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Anatomical Distribution of Small Cell Lung Cancer: Effects of Lobe and Gender on Brain Metastasis and Survival

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Abstract. *Background: Primary small cell lung cancer (SCLC) has a predilection for the right rather than the left lung. The aim of this study was to examine the association between gender and pulmonary location and to examine the effects of these variables on the incidence of brain metastasis and the survival rate of patients with SCLC. Materials and Methods: We conducted a retrospective review of medical charts of patients diagnosed with SCLC between January 1989 and December 2002 at MeritCare Hospital in Fargo, ND, USA. The effects of the anatomical site of SCLC, age, gender, body mass index, stage of SCLC and treatment of SCLC on the incidence of brain metastasis and survival were examined using univariate and multivariable Cox proportional-hazards regression models. Results: Two-hundred and thirty patients were identified with SCLC. One hundred and forty-eight (64%) were male and 82 (36%) were female. SCLC was significantly more common in the right upper lobe for females (51%) than for males (32%) (p-value=0.005) and in the left upper lobe for males (28%) compared to females (11%) (p-value=0.003). Survival was significantly longer in both younger patients (48 weeks vs. 26 weeks; log-rank p-value=0.03) and female patients (50 weeks vs. 36 weeks; log-rank p-value=0.01). The multivariable Cox model showed an adjusted HR of 1.52 (95% confidence interval 1.01-2.3) for the right lung relative to the left lung. We found no impact of anatomical distribution or pulmonary location on the incidence of brain metastasis. Conclusion: In these data, SCLC is more common in the right upper lobe for females. Right lung and male gender are associated with a worse prognosis, which may suggest that more aggressive therapy is needed in these patients.*

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Approximately 173,770 new cases of lung cancer will be diagnosed in 2004 (1) and approximately 43,000 of these cases will be small cell lung cancer (SCLC). The 3-year overall survival in SCLC is only 5 to 10% (2). SCLC accounts for almost 10% of all cancer-related deaths in men and 5% in women (1, 3). Despite the apparent initial sensitivity of SCLC to chemotherapy, acquired drug resistance is the major treatment problem. At autopsy, the majority (>85%) of SCLC patients who die with disease after treatment have pure SCLC histology (4). Several studies have found that lung cancer occurs more commonly in the upper than the lower lobes and in the right more often than the left lung (5, 6). Byers *et al.* (7) found that there is an upper lobe predominance of SCLC in men and women at all ages. Celikoglu *et al.* (8) reported similar findings. Within the upper lobes, there is a predominance of SCLC on the right side. For example, based on autopsy data from 1928 to 1972, Parkash (9) found that the right upper lobe was more often the seat of carcinoma than the left lower lobe.

Although some studies have shown that SCLC is more common in the upper than in the lower lobes and in the right than in the left lobes, to our knowledge, very few studies have investigated whether the anatomical distribution of SCLC differs by gender. This topic is of interest given the recent controversies about gender differences in lung cancer rates among smokers.

Patients with SCLC develop brain metastasis (BM) at an extremely high rate (10). At the time of diagnosis of SCLC, 10% of patients present with brain metastases when the screening is performed with a CT-scan and this percentage is higher if Magnetic Resonance Imaging is used. The actuarial probability of developing BM from SCLC increases with length of survival and reaches 50% to 80% at two years from diagnosis (10, 11). The presence of BM is associated with considerable morbidity compared to other metastatic sites (12).

BM are known to be associated with a shorter survival regardless of treatment. A recent phase III study by Postmus *et al.* (13) found that the combination of whole

Table I. *Characteristics of small cell lung cancer (SCLC) at diagnosis by gender.*

	Males (N=148)	Females (N=82)	*p*-value
Age	67 (41-89)†	66 (41-87)	0.74
Anatomical distribution of SCLC			
Right upper lobe	48 (32%)	42 (51%)	0.005
Right middle lobe	17 (11%)	6 (7%)	0.31
Right lower lobe	12 (8%)	11 (13%)	0.20
Left upper lobe	41 (28%)	9 (11%)	0.003
Left lower lobe	22 (15%)	7 (9%)	0.17
Lingula	8 (5%)	7 (9%)	0.36
Stage of SCLC			
Limited-stage disease	18 (12%)	15 (18%)	0.20
Extensive-stage disease	130 (88%)	67 (82%)	
Body mass index			
Normal (<25 Kg/m^2)	70 (47%)	34 (41%)	0.39
Overweight (≥25 Kg/m^2)	78 (53%)	48 (59%)	
Treatment of SCLC			
Chemotherapy and radiation	84 (57%)	50 (61%)	0.19
Chemotherapy alone	36 (24%)	12 (15%)	
No treatment	28 (19%)	20 (24%)	
Brain metastasis at diagnosis of SCLC			
Yes*	10 (7%)	11 (13%)	0.09
No	138 (93%)	71 (87%)	

†Median (range).
*These patients will be excluded from BM incidence and survival analyses.

