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The role of adjuvant therapy for atypical bronchopulmonary carcinoids

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ABSTRACT

Background: Atypical bronchopulmonary carcinoid tumors are rare but carry high recurrence rates following resection. The role of adjuvant therapy remains unclear owing to a lack of high-volume data. To address this knowledge gap, we examined predictors of adjuvant therapy and effects on outcome.

Methods: We queried the National Cancer Database for patients with resected stage I-III atypical carcinoid. Adjuvant therapy was defined as chest radiation, chemotherapy, or a combination thereof. Multivariable logistic regression identified predictors of adjuvant therapy. Multivariable Cox regression evaluated predictors of survival. Propensity matching accounted for indication biases.

Results: Overall, 533 stage I/II and 129 stage III patients were identified. Predictors for adjuvant therapy in stage I/II disease were stage II, positive margins, lymph node ratio (LNR) of 1–25%, and more remote year of treatment. Predictors for adjuvant therapy in stage III were female gender and LNR of 26–50%. Median overall survival in stage I/II and III was 116 months and 61 months, respectively. Predictors for survival in stage I/II were age, margins, comorbidity score, and LNR; factors for stage III disease were LNR and more remote year of treatment. Delivery of adjuvant therapy was not independently associated with survival in either stage I/II or III patients. Furthermore, propensity matched analysis did not reveal a benefit to adjuvant therapy.

Conclusions: This study shows no clear survival benefit with adjuvant radiotherapy and/or chemotherapy, even in stage III disease. Although this implies that adjuvant therapy should not be routinely delivered, individualized judgment is still recommended.

1. Introduction

Bronchopulmonary carcinoid is a rare neuroendocrine tumor accounting for only 1–2% of all lung malignancies [1]. Typical bronchopulmonary carcinoids follow a relatively indolent natural history owing to their low grade and low mitotic rate [1,2]. Atypical bronchopulmonary carcinoids, on the other hand, are rarer and characterized by an intermediate grade, higher mitotic rate, and presence of necrosis. For operable patients with localized, resectable bronchopulmonary carcinoids, surgical resection with regional nodal sampling remains the standard of care [3]. As expected, atypical bronchopulmonary carcinoids have a worse prognosis, with a higher likelihood of both local failure and distant metastasis, and ten year survival rates around 50% [4,5]. As such, there is a potential role for adjuvant therapy; however, that role remains unclear due to the lackof randomized evidence and the rare nature of the disease. To that end, the National Comprehensive Cancer Network (NCCN) guidelines endorse several options, ranging from observation to concurrent chemoradiation [6]. As such, we sought to use the National Cancer Database (NCDB) to examine predictors of adjuvant therapy and any potential effect on outcome in patients with surgically resected atypical bronchopulmonary carcinoids.

2. Methods

The methods for analyzing the NCDB have been described [7,8]. This retrospective review consisted of de-identified data from the NCDB, therefore was exempt from institutional review board evaluation. Overseen by the American Cancer Society and American College of Surgeons, the NCDB encompasses an estimated 70% of annual cancer cases in the United States. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

Patients with documented clinical stage I-III atypical pulmonary carcinoids (ICD-O-3 code 8249/3) treated with surgical resection (lobectomy or pneumonectomy) were included in this study. Fig. 1 is a

