Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Surgical resection versus stereotactic body radiation therapy in early stage bronchopulmonary large cell neuroendocrine carcinoma

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Keywords
Bronchopulmonary; large cell tumor neuroendocrine tumor; lobectomy; pneumonectomy; stereotactic body radiation therapy.

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Received: 23 October 2019;
Accepted: 8 November 2019.

doi: 10.1111/1759-7714.13260

Thoracic Cancer **11** (2020) 305–310

Abstract

Background: Surgery is the standard of care for early stage non-small cell lung cancer (NSCLC). Stereotactic body radiotherapy (SBRT) is another definitive treatment option for those patients who have not been treated surgically. Comparison of approaches is being explored in NSCLC, but has yet to be compared exclusively in large cell neuroendocrine carcinoma (LCNEC) of the lung. We used the National Cancer Database (NCDB) to conduct such a comparison.

Methods: We accessed the NCDB for patients with LCNEC who were recorded as having lung stage T1-2N0M0 treated with lobectomy/pneumonectomy or SBRT. Multivariable logistic regression identified predictors of SBRT. Multivariable Cox regression was used to identify predictors of survival propensity matching and account for indication bias.

Results: A total of 3209 patients met the criteria, of which 238 (7%) received SBRT. The median SBRT dose was 50 Gy (48–60) in four fractions (3–5). Predictors of SBRT were age >68, T1 disease, and most recent year of treatment. Predictors of survival were younger age, surgical treatment, female sex, and T1 disease. After propensity matching, median survival was 57 months versus 35 months in favor of surgical resection, $P < 0.0001$.

Conclusion: Surgical resection in comparison to SBRT has improved survival for patients with early stage LCNEC of the lung. SBRT represents a viable treatment alternative for those patients who do not meet the criteria for surgery.

Introduction

Bronchopulmonary large cell neuroendocrine carcinomas (LCNEC) comprise approximately 3% of malignant lung neoplasms.[1] Similar to small cell lung carcinoma (SCLC), LCNEC is of neuroendocrine derivation; however, it is most commonly classified as a form of non-small cell lung cancer (NSCLC). Considering the high grade nature of LCNEC, patients often present with locally advanced or metastatic disease.[2] Given the rarity of early stage disease, highly powered studies are lacking as are consensus recommendations regarding treatment. Additionally, the discordance between embryologic origin and oncologic classification of LCNEC complicate matters further as treatment paradigms for SCLC and NSCLC differ significantly.

In early stage NSCLC, long-term survival data has established surgical resection; either lobectomy or pneumonectomy as the standard of care.[3] As LCNEC is classified under NSCLC, surgical management is recommended when LCNEC is diagnosed early (ie, stage I or II disease).[4] However, a proportion of patients may be medically and/or technically inoperable, or refuse surgery altogether. In these circumstances, stereotactic body radiation therapy (SBRT) is a local modality that affords high local control and satisfactory outcomes for inoperable early-stage non-small cell lung cancer (NSCLC).[5] SBRT experiences for early-stage

LCNEC tumors have been limited to two case reports.[6,7] Furthermore, SBRT has not previously been compared with the current standard of surgical resection. As a result, we sought to compare these modalities using a large, contemporary national database to compare treatment approaches and outcomes in T1-2N0 LCNEC.

Methods

The NCDB is a joint project managed by the Commission on Cancer (CoC), American College of Surgeons, and the American Cancer Society. Information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the United States annual oncologic cases have been captured within the dataset.[8] The American College of Surgeons and the CoC have not verified and are neither responsible for the statistical and analytical methodology employed nor the conclusions drawn from these data. All data including patient information in the NCDB database has been excluded from this study and it was exempt from institutional review board evaluation.

The NCDB 2004 to 2015 Participant User File containing Large cell neuroendocrine carcinomas (LCNEC) histology code 8012/3 was utilized for this study. Inclusion criteria for this investigation were patients with newly-diagnosed, histologically-confirmed T1-2N0M0 LCNEC tumors. Those patients who received no treatment were excluded, as were those who received nonablative radiotherapy (RT) and postoperative RT. In addition to removing patients with no follow-up information, subjects with <one month follow-up were also excluded to account for immortal time bias.

