Hypertension and Risk of Brain Metastasis from Small Cell Lung Cancer: A Retrospective Follow-up Study

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Abstract. Background: Although metastatic brain cancer is one of the most common forms of cancer, little is known about the factors associated with its development. We examined the hypothesis that hypertension may increase the risk for brain metastasis (BM) in patients with primary small cell lung cancer (SCLC). Materials and Methods: A retrospective review of medical charts of patients diagnosed with SCLC between June, 1986 and June, 2003 at MeritCare in Fargo, ND, USA, was done to determine which of these patients subsequently developed brain metastases. The effects of hypertension, age, gender, body mass index and the site of SCLC on the risk of developing BM were examined using both univariate and multivariable Cox proportional-hazards regression models. Two-way interactions between hypertension and other covariates were also included in the analyses. Results: Two hundred and thirty-two patients were identified with SCLC and 185 patients were eligible for this study. Eighty-five (45.9%) patients developed BM. Over 54% of SCLC occurred in the right lobe and more than 70% of the patients with BM had them in multiple locations. The risk of BM is significantly higher in younger patients (p-value < 0.03). Univariate analysis showed a hazard ratio (HR) for hypertension of 1.01 (95% Confidence Interval (CI) 0.6-1.6) for BM from SCLC. The multivariable Cox model showed an adjusted HR for hypertension of 1.06 (95%CI 0.7-1.6) for BM from SCLC. Conclusion: As has been consistently observed for other lung cancers, SCLC is more common in the right lung. The higher incidence of BM in younger patients suggests that more aggressive therapy is needed in these patients. Hypertension does not appear to increase the risk of BM from SCLC.

Brain metastases (BM) are the most common intracranial tumor, significantly outnumbering primary brain tumors (1-3). In men, primary tumors of the lung are the most common cause of brain metastasis and account for approximately 30% to 60% of all brain metastases (4-13). Patients with small cell lung cancer (SCLC) develop brain metastases at an extremely high rate (14). At the time of diagnosis of SCLC, 10% of patients present with brain metastases. This figure rises to 20% during therapy (15-20). The actuarial probability of developing brain metastases from SCLC increases with length of survival and reaches 50% to 80% at two years from diagnosis (21, 22).

Regardless of treatment, BM are associated with a poor prognosis. Untreated patients have a median survival of only about 1 month (23), and nearly all untreated patients die as a direct result of the brain tumor. Treatment of BM usually involves whole brain radiotherapy. A recent phase III study by Postmus et al. (24) found that the combination of whole brain radiotherapy and teniposide results in a median survival of 3.5 months.

Metastases spread to the brain via arterial microemboli (25). This suggests that mechanical factors such as increased blood flow or blood pressure may cause more microemboli to dislodge and eventually be trapped within small cerebral vessels. According to the hemodynamic or mechanical theory of metastasis (26), the major factor determining the frequency of organ involvement in metastasis is the number of cancer cells delivered to target organs in their arterial blood supply. Thus, metastatic frequency should correlate with some parameter of target organ arterial blood flow. In a recent test of this theory using human autopsy data (27), a significant correlation was demonstrated between documented arterial blood flow (ml/min/g target organ) and metastatic frequency.

Virdis et al. (28) noted an apparent association between hypertension and primary cerebral cancers. We examined whether the risk for BM in patients with SCLC is increased in hypertensive patients. The rationale for this hypothesis is...
that cerebral metastases are found along the paths of arterial supply to the brain. Thus, factors which increase cerebral blood flow or velocity, or damage the arterial wall may increase the incidence of BM.

Materials and Methods

A retrospective analysis of charts of patients diagnosed with SCLC between June 1986 and June 2003 were identified from the cancer registry of MeritCare, Fargo, ND, USA. MeritCare is a private institution that serves Fargo-Moorhead and surrounding areas. The study was approved by the Institutional Review Board.

Study design. Data on age, gender, race, tumor site, body mass index, treatments, cigarette and alcohol use, blood pressure and brain metastases from patients with SCLC were abstracted using electronic records and medical charts. Inclusion and exclusion criteria for this study are presented below:

Inclusion criteria:
1. Diagnosis of SCLC as a primary site using a pathology report present in the medical records.

Exclusion criteria:
1. Diagnosis of any cancer other than primary SCLC;
2. Diagnosis of brain metastases as a secondary site from cancers other than SCLC;
3. Date of brain metastases is equal to or before the date of SCLC diagnosis;
4. Patients who received a prophylactic cranial irradiation (29, 30).

Exposure definition. Hypertension, "high blood pressure", is defined as systolic blood pressure higher than 140 or diastolic blood pressure over 90 (31). The review of patients' medical charts showed that blood pressure was measured at each medical exam. Three successive measures were read. We took the average of these measures at the time of SCLC diagnosis. If these average values were higher than 140 or 90, then the patient was considered hypertensive. In addition, if the patient was on antihypertensive medication, he or she was also considered hypertensive.