Table II. *Incidence of brain metastasis by gender from small cell lung cancer (SCLC).*

	Males (N=138)	Females (N=71)	*p*-value
Brain metastasis(es)			
Yes	60 (43%)	38 (54%)	0.17
No	78 (57%)	33 (46%)	
Brain metastasis(es) status			
Single	7 (5%)	2 (3%)	0.21
Multiple	53 (38%)	36 (51%)	
None	78 (57%)	33 (46%)	
Brain metastases site			
Pons	2 (1%)	3 (4%)	0.44
Medulla	3 (2%)	0 (0%)	
Cerebrum	50 (36%)	26 (37%)	
Cerebellum	18 (13%)	11 (15%)	
Prophylactic cranial irradiation			
Yes	9 (7%)	3 (4%)	0.75
No	129 (93%)	68 (96%)	
Corticosteroids if brain metastasis (es)			
Yes	55 (40%)	32 (45%)	0.47
No	83 (60%)	39 (55%)	
Other metastases incidence			
Liver	14 (10%)	3 (4%)	0.14
Bone	6 (4%)	4 (6%)	0.74
Adrenals, Lymphatics, Pancreas	26 (19%)	8 (12%)	0.16

brain radiotherapy and teniposide results in a median survival of only 3.5 months. It is well established that prophylactic cranial irradiation (PCI) decreases significantly the incidence of BM and increases overall survival (14, 15).

The aim of this study was to examine the association between gender and pulmonary location and to examine the effects of these variables on the incidence of brain metastasis and the survival rate of patients with SCLC.

Materials and Methods

Patients diagnosed with SCLC between January 1989 and December 2002 were identified from the cancer registry of MeritCare Hospital in Fargo, ND, USA, and a retrospective review of the medical charts was performed. The study was approved by the Institutional Review Board.

Study design. This is a retrospective follow-up study. Data on age, gender, anatomical site distribution, body mass index, treatments of primary SCLC, palliative treatment of SCLC, prophylactic cranial irradiation, cigarette and alcohol use, stage of SCLC, incidence of BM, and survival of patients with SCLC were abstracted from the medical charts. Inclusion and exclusion criteria were: *Inclusion criteria:* i. Diagnosis of SCLC as a primary site using a pathology report present in the medical records. *Exclusion criteria:* i. Diagnosis of any cancer other than primary SCLC; ii. Diagnosis of BM as a secondary site from cancers other than SCLC.

The majority (96%) of the population in the Fargo-Moorhead area are Caucasians, thus we limited our analysis to this group. Patients discharged with a BM (198.x) and SCLC (162.x) in any diagnosis field, using the International Classification of Diseases, Ninth Revision (16) codes, were considered to have brain metastasis.

Statistical analysis. The time from the diagnosis of SCLC to the development of brain metastasis and the time to death or last date of follow-up are the outcomes. Kaplan-Meier methods were used to obtain estimates of these distributions. Log-rank tests were used to assess the univariate effect of each of the covariates on these distributions, and Cox proportional-hazards regression models (17) were used to assess the joint effect of the covariates. All two-way interactions involving anatomical sites of the primary SCLC were assessed. Prevalent cases of brain metastasis were excluded from the analysis of incident brain metastasis and survival. All *p*-values are two-sided, and *p*-values≤0.05 were considered significant. Analyses were performed using SAS Software V8.0 (SAS Institute, Cary, NC 25513, USA).

