

# Prophylactic Cranial Irradiation in Limited-Stage Small-Cell Lung Cancer: A Retrospective Analysis

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## Abstract

**Objective:** It is well established that prophylactic cranial irradiation (PCI) decreases significantly the incidence of brain metastases (BM) and increases overall survival in limited-stage small-cell lung cancer (LS-SCLC) patients with complete response to induction therapy. The aim of this study was to complete a review analysis of PCI use among patients diagnosed with LS-SCLC in a community hospital.

**Method:** A retrospective review of medical charts of patients diagnosed with LS-SCLC between January 1997 and December 2002 at a local community hospital in Fargo, North Dakota, was done to determine which of these patients subsequently received PCI. Data on patient's age, gender, body mass index at diagnosis, SCLC anatomical site, other comorbidities at diagnosis, treatment of SCLC, chemotherapeutic agents used at diagnosis of SCLC, response to induction treatment, PCI use, reason(s) for no PCI, BM status, BM site, metastases to other sites, and survival were abstracted.

**Results:** A total of 32 patients with LS-SCLC were identified. Twenty-three (71.9%) of the patients received concurrent chemotherapy and radiation therapy. Of the remaining 9 (28.1%) patients, 6 (18.7%) did not receive any treatment because of poor performance status, and 3 (9.4%) received only chemotherapy because of coexisting comorbidity. Thirteen (40.6%) of the patients achieved a complete response but only 4 (30.8%) patients had PCI. Among the 9 (69.2%) patients who appeared eligible to receive PCI, 1 (11.2%) refused, 4 (44.4%) had coexisting comorbidities, and 4 (44.4%) had no notes indicating why they did not receive PCI. Of those who had PCI, only 1 (25%) patient developed BM 35 months later.

**Conclusion:** This review found that although only a few patients were eligible to receive PCI, nevertheless, the benefits could be significant. We concluded that oncologists should be more willing to offer this procedure.

**Keywords:** Limited-stage small-cell lung cancer, treatment response, prophylactic cranial irradiation, brain metastasis, survival

## Introduction

An estimated 173,770 new cases of lung cancer will be diagnosed in 2004<sup>1</sup> and approximately 25% of these cases will be diagnosed as small-cell lung cancer (SCLC). SCLC is the most aggressive type of lung cancer. Nearly one third of the patients with SCLC present with limited-stage disease (LS-SCLC).<sup>2</sup> In patients with LS-SCLC, chemotherapy combined with thoracic radiotherapy yields complete response rates of 50–85%, a median duration of survival of 12–20 months, and 2-year disease-free survival rates of 15–40%.<sup>3–5</sup> Five-year survival rates may exceed 20% for patients who have a complete response.<sup>5</sup> With combined treatment, the risk of a thoracic recurrence decreases; as a consequence, the brain is the most common site of relapse. Although only 10% of patients have brain metastases (BM)

at the time of diagnosis, the cumulative incidence at 2 years is more than 50%.<sup>6,7</sup>

The central nervous system is refractory to chemotherapeutic agents because of the blood-brain barrier. Therefore, the prognosis after BM is very poor regardless of brain radiation therapy.<sup>8</sup> This led Hansen in the early 1970s to suggest prophylactic cranial irradiation (PCI) to prevent BM.<sup>9</sup> PCI is known to be effective in reducing the frequency of occurrence of brain metastases. In earlier studies, up to 20% of SCLC patients treated without PCI developed isolated brain metastases.<sup>10</sup> More recent series have reported distinctly higher rates of isolated brain metastases, in the range of 45–54% at 2–3 years in patients treated without PCI. PCI also improves both overall survival and disease-free survival among patients with LS-SCLC in complete remission.<sup>11</sup> Many studies showed a 5–6% absolute benefit in overall survival at 3 years.<sup>11–15</sup> A meta-analysis indicated that PCI in patients with LS-SCLC who achieved complete remission decreased the

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risk of developing BM by 50% and also resulted in a 5% improvement in survival after 3 years.<sup>11</sup>

Glantz et al<sup>14</sup> suggested that PCI be restricted to patients with limited-stage disease at presentation, and a complete response to initial therapy. A review of retrospective data suggested that any prolongation of survival would be restricted to patients in complete remission, because those with residual extracranial cancer die of systemic cancer.<sup>10</sup> In a retrospective study,<sup>11</sup> patients who did not achieve a complete response to initial therapy had a very high rate of brain metastases, irrespective of the use of PCI.

The aim of this study was to complete a review analysis of PCI use among LS-SCLC in a community hospital.

### Materials and Methods

A retrospective analysis of medical charts of patients with LS-SCLC identified from the cancer registry at a local community hospital in Fargo, North Dakota, between January 1997 and December 2002 was conducted after the Institutional Review Board approved the study. The information was abstracted from the patients' medical charts. Inclusion and exclusion criteria for this study are presented below:

#### Inclusion criteria

- 1) All patients with LS-SCLC using a pathology report present in the medical records.

