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Prophylactic Cranial Irradiation after Definitive Chemoradiotherapy for Limited-Stage Small Cell Lung Cancer: Do All Patients Benefit

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Abstract

Purpose—Prophylactic cranial irradiation (PCI) can improve overall survival (OS) and suppress brain metastases (BM) in patients with limited-stage small cell lung cancer (LS-SCLC) after complete response to primary therapy. However, PCI can be toxic. We sought to identify characteristics of patients who may not benefit from PCI.

Methods—We identified 658 patients who received chemoradiotherapy at MD Anderson in 1986–2012; 364 received PCI and 294 did not. Median follow-up time was 21.2 months (range 1.2–240.8 months). Cox proportional hazards regression, competing-risk regression, and Kaplan-Meier analyses were used to identify factors influencing OS and BM.

Results—PCI reduced risks of death [HR 0.73, 95% CI 0.61–0.88, $P=0.001$] and BM [HR 0.54, 95% CI 0.39–0.76, $P<0.001$]. Having tumors ≥ 5 cm increased the risk of BM [HR 1.77, 95% CI 1.22–2.55, $P=0.002$] but not death [HR 1.16, 95% CI 0.96–1.40, $P=0.114$]. Among patients ≥ 70 years with ≥ 5 -cm tumors, PCI did not improve OS [2-year rates 39.4% vs 40.9%, $P=0.739$].

Conclusions—PCI remains standard therapy after complete response to chemoradiotherapy for LS-SCLC. However, older patients may be at risk from comorbidity or extracranial disease. Further work is warranted to identify patients who may not benefit from PCI.

Keywords

small cell lung cancer; chemoradiation; prophylactic cranial irradiation; elderly patients; overall survival; prognostic factors

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INTRODUCTION

Lung cancer is the leading cause of mortality from cancer worldwide [1,2]. Small cell lung cancer (SCLC) is a neuroendocrine tumor that accounts for 15%–20% of all lung cancers, and is well known for its rapid doubling time and potential for widespread metastases [3,4]. Although SCLC initially responds to chemoradiation therapy, the central nervous system is a frequent site of relapse, with a 2-year cumulative risk of developing brain metastases (BM) of >50% and approximately 65% of patients having detectable BM on autopsy [5–7].

The role of prophylactic cranial irradiation (PCI) in reducing the risk of developing BM has been extensively studied in patients with limited-stage SCLC that responds completely to definitive chemoradiotherapy. A seminal meta-analysis of 7 randomized trials conducted in 1977–1995 showed that PCI not only decreased the incidence of BM among such patients but also increased their overall survival (OS) rates by approximately 5% at 3 years [8]. A second meta-analysis with nearly identical results confirmed that PCI reduced the incidence of BM and provided a survival advantage [9]. However, neither of these studies addressed its potential toxicity.

PCI is known to be associated with acute toxic effects including alopecia, nausea, headache, and fatigue [10]. However, these symptoms are typically self-limited and resolve over time. Long-term toxic effects have been more difficult to assess and quantify, and thus reports are limited. However, in an early retrospective study of 20 long-term survivors of SCLC (18 of whom had received PCI), 15 patients (75%) showed impaired neurocognitive function manifesting as memory loss, ataxia, and weakness [11]. Other studies have identified factors that increase the risk of neurotoxicity after PCI, including age >60 years, total dose >30 Gy, and receipt of chemotherapy concurrent with the PCI [12–15]. In RTOG 0212, approximately 62% of patients who received 25 Gy of PCI went on to develop chronic neurotoxicity, and age was the most significant risk factor [16,17].

A recent large retrospective analysis of patients aged >70 years with limited-stage SCLC from the National Cancer Database showed that chemoradiotherapy conferred an OS benefit over chemotherapy alone [18]. These findings suggest that, for elderly patients who can tolerate the toxicity of combined chemoradiotherapy, the intent of treatment should be achievement complete response. However, the role of PCI for such patients has yet to be addressed. In this study, we sought to identify factors that correlate with brain recurrence and survival in patients with limited-stage SCLC who received definitive chemoradiotherapy and to identify subgroups of such patients for whom PCI may be more (or less) beneficial. We hypothesized that patients who were 70 years old may not show a survival benefit after PCI owing to their susceptibility to severe toxicity from PCI and possibly also greater risks of death from other comorbid conditions.