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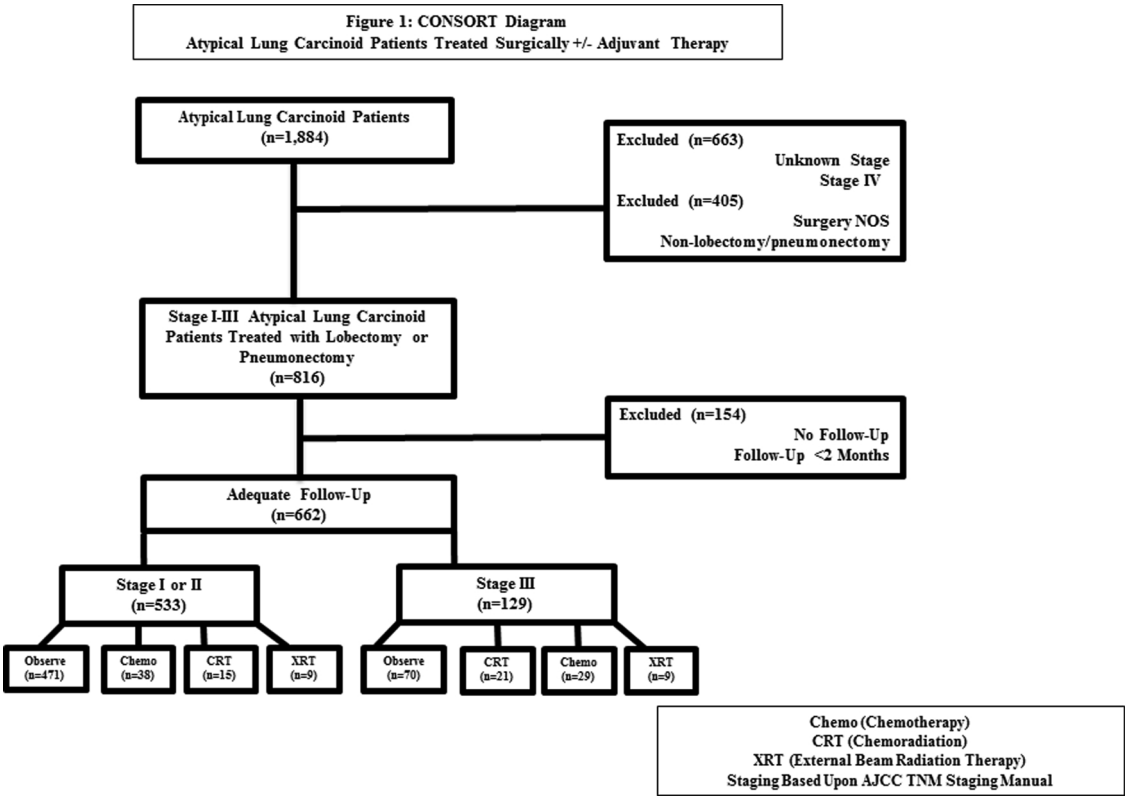

Fig. 1. CONSORT Diagram.

CONSORT diagram outlining the cohort selection criteria. We excluded patients not treated surgically, or having unknown/inadequate (i.e. < 2 months) follow up to account for immortal time bias.

Race was categorized as Caucasian, African American, or other. The Charlson/Deyo comorbidity index quantified the degree of comorbidities [9]. Socioeconomic data in the patients' residence census tract were divided into quartiles based upon the percentage of persons with less than a high school education and median household income. Facility type was grouped according to the Commission on Cancer accreditation category. Locations were described based on data provided by the US Department of Agriculture Economic Research Service. Insurance status is documented in the NCDB as it appears on the admission page.

Data were analyzed using Medcalc Version 18 (Ostend, Belgium). Summary statistics are presented for discrete variables. Chi-squared tests compared sociodemographic, treatment, and tumor characteristics between the treatment groups. Multivariable logistic regression was done to identify predictors of observation versus adjuvant therapy (chemotherapy, chest radiation, or chemoradiation). Overall survival is recorded in the NCDB in months from time of diagnosis to death, or censored at last contact. Kaplan-Meier curves were used to calculate cumulative probability of survival [10]. Log-rank statistics were used to test for a statistically significant difference in the cumulative proportions across groups. A multivariable survival analysis was conducted using a Cox proportional hazards model [11]. Factors significant on univariable analysis were entered using a stepwise elimination process. Adjusted hazard ratios and 95% confidence intervals are reported, using an alpha level of 0.05 to indicate statistical significance.

To account for indication biases associated with lack of randomization, propensity score-matching was applied to the cohort [12]. Multivariable logistic regression was used to calculate a propensity score indicative of the conditional probability of receiving radiation. The propensity model included observable variables associated with treatment selection on multivariable logistic regression. Patients were then matched based on propensity score and analyzed using Kaplan-Meier curves.