Table III. *Univariate and multivariable Cox proportional-hazards regression models of brain metastasis incidence from small cell lung cancer (SCLC).*

Variables	No.	Events	Median(95%CI)	HR*(95% CI)	HR†(95% CI)
Age					
≤67	114	43	48(30-64)‡	0.92(0.62-1.37)	0.67(0.41-1.12)
68+	95	55	35(31-59)	Ref	Ref
Gender					
Male	138	71	46(34-64)	Ref	Ref
Female	71	27	36(24-55)	1.10(0.75-1.62)	1.11(0.67-1.83)
Pulmonary location of SCLC					
Left lung	77	41	51(30-94)	Ref	Ref
Right lung	132	58	38(31-56)	1.25(0.84-1.89)	1.42(0.87-2.32)
Anatomical site of SCLC					
Lower lobe	52	22	33(17-59)	Ref	Ref
Upper lobe	140	70	50(35-64)	0.74(0.48-1.14)	0.70 (0.42-1.16)
Body mass index at diagnosis					
Normal (<25 Kg/m^2)	90	40	48(34-54)	Ref	Ref
Overweight (25+ Kg/m^2)	119	58	46(28-94)	1.25(1.8-2.04)	0.94(0.57-1.54)
Stage of SCLC					
Limited-stage disease	33	27	140(108-308)	Ref	Ref
Extensive-stage disease	176	71	34(26-48)	5.47(2.39-12.5)	4.63(1.80-11.9)
Treatment of SCLC					
Chemotherapy and radiation	123	43	79(54-110)	Ref	Ref
Chemotherapy alone	47	37	37(31-53)	2.60(1.34-5.0)	2.46(1.41-4.28)
No treatment	39	18	16(5-25)	2.66(1.60-4.42)	2.65(1.26-5.64)
Prophylactic cranial irradiation					
No	197	91	38(31-52)	Ref	Ref
Yes	12	7	140(59-140)	0.43(0.17-1.06)	0.56(0.20-1.57)

*Univariate analysis.
†Multivariable analysis.
‡Survival in weeks.

Results

We identified 230 patients with primary SCLC. One hundred and forty-eight (64%) were male and 82 (36%) were female (Table I). The mean (±SD) age at diagnosis for these patients was 65.5±10.5 years. Women and men were diagnosed at approximately the same age (64.8±10.7 *vs.* 65.6±10.4). Twenty-one (9%) patients had synchronous BM at presentation. For both male and female patients, over 80% of patients had extensive stage disease. Essentially all of our patients were smokers (99%) and social alcohol drinkers (95%). Approximately (55%) of the patients were overweight at diagnosis.

The primary SCLC occurred significantly more often in the right upper lobe in females (51%) compared to males (32%) (p-value=0.005), while it occurred significantly more often in the left upper lobes in males (28%) compared to females (11%) (p-value=0.003). There was no statistical difference in the occurrence of SCLC in the lower lobe by gender.

The majority of males (57%) and females (61%) received the standard treatment, which consisted of four to six cycles of chemotherapy using mostly the combination Cisplatin and VP-16, with early concurrent thoracic radiotherapy. Of the 12 patients who achieved a complete response and received prophylactic cranial irradiation (PCI), 9 were males and 3 were females. The patients who received PCI had a dose of 25 Gy in 10 fractions over 2 weeks given within 6 to 8 weeks of the complete remission.

Ninety-eight patients of the 209 patients without BM at diagnosis subsequently developed BM (Table II). Of the patients who developed BM, the majority (89%) had

Table IV. *Univariate and multivariable Cox proportional-hazards regression models of survival from small cell lung cancer (SCLC).*

Variables	No.	Events	Median(95%CI)	HR*(95% CI)	HR†(95% CI)
Age					
≤67	114	75	48(36-55)‡	0.65(0.46-0.91)	0.62(0.41-0.95)
68+	95	58	26(21-41)	Ref	Ref
Gender					
Male	138	96	36(26-46)	Ref	Ref
Female	71	37	50(28-88)	0.64(0.44-0.94)	0.55(0.34-0.88)
Pulmonary location of SCLC					
Left lung	77	46	41(26-51)	Ref	Ref
Right lung	132	88	36(26-48)	1.13(0.78-1.63)	1.52(1.01-2.3)
Anatomical site of SCLC					
Lower lobe	52	22	30(17-53)	Ref	Ref
Upper lobe	140	56	46(34-51)	0.85(0.55-1.30)	0.90(0.54-1.53)
Body mass index at diagnosis					
Normal (< 25 Kg/m^2)	90	56	48(28-56)	Ref	Ref
Overweight (25+ Kg/m^2)	119	77	36(26-46)	1.41(1.01-2.04)	1.85(1.25-2.86)
Stage of SCLC					
Limited-stage disease	33	20	83(37-140)	Ref	Ref
Extensive-stage disease	176	113	36(26-46)	2.27(1.34-3.85)	2.24(1.17-4.3)
Treatment of SCLC					
Chemotherapy and radiation	123	74	50(36-60)	Ref	Ref
Chemotherapy alone	47	35	41(24-48)	1.50(1.01-2.25)	1.17(0.74-1.8)
No treatment	39	15	12(4-22)	3.46(2.10-5.67)	3.30(1.87-5.8)