PATIENTS AND METHODS

Patient Selection and Data Collection

After obtaining institutional review board approval, we identified 658 patients with limited-stage SCLC who had received definitive chemoradiotherapy at The University of Texas MD

Anderson Cancer Center from 1985 through 2012. Information on patient demographics, diagnostic and staging work-up, treatment, and treatment response was extracted from medical records. Primary tumor size at the time of treatment initiation was measured by a radiologist on diagnostic images (when available) as the largest dimension of the primary parenchymal tumor or, if the primary tumor could not be visualized, the largest regional node.

Treatment Characteristics

All patients had received radiotherapy doses of at least 45 Gy to the primary intrathoracic disease. Most patients received concurrent chemotherapy with the radiation. However, some patients (generally those with poor performance status or large lesions) were given induction chemotherapy before concurrent chemoradiotherapy, and others received induction chemotherapy followed by radiotherapy. Radiotherapy typically consisted of 45 Gy in 30 fractions delivered twice daily to the entire involved field; 70 Gy in 35 fractions delivered once daily; or 61.2 Gy delivered in 34 fractions, with the first 18 fractions delivered daily to the involved field followed by 16 fractions delivered twice daily to a reduced field based on response. Patients who received surgery as part of treatment were excluded from this analysis. Disease was staged in all cases with computed tomography (CT) and, after 2000, with positron emission tomography (PET) or PET/CT. All patients underwent brain scanning as part of the staging process, most with magnetic resonance imaging except for a few patients who underwent brain CT because of having claustrophobia or a cardiac pacemaker.

The standard practice at the authors' institution is to recommend PCI for all patients with limited-stage SCLC whose intrathoracic disease has responded to local therapy and who do not have evidence of distant metastasis. PCI typically consisted of 25 Gy delivered in 10 daily fractions to the whole brain using opposed lateral or left anterior oblique/right anterior oblique beams. PCI was typically initiated 4–6 weeks after completion of primary chemoradiotherapy if disease restaging examinations at that time showed response of intrathoracic disease and no evidence of distant metastasis.

Statistical Analysis

Pearson's chi-square tests were used to assess measures of association in frequency tables, and a nonparametric test of medians was used for between-group comparisons of continuous variables. We compared demographic and treatment-related characteristics between patients who received PCI and those who did not. Next, we used the Kaplan-Meier method to calculate cumulative freedom from BM and OS over time. The time points in this study were calculated from the date of treatment initiation to the date BM was diagnosed, or the date of death or last clinic follow-up visit, as applicable. Cox proportional hazards regression analyses were used to identify factors potentially associated with OS. To analyze freedom from BM, competing-risks regression analysis was used, with the endpoint being development of BM and the competing risk being development of extracranial metastasis. Log-rank tests were used to compare freedom from BM and OS between various groups. Data were analyzed with Stata/MP 14.0 (StataCorp LP, College Station, TX), and $p < 0.05$ was considered to indicate statistically significant differences.

RESULTS

Of the 658 patients who received definitive chemoradiotherapy for limited-stage SCLC included in this analysis, 364 (55.3%) received PCI and 294 (44.7%) did not. Those who did not receive PCI showed no response or early disease progression, had poor performance status, or chose to decline PCI against medical advice. The median age of all patients was 62 years (range 27–95 years), and 151 (22.9%) were ≥70 years old at when treatment was begun. Tumor size was known for most patients (601 [91.3%]); 265 (44.1%) had primary intrathoracic disease that was <5 cm in diameter at the time of treatment initiation, and 336 (55.9%) had disease ≥5 cm. When demographic and treatment characteristics were compared between patients who received PCI and those who did not, patients who received PCI were more likely to have had a Karnofsky performance status (KPS) score of 80 or higher (87.4% vs. 78.6%; $p=0.002$). Patient and treatment characteristics are summarized in Table 1.