3. Results

Using the above eligibility criteria, we identified 816 patients (Table 1). The vast majority (81%) were stage I/II. The median age was 64 (range: 40–88) years. Almost all patients had a lobectomy (91%) with nodal evaluation (97%). Most patients (82%) across all stages were observed after surgery. Predictors of adjuvant therapy in stage I/II were: positive margins, lymph node ratio (LNR) of 1–25% (reference: 0), stage II, and more remote year of treatment (Table 2). Predictors of adjuvant therapy in stage III patients were LNR of 26–50% (reference: 0) and female gender (Table 2).

Median follow up for the cohort was 42 months (2–147) for all patients. For stage I/II disease, multivariable Cox regression identified older age, higher comorbidity score, positive margins, and higher LNR as predictors of worse survival (Table 3). Propensity matched Kaplan-Meier analysis showed no significant benefit to adjuvant therapy in stage I/II, with a median survival of 114 months versus 117 months with observation ($p = 0.30$) (Fig. 2). Five year overall survival for observation and adjuvant therapy was 78% and 73%, respectively. For stage III patient's multivariable Cox regression identified rural location and higher LNR as predictive of worse survival (Table 3). Propensity matched Kaplan-Meier analysis did not show a benefit to adjuvant therapy, with median survival of 79 months with observation as compared to 63 months with adjuvant therapy ($p = 0.89$) (Fig. 3). Five year overall survival for observation and adjuvant therapy was 57% and 50%, respectively.

4. Discussion

Atypical bronchopulmonary carcinoid is a rare, intermediate grade neuroendocrine tumor with higher likelihood of distant spread and

Table 1
Patient Demographics and Clinical Characteristics at Baseline (n = 662).

Characteristics	No. (%)
Sex	
Male	230 (35)
Female	432 (65)
Race	
White	591 (89)
African American	51 (8)
Other	20 (3)
Comorbidity Score	
0	414 (63)
1	184 (28)
≥2	64 (9)
Insurance	
Not Insured	13 (2)
Private Payer	295 (45)
Government	348 (52)
Unrecorded	6 (1)
Education %	
≥29	92 (14)
20 to 28.9	180 (27)
14 to 19.9	247 (38)
< 14	137 (21)
Treatment Facility type	
Community cancer program	34 (5)
Comprehensive community cancer program	252 (38)
Academic/research program	376 (57)
Treatment facility location	
Metro	533 (82)
Urban	104 (16)
Rural	10 (2)
Income, US dollars	
< 30,000	89 (14
30,000 to 35,000	147 (22)
35,000 to 45,999	207 (32)
> 46,000	213 (32)
Distance to treatment facility, miles	
≤13 miles	328 (50)
> 13 miles	334 (50)
Age distribution, years	
≤64	345 (52)
> 64	317 (48)
Year of Diagnosis	
2004-06	61 (9)
2007-09	120 (18)
2010-12	265 (40)
2013-14	216 (33)
Stage	
I/II	534 (81)
III	128 (19)
Treatment	
Observation	541 (82)
Chemoradiation	36 (5)
Chemotherapy	67 (10)
Radiation	18 (3)
Type of Surgery	
Lobectomy	605 (91)
Pneumonectomy	57 (9)
Nodal Evaluation	
No	13 (2)
Yes	648 (97)
Unknown	1 (1)
Margin Status	
Negative	617 (93)
Positive	41 (6)
Unknown	4 (1)
Lymph Node Ratio*	
0-25%	121 (18)
26-50%	58 (9)
51-75%	23 (3)
76-100%	15 (2)
NA/NR	445 (68)

* Lymph node ratio = number of positive nodes divided by number of nodes harvested.

local recurrence compared to the more common typical variant. Surgical resection remains the preferred standard of care option in operable patients [13,14]. However, adjuvant management remains debated, providing the impetus for the current study, the largest to date.

