**Introduction**

Lung cancer is the leading cause of cancer deaths (18.4% of the total cancer deaths) and the second most common cancer among both men and women. [1, 2] More people die of lung cancer than colon, prostate, ovarian and breast cancers combined. [3] Small cell lung cancer (SCLC) is an aggressive malignant disease, which accounts for about 15% of lung cancer cases. [4-6] SCLC is distinguished from the more common non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, early development of widespread metastases, and dramatic initial response to chemotherapy and radiation. [7]

Small cell lung cancers usually begin in the bronchi of the lungs and tend to travel to other parts, often to the brain. Veterans Administration Lung Study Group (VALG) staging system has been developed for SCLC, classifying SCLC as limited or extensive disease.[8] At the time of diagnosis, approximately 70% of patients have been diagnosed with extensive-stage disease (ES-SCLC), defined as the presence of overt metastatic disease by imaging or physical examination; the remainder have limited-stage disease (LS-SCLC), defined as disease restricted to one hemithorax with regional lymph node metastases [9, 10].

Systemic treatment options for patients with SCLC has been unbeaten for about three decades, and few therapies are in late-stage development. [11] The current standard of first-line care for ES-SCLC is platinum based (cisplatin-etoposide or cisplatin-irinotecan or cisplatin-topotecan) with or without concurrent radiation therapy. [12, 13] Although SCLC often responds well to chemotherapy initially, it tends to recur after first-line treatment and become more resistant to subsequent chemotherapy treatment. Approximately 80% of LS-SCLC and almost all ES-SCLC patients relapse within the first year of treatment. [12] Subsequent-line treatment options are limited; only two agents, topotecan and amrubicin, are approved as second-line therapy. [14, 15] Beyond second-line therapy, there is no standard of care [16]. The great strides recently made with tumor genomics and molecular targeted therapy in NSCLC. But they have not been matched in SCLC, because no actionable mutation has been identified to date. Consequently, the prognosis for patients with SCLC remains poor, with a median overall survival (OS) of 15–20 months for LS-SCLC and 8–13 months for ES-SCLC [10]. The 5-year survival rate is 10%–13% with LS-SCLC and 1%–2% with ES-SCLC [10, 17]. Thus, there is a significant need for effective therapy for SCLC patients, especially for ES-SCLC patients.

Lack of progress in the current standard-of-care options for patients with SCLC pushes scientists to investigate creative therapeutic approaches, including immunotherapy. The goal of immunotherapy is to enhance the immune system’s ability to detect and eradicate tumor cells. Several lines of evidence prove that immunotherapy plays a role in eliciting an anticancer response by modulating the patient's immune response of the tumor. [18–20] Therefore, approaches aimed at counteracting immune evasion mechanisms by tumor cells are especially attractive. In this study, we evaluated the impact of immunotherapy by comparing survival outcomes in patients with ES-SCLC receiving chemotherapy alone vs chemotherapy and immunotherapy as part of initial treatment. And potential subgroups that may derive clinically meaningful benefit to the addition of immunotherapy as first line treatment were also identified.

**Materials and Methods**

**Data Source and Patient Selection**

The National Cancer Database (NCDB) is jointly sponsored by the American College of Surgeons and the American Cancer Society. It is a clinical oncology database sourced from hospital registry data collected by more than 1500 Commission on Cancer (CoC)-accredited facilities tracking treatment and outcomes of patients. [21] This database includes patient demographics, socioeconomic factors, disease characteristics, treatment details and survival outcomes.

