease of the current sum of the products of maximum dimensions of the measured lesions to 50% to 99% of the baseline sum. Minor response (MR) was any decrease short of a 50% response. Hence, patients with IR could have PR or MR. Other response outcomes were stable disease (SD), progressive disease (PD), and unknown.

The cause-specific survival (CSS) was the time interval from the date of diagnosis to the date of death from SCLC, or the last follow-up date for censoring purposes if the patient was alive and still being followed at the time of analysis. The overall survival (OS) was defined as the time from diagnosis to the date of death regardless of cause or the last follow-up date for censoring purposes if the patient was alive and still being followed at the time of analysis. Progression-free interval (PFI) was calculated from the date of diagnosis to the date of symptomatic progression, as we would be more interested in the quality of life of patients rather than asymptomatic radiologic disease progression. CSS, OS, and PFI comparisons of patients who received PCI and patients who did not were made using the Wilcoxon test[13] to detect early separations in survival. Rates of brain metastases and brain recurrences between patients

Figure 1 Overall Survival of the Whole Group of 289 Patients, Divided According to Whether or Not They Received PCI

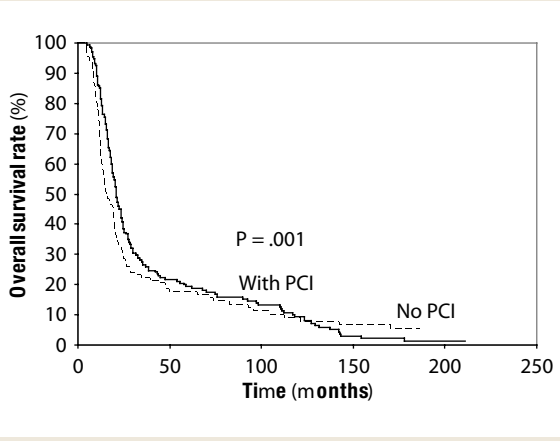

Figure 2 Cause-Specific Survival of the Whole Group of 289 Patients, Divided According to Whether or Not They Received PCI

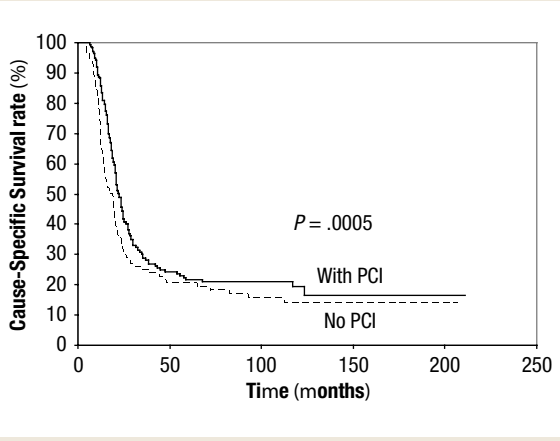

Table 2A Overall Survival Rates With and Without PCI

Variable	PCI Status	1-Year OS (%)	2-Year OS (%)	Wilcoxon Test *P*
All Patients (N = 289)	PCI (n = 177)	84.9	42.6	.0011
	No PCI (n = 112)	65.5	29.6	
Patients With CR (n = 185)	PCI (n = 132)	89.6	49.5	.15
	No PCI (n = 53)	77.8	33.7	
Patients With IR (n = 93)	PCI (n = 42)	69.7	18.1	.32
	No PCI (n = 51)	53.6	25.6	

Abbreviations: CR = complete response; IR = incomplete response; PCI = prophylactic cranial irradiation.

Table 2B CSS Rates With and Without PCI

Variable	PCI Status	1-Year CSS (%)	2-Year CSS (%)	Wilcoxon Test *P*
All Patients (N = 289)	PCI (n = 177)	88.6	48.0	.0005
	No PCI (n = 112)	75.5	32.3	
Patients With CR (n = 185)	PCI (n = 132)	92.5	55.4	.10
	No PCI (n = 53)	84.8	36.8	
Patients With IR (n = 93)	PCI (n = 42)	73.5	21.0	.39
	No PCI (n = 51)	59.3	28.3	

Abbreviations: CR = complete response; CSS = cause-specific survival; IR = incomplete response; PCI = prophylactic cranial irradiation.