*Univariate analysis.
†Multivariable analysis.
‡Survival in weeks.

multiple metastases and they occurred mostly in the cerebrum (73%). The overall estimated median time to BM was 40 weeks (95% confidence interval 32-48). The right lobe and upper lobes were not associated with increased risk for brain metastases (Table III). Patients with limited-stage disease and those who received the standard treatment had a lower incidence of BM.

The overall median survival was 48 weeks (95% confidence interval 36-56). Univariate and multivariable results are summarized in Table IV. Survival was significantly longer for younger patients (48 weeks *vs.* 26 weeks; log-rank *p*-value=0.03) and female patients (50 weeks *vs.* 36 weeks; log-rank *p*-value=0.01). The right lung had a univariate HR of 1.13 (95% confidence interval 0.8-1.6) for death from SCLC, indicating that survival for patients with SCLC located in the right lung was not significantly different from that of patients with SCLC in the left lung. However, a greater proportion of the right upper lobe tumors occurred in women, who had a better survival rate than men. Once we adjusted for gender, as well as other covariates, the right lung had a HR of 1.52 (95% confidence interval 1.01-2.3) for death from SCLC, indicating that patients with a right lung disease site had a worse survival rate than patients with left lung involvement. There was no significant difference in survival between those with upper or lower lobe disease. Extensive stage disease, no treatment or chemotherapy alone, and overweight were associated with a worse prognosis. The analysis of the interactions between anatomical site and other covariates showed no statistical significance for these terms.

Discussion

Several studies have shown that in SCLC, the right lung is a more common site than the left lung. This was also true in our study, particularly for females for whom the right upper lobe is a significantly more common site than for males. Right lung involvement was associated with a worse prognosis than involvement of the left lungs and survival rate was significantly lower in both males and older patients.

The subject of gender difference in lung cancer rates among smokers is controversial. This controversy about women being more or even less susceptible to the carcinogenic effects of cigarette smoke began in the 1990s with several reports from case-control studies. In a recent commentary, Blot *et al.* (18) proposed that some differences (as yet undefined) in the way females and males are exposed to and/or respond to carcinogenic agents may exist. Several studies (22-37) indicated that the relative risk of lung cancer associated with smoking may be higher in females than in males.

Although cigarette smoking appears to induce lung cancer of all histological types, there are clear differences in the magnitude of risk by cell type and gender (19). Smoking-related lung cancer risk seems to be strongest for small cell and squamous cell lung cancer (20-22).

Lee *et al.* (38) found that the strength of association between cigarette smoking and lung cancer in both sexes differed by histological types. Smoking accounts for relatively more SCLC in women than in men (36). Male smokers have a similar odds ratio for the development of squamous cell and SCLC, whereas women smokers appear to have a much higher likelihood of developing SCLC (OR=37.6 (28.5-49.3) *vs.* 11.4 (9.1-14.2) in ever smokers; OR=29.8 (22.0-40.3) *vs.* 7.9 (6.2-10.0) in former smokers; and OR=42.5 (32.1-56.6) *vs.* 15.1 (12.0-19.0) in current smokers) (35, 39, 40). In a large study (41) of women, the most marked shift in response to cigarette smoking is an increased proportion of small cell carcinoma. Tumors that arise in association with tobacco smoke exposure tend to occur in the upper lobes with a typical upper:lower ratio of roughly 2.5:1.0 (5, 7, 42-44).

The pathophysiological basis for the predominance of the upper lobe location of lung cancer among smokers is unclear, particularly since the upper lobes of the lungs are smaller than the lower lobes and move less air. This topic has engendered considerable speculation. For example, (1) many anatomic, physiologic and functional differences between upper and lower lobes; (2) higher tissue PO_2 levels in the upper lobes; (3) deficient ventilation in the upper lobes; and, finally, (4) SCLC may arise adjacent to scar tissue, which occurs more frequently in the upper lobes as a result of previous infections (45), have been suggested as possible explanations.