Demographic covariates analyzed included age, gender, hypertension and the site of SCLC. Factors such as obesity, corticosteroids use, non-steroidal anti-inflammatory use and chronic kidney disease contribute to elevated blood pressure and may confound the association between hypertension and BM. Therefore, these factors were also included in our analyses. Most patients were smokers (99%) and alcohol drinkers (97%). The majority (96%) of the population in the Fargo-Moorhead area are Caucasians, thus we limited our analysis to this group. Age was a continuous variable but since the relationship with BM was not linear, we categorized age into the following groups (<64, and 65+). Patients discharged with BM (198.x) and SCLC (162.x) using the International Classification of Diseases, Ninth Revision (32) codes among any diagnosis field were considered to have metastases.

Statistical analysis. The outcome variable was the time from the diagnosis of SCLC to the development of BM or last date of contact. Univariate and multivariable analysis were performed using Cox proportional-hazards regression models (33). All p-values are two-sided, and p-values<0.05 are considered significant. All two-way interactions involving hypertension were assessed. Analyses were performed using SAS Software V8.0 (SAS Institute, Cary, NC 25513, USA).

Table I. Small cell lung cancer by demographic characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>67 (44-89)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55 (30%)</td>
</tr>
<tr>
<td>Male</td>
<td>130 (70%)</td>
</tr>
<tr>
<td>Small cell lung cancer site</td>
<td></td>
</tr>
<tr>
<td>Right lobe</td>
<td>101 (55%)</td>
</tr>
<tr>
<td>Left lobe</td>
<td>65 (35%)</td>
</tr>
<tr>
<td>Lingula</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (8%)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>71 (46-110)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>127 (78-190)</td>
</tr>
<tr>
<td>Blood pressure status</td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>98 (53%)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>85 (46%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>99 (54%)</td>
</tr>
<tr>
<td>No</td>
<td>83 (45%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19 (10%)</td>
</tr>
<tr>
<td>No</td>
<td>162 (88%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>No</td>
<td>177 (96%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Body mass index at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;25 Kg/m²)</td>
<td>91 (49%)</td>
</tr>
<tr>
<td>Overweight (25+ Kg/m²)</td>
<td>77 (42%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (9%)</td>
</tr>
<tr>
<td>Brain metastases status</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>13 (15%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>60 (71%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (14%)</td>
</tr>
<tr>
<td>Brain metastases site</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td>7 (10%)</td>
</tr>
<tr>
<td>Medulla</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>60 (82%)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>22 (30%)</td>
</tr>
</tbody>
</table>
We identified 232 patients with primary small cell lung cancer. Twelve patients (5.2%) received prophylactic cranial irradiation and were excluded from this study. Of the 220 remaining patients, 24 (11%) presented with confirmed or suspected synchronous BM. Eleven patients had missing values and therefore these 35 patients were excluded. A total of 185 patients with SCLC were included in the analysis (Table I). The mean (±SD) age at diagnosis for these patients was 65.7±10.4. Women were diagnosed at a slightly earlier age than men (64.5±10.4 vs. 66.4±10.4). Most of the patients (70.3%) were male, and the majority (52.9%) were normotensive. Eight-five (45.9%) patients developed BM. Forty-nine (57.6%) of these patients were in the younger age group and 36 (42.3%) patients in the older group (p-value<0.0001). The estimated median time to BM was 12 (9-13) months. Over 70% of patients with BM had multiple metastases and the cerebrum was the most (82.2%) metastatic site. The majority (54.6%) of SCLC occurred in the right lobe.

Fifty-eight (55%) patients with hypertension were in the younger age group (<65) and 27 (35%) patients in the older age group. The distribution of patients with blood pressure at various ranges is presented in Table III. Twenty patients were taking antihypertensive medication. Fifteen of these patients were at stage 2 hypertension and 5 patients at stage 1 hypertension (Table III). There were no patients with normal blood pressure who were taking antihypertensive medication. The duration between the diagnosis of primary SCLC in patients with hypertension and BM was 10 months.

Univariate analysis (unadjusted HRs) (Table II) showed that patients with hypertension had a HR of 1.01 (95%CI
0.6-1.6) for developing BM metastases from SCLC, indicating that hypertension is unlikely to be a risk factor for BM. After adjusting for all the covariates, hypertension had a HR of 1.06 (95% CI: 0.7-1.6) for developing BM metastases from SCLC, indicating that there is no association between hypertension and BM (Table II). The analysis of the interactions between the age by hypertension, gender by hypertension, and primary site by hypertension showed no statistical significance for these terms.