Given the higher likelihood of failure, the utilization of adjuvant therapy seems clinically reasonable. A series reviewed over 300 patients with bronchopulmonary carcinoids, with atypical cases representing the minority (14%) [5]. In that series, almost all patients (95%) did not receive adjuvant therapy. The risk of recurrence (95% of which were distant) in typical patients was < 5%, but as high as 25% in those with atypical carcinoids. Predictors for recurrence included positive nodes and atypical histology. Another series, from MD Anderson, reviewed outcomes in over 200 patients with bronchopulmonary carcinoid, 30% of which were atypical [4]. In stage I atypical cases, local and distant failure rates were both approximately 25%. Again, patients with atypical carcinoids had worse outcomes, with a median survival of 78 months (compared to 217 months across all stages). Of the atypical cases treated surgically, 35% received some form of adjuvant therapy. However, there was no discernible benefit to adjuvant therapy, although the sample size was small and heterogeneous. The authors did conclude, however, that given the high rate of local and distant failure for stage I patients (who were mostly observed), perhaps adjuvant therapy in the form of chemoradiation is reasonable. Lastly, a small Italian series reviewed 42 cases of bronchopulmonary carcinoid, of which 16 had atypical histology [15]. There were only 7 stage III patients in this series, all of whom received radiation +/- cisplatin/etoposide. Despite adjuvant therapy, 5 of those 7 patients recurred and died, calling into question its utility.

In light of the scant data discussed above, as well as the rarity of bronchopulmonary carcinoids, it is apparent why concrete recommendations are lacking. Currently, the NCCN guidelines recommend observation, chemotherapy, or combined chemoradiation for resected stage III atypical bronchopulmonary carcinoid [6]. Likewise, the North American Neuroendocrine Tumor Society guidelines state that there are insufficient data to recommend adjuvant therapy after complete resection of bronchopulmonary carcinoids, even those of atypical histology [16]. To that extent, our current NCDB analysis showed no significant benefit to adjuvant therapy, and that overall, most (> 80%) atypical cases throughout the United States were observed. As expected, margin status and LNR played a role in administering adjuvant therapy, although not universally across all stages, likely due to the lack of consensus as mentioned above.

What may be likely is the presence of unrecorded clinicopathologic factors in patients warranting adjuvant therapy. In this manner, although adjuvant therapy may have provided clinical benefits, the magnitude of such was not enough to provide a statistically significant benefit over the “lower risk” cases not warranting adjuvant management. As a result, we recommend that adjuvant therapy continue to be evaluated on a case-by-case basis, because this analysis merely illustrates that routine administration of adjuvant therapy may not be required.

The limitations of the current study include its retrospective nature and inherent selection bias which are present in essentially all NCDB analyses. In addition, the NCDB does not record outcomes outside of survival, such as local failure, regional failure, and salvage therapy, which are all important and can contribute to management decisions, as well as, outcomes. In addition, toxicity data is not captured either, which is an important consideration when discussing adjuvant therapies such as chemotherapy with or without radiation. Furthermore, the number of Stage 1/II atypical carcinoid patients receiving adjuvant treatment was relatively low; potentially a reflection of the inherent rarity of the disease and paucity of high level supporting evidence.

Table 2
MVLR for receipt of adjuvant therapy for atypical bronchopulmonary carcinoid.