Experimental work based on casts of the human tracheobronchial tree have shown that particle deposition occurs more readily in the upper lobes because of stronger particle impaction due to the aerodynamic characteristics of the upper lobe bronchial branches (46). Fisher (47) first theorized that the larger volume of the right lung may be responsible for the higher prevalence. A similar idea was expressed later by Lulu and Lawson (44), who postulated that the higher incidence of right lung involvement may be related to its relatively larger mass, which may promote a greater amount of contaminated air or tobacco smoke. The right bronchus is wider, shorter and runs very nearly contiguous with the trachea (48), which potentially increases the carcinogens entering the right lung, compared to the left lung.

Tumor initiation may occur more readily in tissues with increased oxygen levels, possibly due to a higher rate of free radical formation (49). Moreover, after initiation, small nests of cancer cells might be able to survive for longer periods of time in tissues with higher ambient PO_2 levels. In support of this, the observation has been made that lower lung cancer rates have been related to higher altitudes, where PO_2 levels were relatively low (50).

The higher prevalence of tumors in the upper lobes might be due to their deficient ventilation, particularly in males who tend to manifest an abdominal mode of respiration. This allows for prolonged retention and incomplete expulsion of the inhaled carcinogens, which in turn may cause a higher prevalence of SCLC in those parts.

SCLC arises from epithelial cells lining the surface of the centrally located large and medium-sized bronchi, which are substantially influenced by the mutagenic and carcinogenic chemicals contained in tobacco smoke (51, 52).

Doll and Peto (53) suggest that the risk of malignant transformation per cell is proportional to the square of the carcinogen dose, and may even be of a higher power still. If correct, then the dilution of the carcinogen dose over a larger area would reduce the total risk in the lower lobes, which might partly account for the fact that lung cancers more often arise in the upper lobe bronchi.

Several reports indicated that disease extent and performance status are predictors of prognosis in SCLC (54-59). The Karnofsky performance scale was not available in the patient's medical chart to assess performance status, but many of our patients had extensive stage disease, and these patients had a significantly decreased survival.

The impact of age and sex on median survival time is still unclear. A significantly lowered median survival for patients over 60 years with extensive disease was reported by two separate groups (60, 61), whereas others did not find any association between survival and age over 50 years (62) or age over 64 years (58). Our study found that, in patients over 68 years, SCLC was associated with a worse prognosis than in younger patients. Because of the varying age limits of subgroups in the different trials, it is difficult to draw any definite conclusions, but decreasing survival with increasing age seems to be a general trend (55, 56, 58, 62, 63). In accordance with the findings reported herein, young female patients (<60 years) seem to have a longer median survival compared to males (57). It has been suggested that this prognostic superiority for females may be due to more aggressive (myelotoxic)

treatment of young female patients (60). However, Wolf *et al.* (57) were not able to find differences in leukocyte nadirs between male and female patients. Greenberg *et al.* (64) found that in men all of the cell types peaked at about the same age (70-74), while in women cell types occurred about equally often but SCLC occurred at 60-69 years of age. Our review found that SCLC occurred at approximately the same age in females and in males at 60-69 years of age.

Ries (65) found that survival rates for SCLC were similar for each race and sex group. They were nearly identical for patients whose tumors arose in the right lung as compared to the left lung. Several studies found a significant survival advantage for females with SCLC (66). Trials on SCLC have shown that women have significantly better response rates and survival rates (67). Other studies also found that female gender in SCLC is a favorable prognostic factor for survival (68, 69, 55). Ouellette *et al.* (70) found that there was a survival advantage in women who lived 12 months longer than men. This is consistent with our findings.

Several studies showed that in 56% to 92% of patients with advanced SCLC and BM, corticosteroids significantly improved neurological symptoms (71-73). In our study, eighty-seven patients with BM received corticosteroids.

Our study found that overweight at diagnosis was associated with a decrease in survival in patients with SCLC. Numerous studies (74-76) have shown that obese women with breast cancer have a decreased disease-free and overall survival when compared with their non-obese counterparts. Additionally, Tarella *et al.* (77) found that in high-risk non-Hodgkin's lymphoma patients undergoing intensive chemotherapy, overweight was associated with a poor outcome. However, Georgiadis *et al.* (78) found that, in small cell lung cancer patients, obesity at the diagnosis was not associated with increased toxicity from treatment or a shortened survival.

Conclusion

This study found that primary SCLC is more common in the right lung for females. Right lobes are associated with a worse prognosis than left lobes. The survival rate was found to be worse in males and older patients, which might suggest that more aggressive therapy is needed in such patients. Finally, the pulmonary location and anatomical site of SCLC did not appear to influence the incidence or the location of BM.

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