Cases were identified using the SCLC Participant User File (PUF). A total of 238,691 adult patients (aged 18 years) were identified who were diagnosed with SCLC between 2004 and 2015. This dataset then was limited to extensive stage patients who received chemotherapy within 183 days of diagnosis. Among patients who received immunotherapy, those whose immunotherapy started before 30 days or after 180 days of receiving chemotherapy were excluded. Patients with unknown immunotherapy status or with all treatment elsewhere, patients who developed secondary malignancy and patients without vital status were also excluded. The eligible patients were then stratified into two groups, one received chemotherapy alone and the other received chemotherapy and immunotherapy. (**Table 1**)

**Patient Demographics and Treatment Variables**

Pertinent patient demographics and treatment characteristics were available in NCDB. The patient’s age, gender, race, insurance coverage, local education level, median household income, treatment facility type and location and urban/rural setting were used in this analysis. Note that patient’s age at diagnosis was classified further as <65 years old and 65years old. Race was categorized as white and non-white. Patient comorbidities were assessed using the Charlson-Deyo comorbidity score. Education level and household income were identified by cross-referencing the patient's zip code to year 2012 US Census data. Education level was defined as the percentage of adults living in a patient's zip code not graduating from high school. The median household income was defined as the median household income for the patient's zip code. Facility type was determined by the Commission on Cancer based on services provided and total annual case number. Community cancer programs treat between 100 – 500 cancer patients/year. Comprehensive community cancer programs treat ≥ 500 cancer patients/year and participate in research. Academic programs, including those with NCI designation, treat >500 cancer patients, participate in research, and also provide postgraduate medical education. Patient’s zip codes were used to determine urban vs. rural location. Metropolitan residence was defined as counties with population > 250,000. Rural (population <2,500) and Urban patients (population > 2,500 but < 250,000) were combined into one group.

The following tumor related variables were evaluated: year of diagnosis, primary site, tumor size and whether receiving radiation. The patients were stratified into receiving chemotherapy alone and receiving combination of chemotherapy and immunotherapy. The primary outcome measure was overall survival, which was defined as time from receiving chemotherapy to time of death or last follow-up.

**Statistical Analysis**

The univariate association between each covariate and study cohorts were assessed using the chi-square test for categorical covariates, and a multivariable (MVA) logistic regression was carried out for predicting utilization of chemotherapy vs. combination of chemotherapy and immunotherapy. The univariate association (UVA) between each covariate including study cohorts and study outcome was assessed using Cox proportional hazards models and log-rank tests. A multivariable Cox proportional hazard model was fit for OS. The MVA models were built by a backward variable selection method applying an α = 0.05 removal criterion. Kaplan-Meier (KM) plots were calculated to compare the survival curves by treatment cohorts.

A newly developed propensity score (PS) weighting schema is implemented in order to control any confounding effects due to baseline patient demographic, clinical, and treatment related differences. First, a logistic regression model was applied to estimate the probability of a patients could receive chemotherapy alone based on his/her baseline characteristics as listed in Table 2, and this probability was defined as the propensity score (PS). Patients in chemotherapy cohort were assigned a weight with value of 1-PS, while for patients in combination therapy cohort the weight was PS. The covariates balance between the two cohorts was evaluated by the standardized differences, and a value of < 0.2 was considered as negligible imbalance. The effects were estimated in the matched sample by a Cox model with a robust variance estimator for OS.

Table Inclusion and Exclusion

| **Selection and Exclusion Criteria** | **Sample Size** | **Excluded** |
| --- | --- | --- |
| NCDB Small Cell Lung PUF Cancer Cases | 238691 | - |
| Include Patients with Extensive Stage | 139085 | 99606 |
| Include Patients Who Received Chemotherapy within 183 Days of Diagnosis | 96942 | 42143 |
| Exclude Patients Who Received Immunotherapy before 30 Days or after 180 Days of Receiving Chemotherapy | 96924 | 18 |
| Exclude Patients with Unknown Immunotherapy Status | 96346 | 578 |
| Exclude Patients with All Treatment Elsewhere | 88481 | 7865 |
| Exclude Secondary Malignancy | 75389 | 13092 |
| Exclude Patients without Vital Status | 66055 | 9334 |