About 3% of hypertensive patients may have high blood pressure induced by corticosteroids (34). In our study, the majority (98%) of patients received corticosteroids after the diagnosis of BM, thus we did not include this variable in our model. Non-steroidal anti-inflammatory drugs (NSAIDs) are known to raise mean blood pressure by approximately 5 mm Hg (35) but only 20 patients were taking NSAIDs and only 4 patients showed this effect therefore it was also not included in the model. Adjusting for body mass index, which was measured at baseline, did not alter the HR for hypertension.

**Discussion**

Small cell lung cancer is known to disseminate to the brain in a fairly large proportion of patients. Why this is the case is not yet fully understood. The present investigation was undertaken to test the hypothesis that hypertension is a risk factor for brain metastases from SCLC. Our study found that hypertension is unlikely to be a risk factor for brain metastases.

In SCLC, the risk of developing brain metastatic disease is approximately 50% at 2 years, being as high as 80% in one series (36). In this study, the incidence of BM that occurred in patients was 48.6%. Our results confirm other findings on the relation between age and metastases frequency. King et al. (37), based on 100 autopsies of patients with bronchogenic carcinoma, and Halpert et al. (38), based on 92 autopsies of similar patients reported an inverse association between age and rate of nervous system metastasis. Galluzzi et al. (39) noted that the rate of metastasis from bronchogenic carcinoma decreased with age and offered a number of possible explanations: 1) the prevalence of squamous cell carcinoma increases with age (although their own data indicate a declining rate of metastasis with age for all histological types of bronchogenic cancer); and 2) older patients may die before there is opportunity for the development of metastasis. A number of published series have a high percentage of bronchogenic carcinomas as the cause of brain metastases with a predominance of males (40, 41). Ries (42) found that age is the strongest predictor of survival in lung cancer of the demographic variables. Our study found that women are diagnosed with SCLC at an earlier age than men, which is in accordance with other studies (55, 56).

Primary lung cancers were significantly more common in the right than in the left lobe of the lung. This finding has been consistently observed yet is poorly understood. For example, in 1977, Parkash (43) described a marked excess of right vs. left lung cancers. Although the right lung is slightly larger than the left, the excess in cancers on this side is far greater than the small difference in lung mass. Parkash speculated that the difference might reflect the easier access of carcinogens to the right than the left lung, though empirical support for this suggestion is scarce.

The clinical and experimental literature on hypertension and metastases is contradictory. For example, Weiss and colleagues (27) have stressed the role of vascular factors in favoring metastases to the brain and have cited both experimental and clinical observations to support this view. Conversely, in an experimental study of the relationship between hypertension and tumor growth and metastases using transplanted Walker tumors in rats, Fisher et al. (44) showed that the incidence or size of metastases did not increase in tumor-bearing rats with hypertension, and tumor growth had no effect on blood pressure. The fact that hypertension does not seem to be a risk factor for metastases may be explained by the death of many of the cancer cells before they reach the host site. For instance, Lang et al. (45) showed that an important factor responsible for the death of circulating cancer cells is their mechanical deformation while they are being squeezed through small blood vessels.

Clinical observations of cancer patients and studies with experimental tumor systems have concluded that tumors metastasize to specific organs independent of the rate of blood flow, vascularity and number of tumor cells that reach an organ. Tumor cells can reach the microvasculature of many organs, but extravasation into the organ parenchyma and growth occur only in some organs (46-48). The metastatic potential and other properties of human tumors depend on whether they are growing in orthotopic or ectopic sites in nude mice (49, 50), in part because of differences in responses to organ-specific growth factors (51, 52), gradients of pH, oxygen, nutrients, and cell waste products that develop within tumors (53, 54).

This was a retrospective follow-up study conducted in a private institution. It is likely that selection bias may be present as well as misclassification of the codification of the disease. It seems unlikely that such misclassification would be directional (i.e. patients who developed BM would be equally likely to have blood pressure accurately measured as those without). However, nondirectional misclassification could bias our results toward the null. It is possible that the presence of occult metastases might have lowered the blood pressure in some patients with BM, leading to a bias away from the null. Although this is possible in theory, our study gives little empirical support to this view. It is possible that patients with controlled hypertension after its diagnosis are
no longer hypertensive. We re-analyzed our data excluding all patients who were on antihypertensive medication. There was no association found between hypertension and BM. The information on the duration of the hypertension prior to the time of the diagnosis of SCLC was not available in the patients’ medical chart.

In summary, this study confirmed a right-sided excess of lung cancer and did not find evidence in support of the hypothesis that hypertension is associated with an increased risk of brain metastases from primary SCLC. The prevalence of BM is significantly higher in younger patients, which may suggest that more aggressive therapy might be appropriate in these patients.

**Acknowledgements**

This research was supported by an intramural grant from the University of North Dakota School of Medicine, USA.

**References**


Received July 12, 2004
Accepted July 26, 2004