The median follow-up time for all patients was 21.2 months (range 1.2–240.8 months); the median OS time was 24.5 months; the 2-year OS rate was 51.3%; and the 5-year OS rate was 23.7%. Rates of disease-free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and BM-free survival (BMFS) at 2 years and 5 years were: DFS 38.1% and 30.9%; LRFS 59.9% and 51.5%; DMFS 48.9% and 39.5%; and BMFS 76.3% and 71.4%.

On univariate competing risk regression analysis, where the primary outcome was development of BM and the competing risk was development of extracranial metastatic disease, the only factor associated with increased risk of BM was primary tumor size ≥5 cm (subdistribution hazard ratio [SHR] 1.66, 95% confidence interval [CI] 1.15–2.40, $p=0.007$ vs. size <5 cm). On the other hand, being treated with 2D or 3D conformal radiotherapy techniques (rather than intensity-modulated radiotherapy [IMRT]), being treated after 2000, and receipt of PCI were all associated with *reduced* risk of developing BM (Table 2). On multivariate competing risk regression analysis, only receipt of PCI (SHR 0.57, 95% CI 0.41–0.79, $p=0.001$ vs. no PCI) and use of 2D or 3D radiation techniques (SHR 0.46, 95% CI 0.30–0.73, $p=0.001$ vs. IMRT) were associated with a reduced risk of developing BM.

On univariate Cox regression analysis, where the primary outcome was mortality from any cause, factors associated with increased overall mortality included age ≥70, KPS <80, and the use of induction chemotherapy followed by sequential radiotherapy. Factors associated with reduced risk of overall mortality were treatment with 2D or 3D conformal radiotherapy techniques (vs. IMRT), treatment after 2000, and receipt of PCI (Table 2). On multivariate analysis, treatment with 2D or 3D radiotherapy techniques (SHR 0.79, 95% CI 0.64–0.99, $p=0.037$ vs. IMRT) and receipt of PCI (SHR 0.76, 95% CI 0.63–0.91, $p=0.003$ vs. no PCI) remained associated with reduced overall mortality.

In considering both the total incidence of BM and the time to diagnosis of BM, patients who received PCI developed BM less often (18.1% vs. 24.8%, $p=0.036$), and when BM did develop, they did so at a longer median interval from the completion of primary chemoradiotherapy in patients who had received PCI than in those who did not (PCI 16.8

months [range 5.6–73.3 months] vs. no PCI 8.2 months [range 2.2–36.6 months], $p<0.001$). Overall, receipt of PCI led to reduced risks of death [HR 0.73, 95% CI 0.61–0.88, $p=0.001$] and BM [HR 0.54, 95% CI 0.39–0.76, $p<0.001$]. Receipt of PCI (vs. no PCI) was associated with significantly increased BMFS and OS (Fig. 1) in the entire group. At 2 years, BMFS rates were 80.6% with PCI vs. 70.9% without PCI (log rank $p<0.001$). No differences were found in DMFS or LRFS. However, the 2-year DFS rates were also better with PCI (40.7% with vs. 34.9% without PCI, logrank $p=0.013$), as were the 2-year OS rates (56.9% with vs. 43.8% without PCI, log rank $p<0.001$).

Among the 151 patients aged ≥ 70 years, the median OS time was 20.3 months, the 2-year OS rate was 42.4%, and the 5-year OS rate was 17.5%. The 2-year BMFS rate for patients ≥ 70 years old was 75.7%. The influence of PCI on OS in patients ≥ 70 years differed by primary tumor size. Specifically, receipt of PCI was associated with a borderline trend toward improved 2-year OS when tumor size was <5 cm (62.5% vs. 35.8%, $p=0.056$, but not when tumor size was ≥ 5 cm (39.4% vs. 40.9%, $p=0.739$) (Fig. 2). Similarly, receipt of PCI for patients aged ≥ 70 years did not affect 2-year BMFS rates for those with tumors <5 cm (88.9% vs. 84.5% for no PCI, $P=0.148$) or tumors ≥ 5 cm (92.8% vs. 72.5% for no PCI, $p=0.122$).