**Results**

Table Descriptive Statistics for Variables of Interests in Database

| **Variable** | **Level** | **N (%) = 66055** |
| --- | --- | --- |
| Immunotherapy at any CoC Facility | None | 65804 (99.6) |
| Immunotherapy administered as first course therapy | 251 (0.4) |
|  | | |
| Age at Diagnosis | <65 | 32407 (49.1) |
| >=65 | 33648 (50.9) |
|  | | |
| Facility Type | Integrated Network/Community Cancer Program | 15358 (23.4) |
| Comprehensive Community Cancer Program | 32152 (48.9) |
| Academic/Research Program | 18239 (27.7) |
| Missing | 306 |
|  | | |
| Facility Location | Northeast | 11999 (18.2) |
| South | 26724 (40.6) |
| West | 27026 (41.1) |
| Missing | 306 |
|  | | |
| Sex | Male | 34227 (51.8) |
| Female | 31828 (48.2) |
|  | | |
| Race | White | 59509 (90.1) |
| Non-white | 6546 (9.9) |
|  | | |
| Primary Payor | Medicaid/Other Goverment/Not Insured/Unknown | 11732 (17.8) |
| Private | 21137 (32.0) |
| Medicare | 33186 (50.2) |
|  | | |
| Percent No High School Degree 2007-2012 | >=21% | 12367 (19.1) |
| 13.0-20.9% | 19781 (30.6) |
| 7.0-12.9% | 21262 (32.9) |
| <7.0% | 11314 (17.5) |
| Missing | 1331 |
|  | | |
| Census Median Income Quartiles 2007-2012 | <$38,000 | 14212 (22.0) |
| $38,000-$47,999 | 17729 (27.4) |
| $48,000-$62,999 | 17543 (27.1) |
| >=$68,000 | 15206 (23.5) |
| Missing | 1365 |
|  | | |
| Urban/Rural 2013 | Metro | 49776 (78.3) |
| Urban/Rural | 13808 (21.7) |
| Missing | 2471 |
|  | | |
| Charlson-Deyo Score | 0 | 38149 (57.8) |
| 1+ | 27906 (42.2) |
|  | | |
| Year of Diagnosis (quartile) | >=2004, <=2007 | 21472 (32.5) |
| >2007, <=2009 | 11686 (17.7) |
| >2009, <=2012 | 19472 (29.5) |
| >2012, <=2014 | 13425 (20.3) |
|  | | |
| Primary Site | Upper, lung | 35601 (53.9) |
| Middle or lower, lung | 14612 (22.1) |
| Overlapping lesion/NOS, lung | 15842 (24.0) |
|  | | |
| Tumor Size (cm) | <= 5cm | 42330 (64.1) |
| > 5cm | 169 (0.3) |
| Unknown | 23556 (35.7) |
|  | | |
| Radiation | No | 34096 (51.8) |
| Yes | 31787 (48.2) |
| Missing | 172 |
|  | | |