Radiation technique was recorded in the NCDB, and was limited to a dose of 48–60 Gy in 3–5 fractions.[9] Surgery was defined as pneumonectomy, bi/lobectomy, or sublobar resection (eg, wedge resection or segmentectomy), all of which are coded for in the NCDB.

Information collected on each patient encompassed demographic, clinical, and treatment data. Statistical analysis was performed via MedCalc Version 18 (Ostend, Belgium). Chi-square testing was used to compare clinical, socioeconomic and treatment characteristics between the surgical and SBRT groups. Summary statistics were reported for discrete variables and multivariable logistic regression models were used to assess the association between independent variables of interest. Overall survival (OS) was calculated from the date of diagnosis to the date of last contact or death.[10] Univariable survival analysis was performed for all characteristics listed on Table 1, and statistically significant factors were then entered in a hierarchical fashion using "enter" selection of the covariates' likelihood ratios, adjusted hazard ratios (HR) and 95%

Table 1 Patient characteristics (n = 3209)

Characteristics	No. (%)
Age	
≤68	1712 (53)
>68	1497 (47)
Chemotherapy	
No	2436 (76)
Yes	773 (24)
Comorbidity score	
0	1480 (46)
1	1250 (39)
≥2	480 (15)
Distance	
≤11 miles	1563 (49)
>11 miles	1646 (51)
Facility type	
Community Cancer Program	236 (7)
Comprehensive Community Cancer Program	1518 (47)
Academic/Research Program	1455 (46)
Grade	
Well differentiated	18 (1)
Moderately differentiated	129 (5)
Poorly differentiated	2533 (94)
Education, %	
≥29	595 (19)
20–28.9	991 (31)
14–19.9	1031 (32)
<14	592 (18)
Income, USD	
<30 000	652 (20)
30 000–35 000	866 (27)
35 000–45 999	875 (27)
>46 000	816 (26)
Insurance	
None	67 (2)
Private	986 (31)
Government	2124 (67)
Location	
Metropolitan	2585 (81)
Urban	547 (17)
Rural	77 (2)
Race	
Caucasian	2832 (88)
African American	303 (9)
Other	74 (3)
Gender	
Male	1674 (52)
Female	1535 (48)
T Stage	
T1	1893 (59)
T2	1316 (41)
Year	
2004–2006	688 (21)
2007–2009	1075 (33)
2010–2012	903 (28)
2013–2014	544 (18)

confidence interval (CI) were reported, with α = 0.05 used to indicate statistical significance.

Propensity score analysis was used to mitigate indication bias caused by lack of randomization.[11–13] Multivariable logistic regression was used to calculate the propensity score providing a score reflecting the conditional probability of a patient receiving of surgery or SBRT. After calculation of the propensity score, a Cox proportional hazards model with adjustment for propensity score was developed.[14] Patients treated with SBRT were also matched with patients treated surgically based on the propensity score using an exact match resulting in 238 pairs. Kaplan-Meier analysis was then used to compare outcomes between these two propensity matched cohorts. In addition, to demonstrating that the groups were balanced, we sorted the matched cohorts by propensity score and compared the means of the quintiles which indicated a difference of less than 0.10.

Results

In summary, 39 036 patients were diagnosed with bronchopulmonary large cell neuroendocrine carcinomas (LCNEC), 6661 of these patients were staged as T1-2N0M0 (see Figure 1 for all inclusion criteria). Of those patients, 2971 (93%) underwent resection and 238 (7%) received SBRT. Of the patients that received SBRT, reasons for not undergoing surgery were as follow: comorbid conditions (n = 65 [27%]), patient refusal despite recommendation (n = 15 [6%]), and the remainder for unknown reasons. The median SBRT dose was 50 Gy (IQR: 48–60) in four fractions (3–5). There were slightly more male patients (52%) and the majority of patients had T1 disease 1893 (59%). A full set of baseline characteristics are given in Table 1.