DISCUSSION

Overall, outcomes and the effectiveness of PCI with regard to BMFS and OS for the patients in this analysis were quite similar to findings reported in two prior meta-analyses establishing PCI as a mainstay of treatment for limited-stage SCLC [8,9]. PCI was associated with both reduced risk of developing BM and improved OS in the entire group. However, we did find that risk of developing BM was significantly increased when the primary tumor was large (≥ 5 cm) at diagnosis. This observation is consistent with prior studies reporting links between higher pathologic tumor stage, which depends on tumor size and locoregional spread, and increased risk of developing BM. In one study, the frequency of BM to be 6.25% (2/32) among patients with TNM pathologic stage I disease, 28.2% (11/39) among those with stage II disease, and 29.1% (16/55) among those with stage III disease (19). Other trials have reported similar findings, with $<10\%$ of pathologic stage I tumors with subsequent BM compared with $>20\%$ of pathologic stage II or III tumors [20–23]. In those studies, tumor size could be measured directly after resection, in contrast to our study, which did not include patients with resected tumors; rather, tumors size was measured on diagnostic CT scans. Tumor size was not associated with poor OS in our study; however, our findings, along with prior studies, suggest that large tumors may indicate a more aggressive phenotype with increased risk of metastases, especially to the brain, and reinforces the use of TNM staging as well as the traditional 2-stage system to help guide clinical decisions [24,25].

Treating elderly cancer patients can often be challenging, as they typically present with other medical issues that can complicate therapy. Moreover, even though 67% of patients with lung cancer are aged ≥ 65 years, they represent only about 35% of patients enrolled in clinical trials of lung cancer [26]. Older patients are often disqualified from participating in clinical trials because of other comorbid conditions or poor performance status, leading to

frequent misrepresentation of such patients. In this study, we sought specifically to look at the benefit of PCI for patients aged ≥ 70 years.

Although PCI was found to be beneficial in terms of BMFS and OS for the entire group, it did not confer a benefit in either OS or BMFS among patients ≥ 70 years old with large (≥ 5 cm) primary tumors. Not surprisingly, age ≥ 70 years was an independent risk factor for increased overall mortality in our analysis, and a KPS score <80 also predicted poor outcome. We hypothesize that such patients do not benefit from PCI because they are at increased risk of death from other comorbid conditions and may not be able to tolerate the side effects of chemoradiotherapy compared with their younger counterparts [28–30]. Our post hoc analysis of cause of death according to age showed that more patients aged ≥ 70 years died of intercurrent disease than did patients aged <70 (13.9% vs. 5.9%, $p=0.005$), and the proportion of patients with unknown cause of death was larger in the older group as well (21.8% vs. 17.1%, $p=0.005$). RTOG 0212 showed that elderly patients are also more susceptible to PCI-induced neurotoxicity than are younger patients; indeed, increasing age was the most significant predictor of chronic neurotoxicity ($p=0.005$) [16,17]. Because patients ≥ 70 years old account for about 60% of new cases of limited-stage SCLC, clinicians should be aware of the risks of toxicity from PCI and be prepared to discuss the relative risks and benefits with patients on an individual basis [31].

Our study further emphasizes the importance of exploring treatment strategies aimed at reducing PCI-induced neurotoxicity, including the use of memantine to improve cognitive function after PCI and conformal avoidance of the hippocampus during PCI, which may improve memory and quality of life [32,33]. Initial reports from patients enrolled in RTOG 0933, a phase II study with historical comparisons of patients who underwent whole-brain irradiation for up to 10 BM from any type of cancer, suggest that about 8.6% of all patients presented with perihippocampal BM at diagnosis [34]. Among patients with SCLC, the incidence of hippocampal BM is generally about 5% both at diagnosis and after PCI [34,35], indicating that the risk of developing metastatic disease in the hippocampal region is relatively low; although another group found this rate to be higher (18.2%), that study included only 6 patients with SCLC [36]. NRG-CC003 (NCT02635009), an ongoing randomized phase II/III trial, is testing whether PCI with hippocampal avoidance will result in fewer intracranial relapses for patients with SCLC. If the two types of PCI are shown to be equally effective, perhaps PCI with hippocampal avoidance should be recommended for older patients with SCLC.