Table Balance Check after Propensity Score Weighting

|  | | | **Immunotherapy at any Facility** | |  |
| --- | --- | --- | --- | --- | --- |
|  | | | **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_** | |  |
| **Covariate** | **Level** | **Statistics** | **No N=236** | **Yes N=236** | **Standardized Difference** |
| Age at Diagnosis | <65 | N (Col%) | 108 (45.8) | 108 (45.8) | 0.000 |
| >=65 | N (Col%) | 128 (54.2) | 128 (54.2) | 0.000 |
|  | | | | | |
| Facility Type | Integrated Network/Community Cancer Program | N (Col%) | 33 (13.92) | 33 (13.92) | 0.000 |
| Comprehensive Community Cancer Program | N (Col%) | 124 (52.54) | 124 (52.54) | 0.000 |
| Academic/Research Program | N (Col%) | 79 (33.54) | 79 (33.54) | 0.000 |
|  | | | | | |
| Facility Location | Northeast | N (Col%) | 26 (10.97) | 26 (10.97) | 0.000 |
| South | N (Col%) | 150 (63.31) | 150 (63.31) | 0.000 |
| West | N (Col%) | 61 (25.72) | 61 (25.72) | 0.000 |
|  | | | | | |
| Sex | Male | N (Col%) | 127 (53.77) | 127 (53.77) | 0.000 |
| Female | N (Col%) | 109 (46.23) | 109 (46.23) | 0.000 |
|  | | | | | |
| Race | White | N (Col%) | 217 (91.99) | 217 (91.99) | 0.000 |
| Non-white | N (Col%) | 19 (8.01) | 19 (8.01) | 0.000 |
|  | | | | | |
| Primary Payor | Medicaid/Other Goverment/Not Insured/Unknown | N (Col%) | 28 (11.78) | 28 (11.78) | 0.000 |
| Private | N (Col%) | 83 (35.26) | 83 (35.26) | 0.000 |
| Medicare | N (Col%) | 125 (52.96) | 125 (52.96) | 0.000 |
|  | | | | | |
| Percent No High School Degree 2007-2012 | >=21% | N (Col%) | 63 (26.84) | 63 (26.84) | 0.000 |
| 13.0-20.9% | N (Col%) | 76 (32.34) | 76 (32.34) | 0.000 |
| 7.0-12.9% | N (Col%) | 64 (26.92) | 64 (26.92) | 0.000 |
| <7.0% | N (Col%) | 33 (13.9) | 33 (13.9) | 0.000 |
|  | | | | | |
| Census Median Income Quartiles 2007-2012 | <$38,000 | N (Col%) | 67 (28.52) | 67 (28.52) | 0.000 |
| $38,000-$47,999 | N (Col%) | 70 (29.42) | 70 (29.42) | 0.000 |
| $48,000-$62,999 | N (Col%) | 64 (26.89) | 64 (26.89) | 0.000 |
| >=$68,000 | N (Col%) | 36 (15.17) | 36 (15.17) | 0.000 |
|  | | | | | |
| Urban/Rural 2013 | Metro | N (Col%) | 156 (66.05) | 156 (66.05) | 0.000 |
| Urban/Rural | N (Col%) | 80 (33.95) | 80 (33.95) | 0.000 |
|  | | | | | |
| Charlson-Deyo Score | 0 | N (Col%) | 150 (63.38) | 150 (63.38) | 0.000 |
| 1+ | N (Col%) | 87 (36.62) | 87 (36.62) | 0.000 |
|  | | | | | |
| Year of Diagnosis (quartile) | >=2004, <=2007 | N (Col%) | 67 (28.18) | 67 (28.18) | 0.000 |
| >2007, <=2009 | N (Col%) | 36 (15.15) | 36 (15.15) | 0.000 |
| >2009, <=2012 | N (Col%) | 43 (18.12) | 43 (18.12) | 0.000 |
| >2012, <=2014 | N (Col%) | 91 (38.54) | 91 (38.54) | 0.000 |
|  | | | | | |
| Primary Site | Upper, lung | N (Col%) | 128 (54.22) | 128 (54.22) | 0.000 |
| Middle or lower, lung | N (Col%) | 55 (23.09) | 55 (23.09) | 0.000 |
| Overlapping lesion/NOS, lung | N (Col%) | 54 (22.69) | 54 (22.69) | 0.000 |
|  | | | | | |
| Tumor Size (cm) | <= 5cm | N (Col%) | 166 (70.14) | 166 (70.14) | 0.000 |
| > 5cm | N (Col%) | 0 (0) | 0 (0) | 0.000 |
| Unknown | N (Col%) | 71 (29.86) | 71 (29.86) | 0.000 |
|  | | | | | |
| Radiation | No | N (Col%) | 131 (55.45) | 131 (55.45) | 0.000 |
| Yes | N (Col%) | 105 (44.55) | 105 (44.55) | 0.000 |
|  | | | | | |
| \*  The parametric p value is calculated by ANOVA for numerical covariates and Chi-Square test for categorical covariates. | | | | | |