Multivariable logistic regression was performed to evaluate independent predictors of receiving SBRT and those results are displayed in Table 2. SBRT patients were older ($P < 0.0002$) and had lower comorbidity scores ($P < 0.0093$). The median follow-up for the entire cohort was 39 months. Predictors of decreased OS on multivariable analysis are listed in Table 3 and include older age, higher comorbidity score, male sex, higher T stage, and treatment with SBRT. As described in Methods, after propensity matching, Kaplan-Meier analysis was used to compare OS in 238 matched pairs having received resection *v*ersus SBRT (Fig 2). Median survival was 34.6 months in the SBRT group and 57.2 months in the surgical group with corresponding five-year OS of 25% versus 48% ($P < 0.0001$). In the unmatched cohorts, overall survival was a median of 68.2 months compared to 34.6 months, again in favor of surgical resection ($P < 0.0001$). Corresponding five year overall survivals were 53% and 24%.

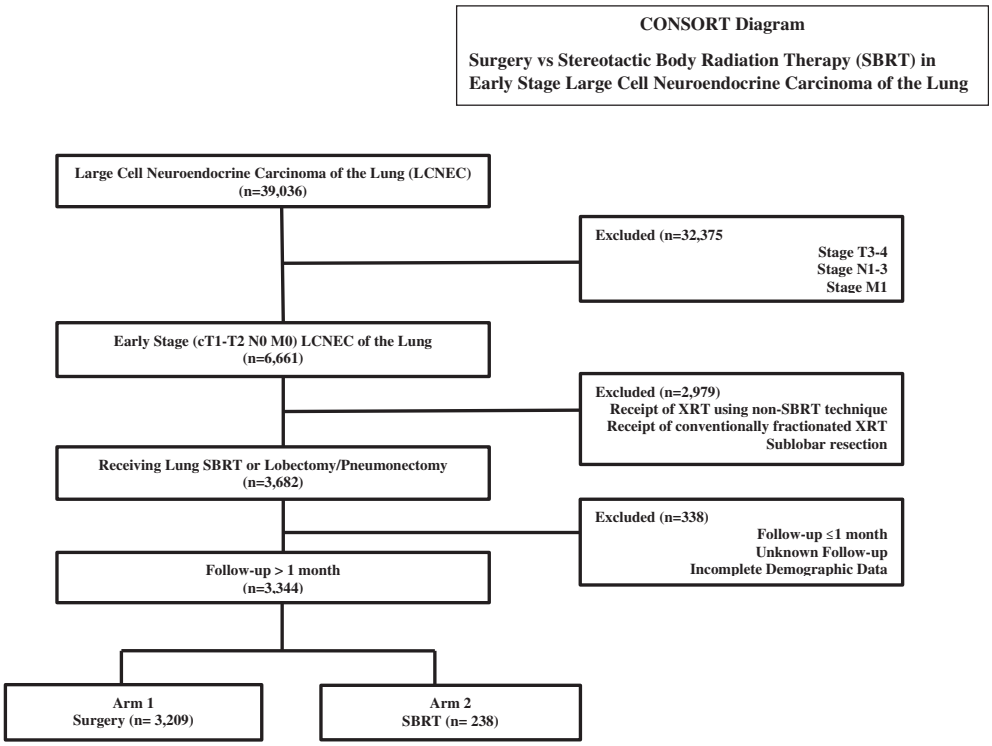

Figure 1 CONSORT diagram showing selection criteria.