#### Exclusion criteria

- 1) Diagnosis of any cancer other than primary SCLC;
- 2) Extensive-stage SCLC.

Demographic covariates analyzed included: age, gender, body mass index at diagnosis, SCLC anatomical site, treatment type, chemotherapeutic agents used at SCLC diagnosis, response to induction treatment, coexistence of other comorbidities, PCI use, main reason if no PCI, BM status, BM site, metastases to other sites, and survival. Most of our patients were smokers (98%) and social alcohol drinkers (95%). The majority (96%) of the population in the Fargo-Moorhead area are white, thus we limited our analysis to this group. Patients discharged with SCLC (162.x) using the International Classification of Diseases, Ninth Revision<sup>15</sup> codes among any diagnosis field was used to identify lung cancer.

Descriptive statistics were used to analyze patient demographics and medical characteristics. Analyses were performed using SAS Software v8.0 (SAS Institute, Cary, NC 25513).

### Results

We identified 32 patients with LS-SCLC who met our criteria. The patient characteristics are shown in Table 1. The mean (±SD) age at diagnosis for these patients was 67.6±9.8. The majority (53.1%) of the patients were males, and most (59.4%) of the SCLC at diagnosis was located in the right lobe. Twenty-three (71.9%) patients received the standard treatment—chemotherapy and radiation therapy—which consists of 4–6 cycles of chemotherapy with early concurrent thoracic radiotherapy. Thoracic radiotherapy was given,

**Table 1.** Patient Characteristics

| Characteristic  | Total, N=32 (%)      |
|---|----------------------|
| Age, median (range)                                   | 69 yr (45–84)*       |
| Gender  |                      |
| Male  | 17 (53.1)            |
| Female  | 15 (46.9)            |
| Body Mass Index at Diagnosis                          |                      |
| Normal (<25 kg/m <sup>2</sup> )                       | 14 (43.7)            |
| Overweight (≥25 kg/m <sup>2</sup> )                   | 18 (56.3)            |
| Small-Cell Lung Cancer Site at Diagnosis              |                      |
| Right lobe  | 19 (59.4)            |
| Left lobe   | 13 (40.6)            |
| Other Comorbidities at Diagnosis                      |                      |
| None  | 6 (18.7)             |
| Hypertension  | 13 (40.6)            |
| Cerebral vascular accident                            | 3 (9.4)              |
| Hypertension and diabetes                             | 2 (6.2)              |
| COPD and heart failure                                | 1 (3.1)              |
| Multiple conditions†                                  | 8 (25)               |
| Treatment of SCLC                                     |                      |
| Chemotherapy and radiation therapy                    | 23 (71.9)            |
| Chemotherapy  | 3 (9.4)              |
| No treatment  | 6 (18.7)             |
| Chemotherapeutic Agents                               |                      |
| Cisplatin and VP-16                                   | 18 (59.4)            |
| Cisplatin and paclitaxel                              | 1 (3.1)              |
| Cisplatin and etoposide                               | 1 (3.1)              |
| Carboplatin and etoposide                             | 1 (3.1)              |
| VP-16 and etoposide                                   | 1 (3.1)              |
| Cisplatin and taxol and VP-16                         | 1 (3.1)              |
| Cisplatin and taxol and etoposide                     | 1 (3.1)              |
| Response to Treatment                                 |                      |
| Complete response                                     | 13 (40.6)            |
| Partial or no response                                | 19 (59.4)            |
| PCI When Complete Response                            |                      |
| Yes   | 4 (30.8)             |
| No  | 9 (69.2)             |
| Reason for no PCI When Complete Response              |                      |
| Patient refused                                       | 1 (11.2)             |
| Coexisting of other comorbidities†                    | 4 (44.4)             |
| Not reported by oncologist                            | 4 (44.4)             |
| Brain Metastasis                                      | 7 (21.9)             |
| Single  | 5 (15.6)             |
| Multiple  | 2 (6.3)              |
| None  | 25 (78.1)            |
| Brain Metastasis Site                                 |                      |
| Cerebrum  | 4 (57.1)             |
| Missing   | 3 (42.9)             |
| Corticosteroid Use for Neurological Symptoms          |                      |
| Yes   | 4 (57.1)             |
| No  | 3 (42.9)             |
| Metastasis, Other Sites                               |                      |
| Bones   | 1 (7.1)              |
| Liver, malignant pleural effusion, adrenals, pancreas | 13 (92.9)            |
| Overall Survival                                      | 22 mo (range: 12–35) |

\* Multiple conditions is a combination of at least 3 of the following problems: arthritis, ulcer, hypothyroidism, dementia, tobacco use disorder, neurohypophysitis disease, anemia, atrial fibrillation, high PSA, breast cancer.