Table 3A Rates of Brain Metastases As First Recurrence With and Without PCI in Deceased Patients

Response After Chemoradiation	Treatment	Brain Recurrence	No Brain Recurrence	Fisher Exact Test *P*
CR (n = 177)	PCI (n = 128)	6	122	.18
	No PCI (n = 49)	5	44	
IR (n = 88)	PCI (n = 40)	2	38	.10
	No PCI (n = 48)	8	40	

Abbreviations: CR = complete response; IR = incomplete response; PCI = prophylactic cranial irradiation.

Table 3B Overall Rates of Brain Recurrence Before Death With and Without PCI in Deceased Patients

Response After Chemoradiation	Treatment	Brain Recurrence	No Brain Recurrence	χ^2 Test *P*
CR (n = 177)	PCI (n = 128)	24	104	.002
	No PCI (n = 49)	20	29	
IR (n = 88)	PCI (n = 40)	11	29	.70
	No PCI (n = 48)	15	33	

Abbreviations: CR = complete response; IR = incomplete response; PCI = prophylactic cranial irradiation.

who received PCI and those who did not were determined using χ^2 tests[14] or when cell sizes were small, the Fisher exact 2-tailed test.

Results

From 1981 to 2007, there were 289 patients with limited-stage SCLC treated with curative intent in the western Canadian province of Saskatchewan. The median age was 65 years (range, 38-86 years). The male-female ratio was 1.47 (178:121). Cisplatin-containing chemotherapy was used in 67.5% (195/289) of patients. Eight patients did not have chemotherapy because of comorbidities or patient choice. The response to chemoradiation was CR in 185 patients, PR in 79 patients, MR in 14 patients, SD in 1 patient, PD in 3 patients, and unknown in 7 patients. There were 177/289 (61.2%) patients treated with PCI. Table 1 shows the OS for 185 patients with CR

Table 4 Progression-Free Interval With or Without PCI

Variable		Median (Range) Time to First Symptomatic Recurrence, Any Site	Wilcoxon Test *P*	Median (Range) Time to First Brain Metastatic Symptoms	Wilcoxon Test *P*
All Patients (n = 289)	PCI (n = 177)	16.9 (0.1-65.8)	.0006	20.7 (8.4-40.7)	< .0001
	No PCI (n = 112)	13.2 (1.6-57.9)		10.6 (1.8-24.6)	
Patients With CR (n = 185)	PCI (n = 132)	20.9 (5.4-65.8)	.12	21.1 (8.4-40.7)	< .0001
	No PCI (n = 53)	13.1 (4.6-57.9)		12.4 (4.1-21.0)	
Patients With IR (n = 93)	PCI (n = 42)	12.2 (3.4-35.7)	.39	18.5 (9.5-34.5)	.03
	No PCI (n = 51)	9.4 (1.8-37.1)		8.9 (1.8-14.6)	

Abbreviations: CR = complete response; IR = incomplete response; PCI = prophylactic cranial irradiation.

and 93 patients with IR. Figures 1 and 2 and Table 2 show that for the whole group of 289 patients, PCI was associated with significant OS and CSS benefit ($P = .0011$ and 0.0005, respectively). In the subgroup analysis among the 185 patients with CR, PCI appeared to confer better OS and CSS, although it was not statistically significant ($P = .15$ and 0.10, respectively). For the 93 patients with IR, PCI did not improve OS or CSS ($P = .32$ and 0.39, respectively). For the subgroup of 62 patients with IR who received cisplatin chemotherapy, PCI did not improve OS or CSS ($P = .84$ and 0.98, respectively).

There were 48 patients with CR in whom disease recurred after PCI, 6 of whom had brain as the first site of recurrence, ie, 12.5% of the first recurrence was in the brain despite PCI. For patients with CR without PCI, 45.5% (5/11) had a first recurrence in the brain. The difference is statistically significant ($P = .02$). Among patients with IR, first recurrence in the brain was 6.1% (2/33) with PCI vs. 27.6% (8/29) without PCI ($P = .051$).