Table 2 Multivariable logistic regression for receipt of Stereotactic body radiotherapy (SBRT)

Characteristic	Odds ratio (95% CI)	*P*-value
Age		
≤68	Reference	
>68	1.88 (1.34–2.62)	**0.0002**
Chemotherapy		
No	Reference	
Yes	0.35 (0.21–0.57)	**<0.0001**
Comorbidity score		
0	Reference	
1	0.36 (0.26–0.51)	**<0.0001**
≥2	0.57 (0.38–0.87)	**0.0093**
Distance		
≤11 miles	Reference	
>11 miles	1.22 (0.88–1.69)	0.2276
Facility type		
Community Cancer Program	Reference	
Comprehensive Community Cancer Program	2.54 (1.17–5.50)	**0.0179**
Academic/Research Program	2.00 (0.92–4.37)	0.0807
Grade		
Well differentiated	Reference	
Moderately differentiated	0.31 (0.02–4.01)	0.3726
Poorly differentiated	0.89 (0.11–7.48)	0.9149
Education, %		
≥29	Reference	
20–28.9	1.00 (0.86–1.17)	0.94
14–19.9	0.92 (0.78–1.09)	0.35
<14	0.85 (0.69–1.05)	0.14
Income, USD		
<30 000	Reference	
30 000–35 000	0.97 (0.59–1.57)	0.8896
35 000–45 999	1.04 (0.61–1.75)	0.8916
>46 000	0.60 (0.33–1.11)	0.1025
Insurance		
None	Reference	
Private	0.80 (0.55–1.18)	0.26
Government	1.06 (0.73–1.55)	0.76
Location		
Metropolitan	Reference	
Urban	0.95 (0.60–1.49)	0.8080
Rural	2.01 (0.92–4.39)	0.0796
Race		
Caucasian	Reference	
African American	1.62 (1.00–2.61)	**0.0499**
Other	0.62 (0.21–1.85)	0.3896
Gender		
Male	Reference	
Female	0.94 (0.70–1.25)	0.6559
T Stage		
T1	Reference	
T2	0.68 (0.49–0.94)	**0.0185**
Year		
2004–2006	Reference	
2007–2009	4.06 (2.32–7.08)	**<0.0001**
2010–2012	4.19 (2.37–7.39)	**<0.0001**
2013–2014	5.49 (3.05–9.89)	**<0.0001**

bold values=statistically significant.

Table 3 Multivariable cox regression

Characteristic	HR (95% CI)	*P*-value
Age		
≤68	Reference	
>68	1.44 (1.29–1.60)	<0.0001
Chemotherapy		
No	Reference	
Yes	0.83 (0.73–0.94)	0.0029
Comorbidity score		
0	Reference	
1	1.12 (1.01–1.25)	0.0344
≥2	1.45 (1.27–1.66)	<0.0001
Treatment		
Surgery	Reference	
SABR	1.61 (1.36–1.92)	<0.0001
Race		
Caucasian	Reference	
African American	0.80 (0.66–0.97)	0.0201
Other	0.80 (0.57–1.11)	0.1861
Gender		
Male	Reference	
Female	0.83 (0.75–0.92)	0.0002
T stage		
T1	Reference	
T2	1.26 (1.14–1.40)	<0.0001

Discussion

In this investigation, we utilized the NCDB to compare outcomes following surgery and SBRT for early stage large cell neuroendocrine carcinomas (LCNEC) and the results indicate that surgery continues to be the standard for patients who are candidates for resection. However, definitive SBRT does appear to provide a viable alternative for patients in whom surgery is not possible. Keeping in mind the rarity of LCNEC, randomized studies would likely suffer from inadequate accrual therefore are unlikely to occur. Further retrospective studies, however, could be helpful in evaluating cancer-related endpoints such as, patterns of failure and salvage therapy.

