Atypical Carcinoid Tumor of the Lung

A Surveillance, Epidemiology, and End Results Database Analysis

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Background: Atypical carcinoid (AC) of the lung is a rare form of thoracic malignancy. The limited knowledge of its biology and outcome stems largely from small, single institution experiences. We analyzed the Surveillance, Epidemiology, and End Results database (SEER) to better understand the clinical characteristics of this disease.

Methods: Demographic, treatment, and outcome data on all patients with pulmonary AC were obtained from the SEER database with 18 reporting sites from 1973 to 2010 using SEER*Stat 8.1.2. Statistical analysis was performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

Results: There were 947,463 patients diagnosed with lung and bronchus tumors in the SEER database, of which 441 had AC (0.05%). Median age of AC patients was 65 years; 69% were women and 87% of white ethnicity. Metastatic disease was present in 20% of patients at diagnosis. In terms of treatment, 78% of patients underwent resection and 12.5% received radiation. The overall 1-year and 3-year survival rates were 86% and 67%, respectively. The 3-year survival rates for distant (M1), regional (lymph node involvement), and localized (lung only) disease were 26% (13 of 50), 69% (50 of 72), and 85% (99 of 116), respectively. On univariate analysis, patients treated with surgery had reduced risk of death (hazard ratio, HR 0.19; $p < 0.001$), whereas radiation treatment was associated with increased risk of death (HR 2.45; $p < 0.001$).

Conclusions: AC accounted for less than 1% of all lung cancers diagnosed and was more frequent in women. The best outcomes were observed with surgical resection for localized disease.

Key Words: Atypical carcinoid, Non–small-cell lung cancer, Outcomes, SEER, Neuroendocrine, Lung cancer.

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Atypical carcinoid (AC) tumor of the lung is a rare subtype of lung cancer. It is estimated that carcinoid tumors overall encompass 1% to 5% of all lung neoplasms, and AC represents 10% of this subpopulation.[1] These tumors belong to a spectrum of pulmonary neuroendocrine tumors (NET) which include, in order of most differentiated to least differentiated, typical carcinoid (TC), AC, large cell neuroendocrine carcinoma (LCNEC), and small cell carcinoma.[2] AC tumors were first defined in 1972,[3] but the classification was not standardized until 1998. A comprehensive examination of the histopathologic and clinical characteristics of 200 cases of pulmonary NET led to a clinically relevant definition of AC by Travis et al. with the requirement for a neuroendocrine morphology and either coagulative necrosis or mitotic counts of 2 to 10 per 2 mm^2 of viable tumor.[4] This definition was subsequently incorporated into the World Health Organization (WHO) and the International Association for the Study of Lung Cancer classifications of lung neoplasms. The overall low prevalence of the disease has curtailed our understanding of the clinical risk factors and prognosis of AC.

Available information suggests that patients with AC tumors often present with early stage disease, and surgical resection is the preferred treatment modality. However, the body of literature on AC largely comes from surgical series and therefore remains skewed toward earlier stage disease with overall better outcomes. The effectiveness of radiation and/or chemotherapy for AC is unknown, either alone or in adjunct with surgery.[5]

Given its rarity and the resulting paucity of data on prognosis and optimal management, we sought to better understand pulmonary AC by using the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute to investigate clinical characteristics and outcomes of patients with this specific tumor type.

METHODS

Data Source

This analysis was performed using the SEER public-use database, including the 18 SEER registries and SEER*Stat 8.1.2 data sets from 1973 to 2010. However, pulmonary AC cases were only available in SEER beginning in 2001 secondary to the standardization in the histological coding of AC at that time.[4] The SEER program is sponsored by the National Cancer Institute and collects information regarding cancer

incidence and survival from 18 population-based cancer registries that cover approximately 28% of the U.S. population.[6]

Patient Population

All patients with a diagnosis of lung and bronchus cancer classified according to the ICD-0–3/WHO 2008 criteria between years 1973 and 2010 were identified in the SEER database for this study. We identified the cases with this diagnosis and extracted the relevant data using the case listing session of SEER*Stat 8.1.2 software. From this group, patients with an ICD-0–3 histology diagnosis of AC tumor were identified and employed for the primary analysis. To provide a broad, clinically relevant characterization of pulmonary AC, none of these patients were excluded from the study.