Table 3A shows rates of brain metastases as first recurrence, with and without PCI, in the 274 patients who had died. There is a trend for PCI to reduce the incidence rate of brain metastases as the first recurrence site in patients with IR ($P = .10$). Table 3B shows the incidence rates of disease recurrence in patients in whom there was brain recurrence within their lifetimes with and without PCI.

Table 4 shows the time to symptoms of first recurrence at any site and in the brain, with or without PCI. For the whole group of 289 patients, the times to symptoms of first recurrence at any site, with or without PCI were significantly different: 16.9 vs. 13.2 months ($P = .0006$). PCI significantly delayed the time to symptoms of first recurrence in the brain: 20.7 vs. 10.6 months ($P < .0001$). The time to development of the first brain recurrence was almost twice as long for those who received PCI compared with those who did not ($P < .0001$ and 0.03, respectively for patients with CR and those with IR).

Discussion

There had been no national consensus on PCI until 2000, when Drs Jaro Kotalik and Edward Yu wrote the practice guideline for Ontario.[15] The National Cancer Comprehesive Network guideline recommended PCI for patients with 90% to 100% response in the past. The most current guideline, published in 2011, recommends it for all patients with CR and PR—ie, not stable or progressive disease.[16] Our current study gives support for the use of PCI in patients with IR. There is a trend for PCI to reduce the incidence rate of brain metastases as the first recurrence site ($P = .10$). The symptom-free time for brain metastases is significantly longer after PCI ($P = .03$). Brain metastases adversely affect the quality of life for the patient, so PCI is justified even if there is no survival benefit in patients with IR.

Our results are consistent with the literature: the reported median survival after a CR was 18.2 months, with a median survival of 9.9 months for those showing a PR.[17] In another series, the median survival for the complete responders was 11.7 months, whereas the partial responders survived for a median of 9.7 months.[18] The European Organisation for Treatment and Research of Cancer study on extensive SCLC showed a benefit for PCI for patients with any response.[19] More oncologists are applying the same argument on limited-stage disease as well.

Strengths of this study include relatively large patient numbers, analysis of patients with CR and those with IR separately, documented times of first symptomatic recurrence, and consecutive patients from population data reflecting real-world community practice without the enrollment bias of a clinical trial. Weaknesses include the retrospective nature of the study, possible bias with more motivated and fit patients among the PCI group, current better imaging and treatments, and the reduced sample size when looking within CR and IR subgroups. Therefore the study is limited to detect differences between subgroups.

Despite the retrospective nature of this study, it is useful to analyze the value of PCI in patients with CR and those with IR separately. Randomized studies would not be possible in view of the small number of cases of limited-stage SCLC. They also have enrollment bias, with more motivated, fit patients in urban areas joining them.

The main focus of this study is the additive value of PCI in patients who had different degrees of response to chemoradiation because chemotherapy by itself is not effective for preventing brain metastases due to the blood-brain barrier. Therefore the actual chemotherapeutic agents used should not affect our result.

Conclusion

The current study shows that in the overall group of 289 patients with limited-stage SCLC, PCI confers OS and CSS benefit ($P = .0011$ and 0.0005, respectively). Although PCI did not significantly

improve survival in the IR subgroup, brain metastasis with its attendant neurologic complications was effectively prevented or delayed.

Our finding has significant impact on daily clinical practice. First, many questions surround the definition of IR concerning what investigations should be performed and when the response should be measured. With modern imaging and chemotherapy, the measurement of response to chemoradiation is more sophisticated. Even with modern imaging, response measurement is still challenging at times. Residual radiologic abnormalities may be due to fibrosis/collapse/consolidation rather than residual tumor. Second, measuring the response right after chemoradiation may not allow the tumor to shrink completely. Omitting PCI if residual disease is present can end up causing a delay in administering PCI, allowing brain metastases to develop while waiting for CR to occur. This study provides the justification to give PCI to patients with IR.

Because it is difficult to differentiate CR from IR accurately despite modern imaging, and the lung primary tumor may continue to shrink after chemoradiation, PCI could be considered for all patients with limited-stage SCLC who respond to chemoradiation.