Three-dimensional conformal radiotherapy and IMRT are widely used in both private and academic settings to treat thoracic disease in limited-stage SCLC. Although IMRT plans tend to restrict the overall dose delivered to the esophagus and thus reduce the risk of esophagitis [37], IMRT carries an increased risk of severe pneumonitis, which increases mortality [38]. In the current study, multivariate analysis identified receipt of IMRT as a negative prognostic factor for OS, which could reflect higher rates of severe pneumonitis in this population; indeed, another post hoc analysis showed that patients aged ≥ 70 were more likely to have had grade 3–4 pneumonitis than were patients <70 (11.3% vs. 4.8%, $p=0.008$). Although IMRT may offer improved dosimetry, the findings from the current analysis suggest that this does not correlate with improved survival. In the ongoing trial RTOG 0538,

patients with limited-stage SCLC are being randomly assigned to receive different doses of thoracic radiotherapy, some by IMRT and others by 3D conformal techniques. Comparing outcomes and toxic effects between patients treated with IMRT versus 3D conformal radiotherapy will provide much-needed insight about the benefits and risks associated with use of either technique for treating limited-stage SCLC.

An important strength of this study is that unmeasured variables such as staffing, infrastructure, radiation treatment strategies, and technical parameters were generally consistent over time, as this population was treated at a single tertiary referral comprehensive cancer center. Minimizing variables such as these helps to better isolate risk factors and trends to be identified. Conversely, the single-institution nature of this study is also a limitation in that our findings may not be applicable to other centers. Indeed, a distinct selection bias was present in the baseline characteristics of patients who present to a tertiary referral comprehensive cancer center. Also, the retrospective nature of our study is subject to confounding influences of other untested variables on the risk factors we identified.

In conclusion, the results of this retrospective study of a large number of patients with limited-stage SCLC treated at a single institution suggest that elderly patients with large tumors may not benefit from PCI in terms of OS, even after a complete response to definitive chemoradiotherapy. These findings, plus the increased risk of neurocognitive side effects among older patients, warrant caution in recommending PCI for patients aged 70 years, especially those with large tumors.

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Fig. 1.

Brain metastasis-free survival (left) and overall survival (right) by receipt of prophylactic cranial irradiation (PCI) for patients with limited-stage small cell lung cancer treated with definitive chemoradiotherapy ($p < 0.001$).

Fig. 2. Overall survival by receipt of prophylactic cranial irradiation (PCI) for patients 70 years old with a primary tumor <5 cm (left) ($p=0.056$) or >5 cm (right) ($p=0.739$).

TABLE 1

Patient and treatment characteristics

Characteristics	All Patients (n=658)	Patients Who Received PCI (n=364)	Patients Who Did Not Receive PCI (n=294)	P Value*
Age, median (range), years	62 (27–95)	61 (34–85)	64 (27–95)	0.061
Race/Ethnicity, no. (%)				0.920
White, non-Hispanic	552 (83.9)	307 (84.3)	245 (84.3)	
White, Hispanic	31 (5.7)	18 (4.9)	13 (4.4)	
Black/African American	60 (9.1)	30 (8.2)	30 (10.2)	
Asian/Pacific Islander	10 (1.5)	6 (1.6)	4 (1.4)	
Other	5 (0.8)	3 (0.8)	2 (0.7)	
Sex, no. (%)				0.731
Male	342 (52.0)	187 (51.4)	155 (52.7)	
Female	316 (48.0)	177 (48.6)	139 (47.3)	
Karnofsky Performance Status, no. (%)				0.002
80	550 (83.6)	319 (87.4)	231 (78.6)	
<80	108 (16.4)	45 (12.6)	63 (21.4)	
Treatment Era, no. (%)				0.116
<2000	320 (48.6)	167 (45.9)	153 (52.0)	
2000	338 (51.4)	197 (54.1)	141 (48.0)	
Treatment Sequence, no. (%)				0.187
Concurrent CRT	394 (59.9)	229 (62.9)	165 (56.1)	
Induction chemo → CRT	137 (20.8)	72 (19.8)	65 (22.1)	
Induction chemo → RT	127 (19.3)	63 (17.3)	64 (21.8)	
Total XRT Dose, median (range)	45 (45–70)	45 (45–70)	45 (45–70)	0.750
XRT Fractionation, no. (%)				0.087
Once Daily	290 (44.1)	150 (41.2)	140 (47.6)	
Twice Daily	357 (54.3)	210 (57.7)	147 (50.0)	
Mixed	11 (1.7)	4 (1.1)	7 (2.4)	
XRT Technique, no. (%)				0.053
2D/3D	472 (71.3)	250 (68.7)	222 (75.5)	
IMRT	186 (28.7)	144 (31.3)	72 (24.4)	
Primary Tumor Size, no. (%)				0.439
<5 cm	265 (40.3)	148 (40.7)	117 (39.8)	
5 cm	336 (51.1)	177 (48.6)	159 (54.1)	
Missing	57 (8.6)	39 (10.7)	18 (6.1)	
Subsequent Brain Metastases, no. (%)				0.036
Yes	139 (21.1)	66 (18.1)	73 (24.8)	
No	519 (78.9)	298 (81.9)	221 (75.2)	
Time to Brain Metastases,				<0.001
	11 (2.2–73.3)	16.8 (5.6–73.3)	8.2 (2.2–36.6)	