As alluded to above, due to the rarity of LCNEC there is no defined optimal treatment which is supported by large randomized trials.[15] Treatment for LCNEC has long been a hybrid of the regimen for non-small cell lung cancer and small-cell lung cancer. For example, cases of operable non-metastatic LCNEC should undergo surgical resection, similar to NSCLC. Conversely, chemotherapeutic regimens, when offered, are comparable to that of a SCLC regimen.[16] In terms of surgery, a recent study comparing sublobar resection (SLR) versus lobectomy for early stage LCNEC utilizing NCDB data found the five year survival to be 38% for both groups and 37.8% and 56.7% ($P < 0.001$), respectively.[17] In another study, data from SEER for patients with early stage LCNEC that underwent resection showed the

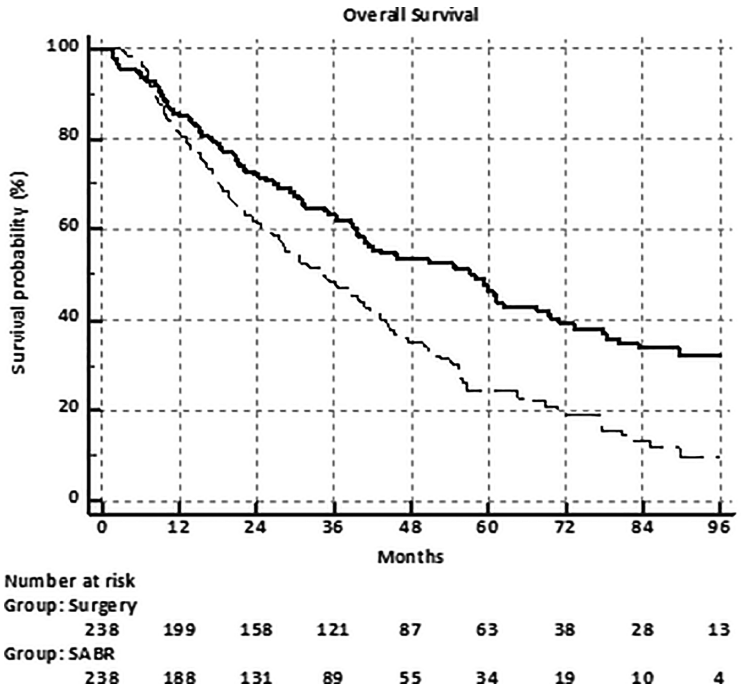

Figure 2 Median survival was 34.6 months in the stereotactic body radiotherapy (SBRT) group and 57.2 months in the surgical group with corresponding five-year OS of 25% versus 48% ($P < 0.0001$). Treatment (——) surgery and (——) SABR.

median survival was 48 months ($P = 0.000$).[3] These results are in line with those herein as we found a similar five year survival of 48% and a median survival of 57.2 months in our study.

Only two case reports regarding early stage LCNEC treatment with SBRT were found on review of the literature. The first case was a 54 year old female who underwent a wedge resection and mediastinal lymph node dissection for a left upper lobe nodule and was diagnosed with a stage 1 LCNEC. The patient later developed a growing nodule in the left upper lobe which was PET-avid, and after multidisciplinary discussion underwent SBRT. She received 50 Gy in five fractions and at four months post SBRT, there was no evidence of local or distant failure. The second case report involved a 78 year old male with multiple comorbidities who was found to have stage IA LCNEC of the left upper lobe, diagnosed by percutaneous needle biopsy. Surgery was recommended; however, SBRT (55 Gy in five fractions) was the chosen treatment due to the patient's reluctance to undergo surgery. At last follow up, (18 months) there was no evidence of disease and no treatment-related toxicity.

NCDB-based studies have inherent limitations since the data does not contain important endpoints such as local failure, distant failure, or treatment related toxicity all of which impact on a generally frail patient population. In this study, the SBRT group was an older cohort, and as such are likely to be other unrecorded biases that could potentially create an imbalance between the groups. In addition, the NCDB is lacking data on performance status, extent of clinical workup, baseline pulmonary function, and salvage therapies, all of which would impact the ultimate outcome in these patients. The above limitations need to be accounted for when interpreting the results of the present study, and hopefully will help generate retrospective investigations that better characterize outcomes in this patient population.

In conclusion, the results presented here suggest that surgical resection is the cornerstone of therapy for early stage LCNEC. In situations where surgery is not feasible, SBRT is a viable alternative.

Acknowledgment

There was no research support for this study.

Disclosure

All authors declare there are no conflicts of interest.

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