Clinical Practice Points

- It is commonly believed that any potential benefit of PCI would be restricted to patients with CR because those with residual extracranial cancer die of systemic metastases. Incomplete responders also have a higher chance of local recurrence.
- In the modern era, new findings in our current study give support for the use of PCI in patients with IR. There is a trend for PCI to reduce the incidence rate of brain metastases as the first recurrence site ($P = .10$). The symptom-free time for brain metastases is significantly longer after PCI (18.5 vs. 8.9 months; $P = .03$).
- Since brain metastases adversely affect the patient's quality of life, PCI is justified even if there is no survival benefit for patients with IR. Because it is difficult to differentiate CR from IR accurately despite modern imaging, PCI could be considered for all patients with limited-stage SCLC who respond to chemoradiation.

Acknowledgments

We thank Saskatchewan Cancer Agency, who provided research grants, and all radiation and medical oncologists in both Allan Blair and Saskatoon Cancer Centers who treated and followed lung cancer patients over the study period.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Rosen ST, Makuch RW, Lichter AS, et al. Role of prophylactic cranial irradiation in prevention of central nervous system metastases in small cell lung cancer. Potential benefit restricted to patients with complete response. *Am J Med* 1983; 74:615-24.
2. Gregor A. Prophylactic cranial irradiation in small cell lung cancer (SCLC) makes a comeback. *Clin Oncol (R Coll Radiol)* 1997; 9:148-9.
3. Arriagada R, Pignon JP, Laplanche A, et al. Prophylactic cranial irradiation for small-cell lung cancer. *Lancet* 1997; 11:349:138.
4. Niiranen A, Holsti P, Salmo M. Treatment of small cell lung cancer. Two-drug versus four-drug chemotherapy and loco-regional irradiation with or without prophylactic cranial irradiation. *Acta Oncol* 1989; 28:501-5.
5. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995; 87:183-90.
6. Bremnes RM, Sundstrøm S, Vilsvik J, et al. Multicenter phase II trial of paclitaxel, cisplatin, and etoposide with concurrent radiation for limited-stage small-cell lung cancerMulticenter phase II trial of paclitaxel, cisplatin, and etoposide with concurrent radiation for limited-stage small-cell lung cancer. *J Clin Oncol* 2001; 19: 3532-8.
7. Woo IS, Park YS, Kwon SH, et al. A phase II study of vp-16-fosfamide-cisplatin combination chemotherapy plus early concurrent thoracic irradiation for previously untreated limited small cell lung cancer. *Jpn J Clin Oncol* 2000; 30: 542-6.
8. Bogart JA, Herndon JE 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004; 59:460-8.
9. Murray N, Sheehan F. Limited stage small cell lung cancer. *Curr Treat Options Oncol* 2001; 2:63-70.
10. Ardizzoni A, Fusco V, Pennucci C, et al. Alternating chemotherapy with cyclophosphamide, doxorubicin, vincristine and cisplatin, etoposide followed by prophylactic cranial and thoracic irradiation for small cell lung cancer (SCLC): long-term results. *Anticancer Res* 1991; 11:681-4.
11. Aroney RS, Aisner J, Wesley MN, et al. Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. *Cancer Treat Rep* 1983; 67:675-82.
12. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; 11:336-44.
13. Wilcoxon F. Individual comparison by ranking methods. *Biometr Bull* 1945; 1:80-3.
14. Analyze a 2 × 2 contigency table. GraphicPad software. Available at: http://www.graphpad.com/quickcalcs/contingency1.cfm. Accessed: May 24, 2012.
15. Kotalik J, Yu E, Markman BR, et al. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001; 50:309-16.
16. National Cancer Comprehensive Network. Available at: http://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Accessed: May 24, 2012.
17. Bishop JF, Kefford R, Raghavan D, et al. Etoposide, carboplatin, cyclophosphamide and vincristine in previously untreated patients with small-cell lung cancer. *Cancer Chemother Pharmacol* 1990; 25:367-70.
18. Broder LE, Selawry OS, Charyulu KN, et al. A controlled clinical trial testing two potentially non-cross-resistant chemotherapeutic regimens in small-cell carcinoma of the lung. *Chest* 1981; 79:327-35.
19. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; 357:664-72.