Characteristic (Stage 1 and 2)	Odds Ratio (95% CI)	P	Characteristic (Stage 3)	Odds Ratios (95% CI)	P
Age			Age		
≤64	Reference		≤64	Reference	
> 64	0.93 (0.34-2.57)	0.89	> 64	0.53 (0.14-2.06)	0.35
Stage			Comorbidity Score		
I	Reference		0	Reference	
II	6.66 (2.40-18.50)	< **0.01**	1	0.75 (0.25-2.28)	0.61
Comorbidity Score			≥2	4.56 (0.67-30.59)	0.12
0	Reference		Distance		
1	0.49 (0.20-1.18)	0.11	≤13 miles	Reference	
≥2	1.59 (0.53-4.73)	0.41	> 13 miles	0.74 (0.24-2.31)	0.60
Distance			Facility Type		
≤13 miles	Reference		Community Cancer Program	Reference	
> 13 miles	1.15 (0.53-4.73)	0.73	Comprehensive Community Program	1.84 (0.24-13.86)	0.55
Facility Type			Academic/Research Program	1.47 (0.20-10.75)	0.70
Community Cancer Center	Reference		Education level, %		
Comprehensive Community Program	8.52 (0.50-143.77)	0.99	≥29	Reference	
Academic/Research Program	6.09 (0.36-102.54)	0.99	20-28.9	0.92 (0.15-5.58)	0.93
Education level, %			14-19.9	6.60 (0.88-49.32)	0.06
≥29%	Reference		< 14	7.76 (0.75-80.34)	0.08
20 to 28.9	1.23 (0.33-4.62)	0.76	Income, USD		
14 to 19.9	1.22 (0.29-5.09)	0.80	< 30,000	Reference	
< 14	1.19 (0.23-6.23)	0.84	30,000-35,000	1.67 (0.18-15.47)	0.65
Income, USD			35,000-45,999	0.23 (0.02-2.35)	0.21
30,000	Reference		> 46,000	0.37 (0.03-4.08)	0.41
30,000-35,000	0.79 (0.20-3.05)	0.73	Insurance Status		
35,000-45,999	0.48 (0.11-1.99)	0.31	None	Reference	
> 46,000	1.32 (0.29-6.00)	0.72	Private	0.69 (0.04-12.84)	0.80
Insurance			Government	0.61 (0.03-13.48)	0.75
None	Reference		Margin Status		
Private	1.31 (0.10-16.87)	0.84	Negative	Reference	
Government	0.67 (0.04-9.93)	0.77	Positive	4.00 (0.87-18.36)	0.07
Margin Status			Location		
Negative	Reference		Metropolitan	Reference	
Positive	10.23 (2.84-36.78)	< **0.01**	Urban	1.50 (0.35-6.51)	0.59
Location			Rural	3.74 (0.15-94.10)	0.99
Metropolitan	Reference		Lymph Node Ratio, %		
Urban	1.20 (0.36-4.02)	0.76	0	Reference	
Rural	0.37 (0.02-6.54)	0.99	1-25	3.42 (0.73-15.90)	0.12
Lymph Node Ratio, %			26-50	7.10 (1.33-37.84)	**0.02**
0	Reference		51-75	5.27 (0.74-37.50)	0.09
1-25	3.00 (1.09-8.21)	**0.03**	76-100	6.89 (0.79-60.32)	0.08
26-50	1.52 (0.34-6.85)	0.59	Race		
51-75	2.62 (0.37-18.45)	0.33	Caucasian	Reference	
76-100	5.45 (0.52-57.02)	0.16	African American	0.43 (0.07-2.65)	0.36
Race			Other	0.14 (0.01-1.25)	0.15
Caucasian	Reference		Sex		
African American	3.29 (0.99-10.94)	**0.05**	Male	Reference	
Other	0.24 (0.01-4.11)	0.99	Female	0.19 (0.05-0.68)	**0.01**
Sex			Surgery Type		
Male	Reference		Lobectomy	Reference	
Female	0.85 (0.42-1.73)	0.65	Pneumonectomy	0.32 (0.09-1.19)	0.08
Surgery Type			Year of Treatment		
Lobectomy	Reference		2004-06	Reference	
Pneumonectomy	0.79 (0.23-2.75)	0.70	2007-09	0.10 (0.01-1.25)	0.07
Year of Treatment			2010-12	0.73 (0.11-5.07)	0.75
2004-06	Reference		2013-15	0.42 (0.06-3.03)	0.39
2007-09	0.37 (0.11-1.19)	0.09			
2010-12	0.38 (0.13-1.08)	0.06			
2013-15	0.17 (0.05-0.53)	< **0.01**			

5. Conclusions

This NCDB analysis, the largest to date, shows that the vast majority of patients with surgically resected atypical bronchopulmonary carcinoids are observed in the United States. There was no clear survival benefit seen with the addition of adjuvant therapy, even in patients with stage III disease. Although this implies that adjuvant therapy should not be routinely delivered, individualized judgment is still recommended.

Conflict of interest statement

The authors have no conflicts of interest or disclosures.