Statistical Analysis

Baseline patient characteristics were compared by summary stage (localized, regional, and distant) using Kruskal–Wallis test for continuous variables, i.e., age at diagnosis, and chi-square test of Fisher's exact test for categorical variables, as applicable. Age at diagnosis, gender, race, grade, stage, summary stage, Contract Health Service Delivery Areas (CHSDA) regions, primary site, surgery of primary site, and radiation variables were included in the survival analysis models. Survival functions were estimated by the Kaplan–Meier method and the log-rank test was used to assess the differences in overall survival (OS) stratified by each covariate.[7] Univariate and multivariable survival analyses were conducted using the Cox proportional hazards model.[8] Multivariable analysis was conducted by entering race, gender, primary site, radiation, and CHSDA region into the Cox proportional hazards model. The best predictive model of OS was identified using a backward variable selection method with an alpha level of removal of 0.1. The model was stratified by summary stage since it was shown to be a time-dependent covariate and by age at diagnosis.

All analyses were done using SAS 9.3 (SAS Institute, Inc., Cary, NC) with a statistical significant level of 0.05.

RESULTS

First, we examined the clinical characteristics of patients presenting with pulmonary AC. A total of 947,463 cases of lung and bronchus tumors were identified and 441 of them were AC. Demographic data for all the AC patients are shown in Table 1. The median age for all the AC patients was 65 years (range, 21–90); 87% patients were white and 8.5% were African American (AA). Women represented a majority of the patients (68.7%). All the analyses were conducted using the SEER historic stage A system classification, as the American Joint Committee on Cancer (AJCC) 6th edition was missing a significant amount of data. SEER historic stage A categorizes disease as local (tumor in lung only), regional (pulmonary lymph node involvement), or distant (M1). In all, 48.7% patients were categorized with localized disease and 20% with distant disease. Regarding treatment, 77.5% of patients were managed by surgery, and 12.5% received radiation treatment. Of the patients who were treated with surgery, 21.5% had a sub-lobar resection, whereas 78.5% had a lobectomy, bilobectomy, or pneumonectomy.

TABLE 1. Patient Demographics and Clinical Characteristics

Variable	Level	AC, *n* (%)
Age at diagnosis	Median (range)	65 (21–90)
Race	Black	37 (8.47)
	Other	19 (4.35)
	White	381 (87.19)
Sex	Male	138 (31.29)
	Female	303 (68.71)
CHSDA region	East	200 (45.35)
	Northern plains	46 (10.43)
	Pacific coast	167 (37.87)
	Southwest	28 (6.35)
Primary site	Main bronchus	10 (2.27)
	Upper lobe, lung	151 (34.24)
	Middle lobe, lung	61 (13.83)
	Lower lobe, lung	177 (40.14)
	Overlapping lesion of lung	10 (2.27)
	Lung, NOS	32 (7.26)
AJCC stage 6	IA	123 (39.3)
	IB	42 (13.42)
	IIA	14 (4.47)
	IIB	15 (4.79)
	IIIA	37 (11.82)
	IIIB	26 (8.31)
	IV	56 (17.89)
	Missing	128
Summary stage	Distant	83 (19.9)
	Regional	131 (31.41)
	Localized	203 (48.68)
	Missing	24
Radiation	Yes	54 (12.5)
	No	378 (87.5)
Surgery of primary site	Yes	341 (77.5)
	No	99 (22.5)
Surgery type	Segmental resection	13 (3.88)
	Wedge resection	59 (17.61)
	Lobectomy or bilobectomy	247 (73.73)
	Pneumonectomy	16 (4.78)

AC, atypical carcinoid; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

Next, we compared the demographic and clinical characteristics across tumor stages. The distribution by stage of AC was not significantly different for race, sex, or region (Table 2). However, patients who presented with distant disease were significantly older ($p = 0.006$), more likely to receive radiation ($p < 0.001$), and less likely to undergo surgical resection ($p < 0.001$).

The overall 1-year and 3-year survival rate was 86% ($n = 374$) and 67% ($n = 254$), respectively. As with other lung cancer histologies, patients who presented with more advanced stages of disease had inferior outcomes: The 1-year and 3-year survival rate for patients with local disease was 92% and 85%, respectively, compared with just 61% and