Characteristics	All Patients (n=658)	Patients Who Received PCI (n=364)	Patients Who Did Not Receive PCI (n=294)	P Value*
months; median (range)				

PCI, prophylactic cranial irradiation; CRT, chemoradiotherapy; chemo, chemotherapy; RT, radiotherapy; 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy.

* Pearson's chi-square tests were used for between-group comparisons of categorical variables, and median tests were used for between-group comparisons of continuous variables. For all comparisons, $p < 0.05$ was taken to be statistically significant.

TABLE 2

Univariate analyses of factors associated with developing brain metastases and overall survival in patients with limited-stage small cell lung cancer after definitive chemoradiotherapy

Variable	Development of BM ¹ SHR [95% CI]	P Value ¹	Overall Mortality ² HR [95% CI]	P Value ²
Age				
<70	Reference	—	Reference	—
70	1.07 [0.71–1.62]	0.734	1.34 [1.08–1.66]	0.007
Race/Ethnicity				
White, non-Hispanic	Reference	—	Reference	—
All Others	1.35 [0.90–2.04]	0.145	0.91 [0.71–1.16]	0.438
Sex				
Female	Reference	—	Reference	—
Male	1.00 [0.72–1.4]	0.981	1.09 [0.91–1.30]	0.345
Karnofsky Performance Status				
80	Reference	—	Reference	—
<80	0.89 [0.52–1.52]	0.668	1.41 [1.09–1.83]	0.010
Treatment Era				
<2000	Reference	—	Reference	—
2000	0.57 [0.40–0.80]	0.001	0.76 [0.63–0.90]	0.002
Treatment Sequence				
Concurrent CRT	Reference	—	Reference	—
Induction chemo → CRT	1.36 [0.92–2.02]	0.120	1.09 [0.87–1.37]	0.431
Induction chemo → RT	1.14 [0.75–1.75]	0.534	1.55 [1.25–1.92]	<0.001
XRT Fractionation				
Once Daily	Reference	—	Reference	—
Twice Daily	1.01 [0.72–1.41]	0.971	0.75 [0.63–0.90]	0.002
Mixed	1.02 [0.25–4.17]	0.981	1.08 [0.53–2.18]	0.831
XRT Technique				
IMRT	Reference	—	Reference	—
2D/3D	0.46 [0.29–0.71]	0.001	0.73 [0.59–0.91]	0.004
Primary Tumor Size				
<5 cm	Reference	—	Reference	—
5 cm	1.66 [1.15–2.40]	0.007	1.16 [0.96–1.40]	0.114
Receipt of PCI				
No	Reference	—	Reference	—
Yes	0.56 [0.40–0.78]	0.001	0.73 [0.61–0.88]	0.001

SHR, subdistribution hazard ratio; CI, confidence interval; PCI, prophylactic cranial irradiation; CRT, chemoradiotherapy; chemo, chemotherapy; RT, radiotherapy; 2D, two-dimensional radiotherapy; 3D, three-dimensional radiotherapy; IMRT, intensity-modulated radiotherapy.

¹Competing risk regression analysis; primary outcome is development of BM and competing risk is development of extracranial metastatic disease.

²Cox regression analysis was for risk of death by any cause. For all comparisons, $P < 0.05$ was taken to indicate statistically significant differences.