Table 3
Multivariable Cox Regression Survival Model for Stage I-III Atypical Carcinoids.

Characteristic	Stage I and II HR 95% CI of HR	P
Age		
≤64	Reference	
> 64	2.14 (1.13-4.05)	**0.02**
Comorbidity Score		
0	Reference	
1	0.90 (0.56-1.45)	0.67
≥2	2.08 (1.16-3.72)	**0.01**
Income, USD		
30,000	Reference	
30,000-35,000	0.49 (0.26-0.92)	**0.03**
35,000-45,999	0.52 (0.17-10.76)	**0.03**
> 46,000	0.48 (0.26-0.87)	**0.02**
Margin Status		
Negative	Reference	
Positive	2.41 (1.13-5.16)	**0.02**
Lymph Node Ratio, %		
0	Reference	
1-25	2.27 (0.93-5.55)	0.07
26-50	3.18 (1.25-8.07)	**0.01**
51-75	3.00 (0.75-12.06)	0.12
76-100	2.39 (0.50-11.49)	0.28
	Stage III	
Characteristic	Hazard Ratio (95% CI)	P
Location		
Metropolitan	Reference	
Urban	1.63 (0.81 to 3.27)	0.16
Rural	27.22 (2.06 to 359.70)	**0.01**
Lymph Node Ratio, %		
0	Reference	
1-25	0.90 (0.33 to 2.46)	0.84
26-50	1.81 (0.71 to 4.61)	0.21
51-75	2.34 (0.78 to 7.01)	0.13
76-100	2.99 (1.02 to 8.76)	**0.05**
Year of Treatment		
2004-06	Reference	
2007-09	1.99 (0.55 to 7.23)	0.30
2010-12	3.96 (1.19to 13.13)	**0.03**
2012-15	2.99 (0.73 to 12.17)	0.13

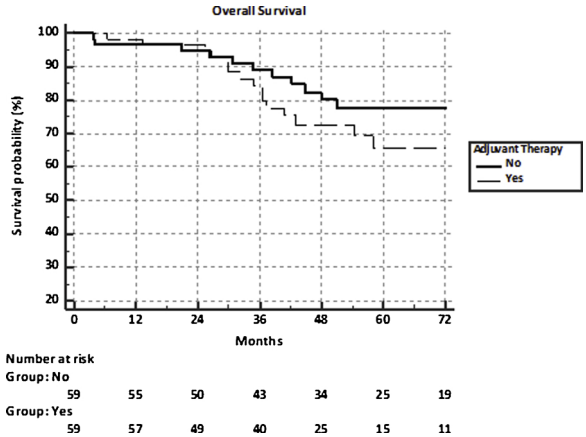

Fig. 2. Propensity-matched Kaplan Meier curve for stage I/II atypical carcinoid. Median survival for observation versus adjuvant therapy was 117 months and 114 months, respectively (p = 0.30). Overall survival at 5 years was 78% and 73% for observation and adjuvant therapy, respectively.

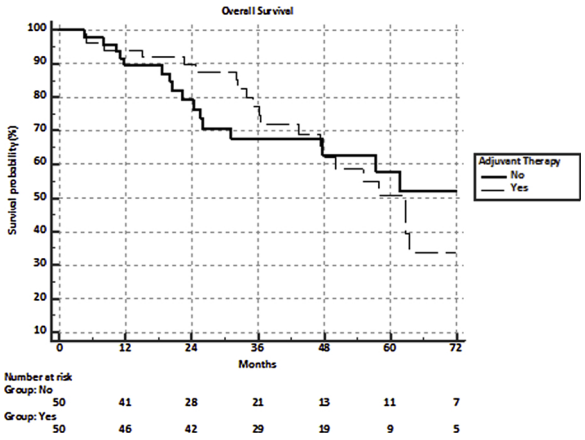

Fig. 3. Propensity-matched Kaplan Meier curve for stage III atypical carcinoid. Median survival was 63 months and 79 months for adjuvant therapy and observation, respectively (p = 0.89). Overall survival at 5 years was 57% and 50% for observation and adjuvant therapy, respectively.

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