|  | | | **OS** | | |
| --- | --- | --- | --- | --- | --- |
|  | | | **----------------------------------------** | | |
| **Covariate** | **Level** | **N** | **Hazard Ratio (95% CI)** | **HR P-value** | **Type3 P-value** |
| Immunotherapy at any CoC Facility | No | 62800 | 1.04 (1.02-1.06) | **<.001** | **<.001** |
| Yes | 238 | - | - |
|  | | | | | |
| Age at Diagnosis | >=65 | 32178 | 1.23 (1.20-1.26) | **<.001** | **<.001** |
| <65 | 30860 | - | - |
|  | | | | | |
| Facility Type | Integrated Network/Community Cancer Program | 14698 | 1.23 (1.19-1.26) | **<.001** | **<.001** |
| Comprehensive Community Cancer Program | 30808 | 1.02 (1.00-1.04) | **0.040** |
| Academic/Research Program | 17532 | - | - |
|  | | | | | |
| Facility Location | West | 26262 | 0.86 (0.84-0.89) | **<.001** | **<.001** |
| South | 25517 | 0.81 (0.78-0.83) | **<.001** |
| Northeast | 11259 | - | - |
|  | | | | | |
| Sex | Male | 32635 | 1.38 (1.35-1.40) | **<.001** | **<.001** |
| Female | 30403 | - | - |
|  | | | | | |
| Race | White | 56738 | 1.17 (1.14-1.21) | **<.001** | **<.001** |
| Non-white | 6300 | - | - |
|  | | | | | |
| Primary Payor | Medicaid/Other Goverment/Not Insured/Unknown | 11156 | 1.22 (1.19-1.26) | **<.001** | **<.001** |
| Medicare | 31823 | 1.05 (1.03-1.08) | **<.001** |
| Private | 20059 | - | - |
|  | | | | | |
| Percent No High School Degree 2007-2012 | >=21% | 12118 | 1.03 (1.00-1.07) | 0.073 | **0.006** |
| 13.0-20.9% | 19224 | 1.01 (0.98-1.05) | 0.442 |
| 7.0-12.9% | 20741 | 0.98 (0.95-1.01) | 0.254 |
| <7.0% | 10955 | - | - |
|  | | | | | |
| Census Median Income Quartiles 2007-2012 | <$38,000 | 13959 | 1.28 (1.23-1.33) | **<.001** | **<.001** |
| $38,000-$47,999 | 17321 | 1.34 (1.29-1.38) | **<.001** |
| $48,000-$62,999 | 17070 | 1.09 (1.06-1.13) | **<.001** |
| >=$68,000 | 14688 | - | - |
|  | | | | | |
| Urban/Rural 2013 | Urban/Rural | 13673 | 0.93 (0.91-0.94) | **<.001** | **<.001** |
| Metro | 49365 | - | - |
|  | | | | | |
| Charlson-Deyo Score | 1+ | 26728 | 1.19 (1.17-1.21) | **<.001** | **<.001** |
| 0 | 36310 | - | - |
|  | | | | | |
| Year of Diagnosis (quartile) | >=2004, <=2007 | 20288 | 1.06 (1.04-1.08) | **<.001** | **<.001** |
| >2007, <=2009 | 11005 | 0.92 (0.90-0.95) | **<.001** |
| >2009, <=2012 | 18717 | 1.02 (0.99-1.04) | 0.196 |
| >2012, <=2014 | 13028 | - | - |
|  | | | | | |
| Primary Site | Overlapping lesion/NOS, lung | 15113 | 1.07 (1.05-1.10) | **<.001** | **<.001** |
| Middle or lower, lung | 13913 | 1.09 (1.07-1.12) | **<.001** |
| Upper, lung | 34012 | - | - |
|  | | | | | |
| Tumor Size (cm) | Unknown | 22452 | 1.13 (1.11-1.15) | **<.001** | **<.001** |
| > 5cm | 163 | 1.10 (0.00-2.892E20) | 0.997 |
| <= 5cm | 40423 | - | - |
|  | | | | | |
| Radiation | No | 32591 | 1.21 (1.19-1.23) | **<.001** | **<.001** |
| Yes | 30447 | - | - |
|  | | | | | |
| \*  Number of observations in the original data set = 63038. Number of observations used = 63038. \*\* Backward selection with an alpha level of removal of 0.05 was used.  No variables were removed from the model. | | | | | |



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