† Comorbidities consist of the combination of several of those mentioned in the table.

1.5 Gy twice daily repeated twice with a 3-week interval to give 45 Gy in 9 weeks. Thirteen (40.6%) patients achieved complete response, and, therefore, were eligible for prophylactic cranial irradiation. Only 4 of these patients (30.8%) received PCI and 9 (69.2%) patients did not. One patient (11.2%) refused PCI, 4 patients (44.4%) had several coexisting comorbidities which precluded them from receiving PCI, and for 4 of the patients (44.4%), no particular reason for not administering PCI was reported by the oncologist in the medical chart. The patients who received PCI had a dose of 25 Gy in 10 fractions over 2 weeks given within 6–8 weeks of the complete remission. Only 1 (25%) developed BM and metastases to the liver and bones. The overall median survival was 22 (12–35) months.

## Discussion

Prophylactic cranial irradiation is known to be effective in significantly reducing the incidence of brain metastases and improves overall survival in patients with LS-SCLC in complete remission. This review found that more than 40% of patients eligible for PCI did not receive it. The reason for not administering PCI was not apparent after reviewing patients' medical charts.

While the impact on survival in SCLC over the last 20 years has been limited, the large number of trials conducted has improved the approach to treatment. Standard treatment consists of a combination of chemotherapy and thoracic irradiation of the site of the primary tumor. Most (71.9%) of the patients in our review study were given standard treatment with the majority of patients receiving 4–6 cycles of VP-16 and cisplatin and twice-daily thoracic radiation therapy. VP-16 and cisplatin, each of which has some single-agent activity in SCLC, have been shown to be remarkably synergistic in SCLC.<sup>16–19</sup> It has been shown also that treatment with VP-16 and cisplatin combination is superior to the combination of cyclophosphamide, doxorubicin, and vincristine in any schedule in the treatment of patients with limited-stage disease.<sup>20</sup>

In this study, we found that PCI was given to patients within 2 months after induction treatment. Suwinski et al<sup>21</sup> found that studies in which PCI was given within 60 days of induction treatment displayed a more clearly linear dose-response relation. The reduction in brain metastases risk was close to 80% at a dose level of 30–35 Gy. This decrease reaches only 60% when PCI was given after 60 days from the beginning of induction treatment.

Several studies<sup>7,22–24</sup> found no significant cognitive impairment related to PCI administration. Most of the patients had significant neuropsychological impairment before PCI. In our review, we have not found any evidence of neurotoxicity after patients received PCI. We also found no evidence of neuropsychological impairment, but it is possible that our follow-up was not long enough and the sample size was too small to draw such a conclusion. The literature suggests that 56–92% of patients with advanced SCLC and brain metastases exhibit significantly improved neurological symptoms following treatment with corticosteroids and conventional cranial irradiation.<sup>26,27,28,29,30,31</sup> In our review, 4 patients (57.1%) with BM had documentation of corticosteroid treatment.

Although data concerning the use of PCI in patients with extensive disease are not as robust as for limited disease, Kotalik et al<sup>32</sup> recommended PCI in both limited and extensive SCLC for patients who achieved a complete remission with induction therapy. It has been suggested that PCI might also be beneficial in patients with a good partial response.<sup>11</sup> None of the patients with extensive SCLC had received PCI in our institution.

It has been shown that age is not a significant prognostic variable in LS-SCLC patients<sup>25</sup>; this is consistent with our finding as well.

Despite the known chemosensitivity of SCLC (response rates of 70–80% with up to 50% complete response with combination chemotherapy in patients with LS-SCLC), the majority of the patients with LS-SCLC die from recurrent cancer.<sup>20</sup> In our study, at least 53% of the patients died from their coexisting comorbidities.

The discordance between our findings and recommended guidelines for PCI use could be explained by several possible factors. Numerous studies have shown that an age of 65 or older in cancer patients is a risk factor for inadequate treatment.<sup>33–35</sup> Oncologists may be concerned about the possibility of increasing vulnerability to neurological impairment in older patients who receive PCI. It is also possible that oncologists are too conservative in PCI use. It is only in recent years that oncologists have agreed on specifically when and which patients qualify for PCI. Therefore, the incorporation of best evidence and clinical practice guidelines might be slow in altering clinical care patterns.

To improve oncologists' compliance with the guidelines, we need to encourage group interactive learning, reminders, audits, and feedback, which have been shown to be highly effective but infrequently used.<sup>36,37</sup> Commonly used continuing medical education methods like lectures and distributing printed materials alone have little or no success in changing oncologist clinical practice.

In summary, this review found that of patients eligible to receive PCI, a significant percentage failed to receive treatment with this modality. Given the proven benefits of PCI, one wonders whether standardized guidelines for administration of PCI should be created.

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