Survival differences of lung neuroendocrine tumors in California by sociodemographic, clinicopathologic, and treatment factors

Claire K. Mulvey[a,b], Alan Paciorek[a,c], Julia Whitman[a], Brandon Shih[a], Matthew A. Gubens[a,b], Emily K. Bergsland[a,b], Iona Cheng[c]

[a] Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco [b] Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco [c] Department of Epidemiology and Biostatistics, University of California, San Francisco

Introduction

- Well-differentiated lung neuroendocrine tumors (NETs) are a heterogeneous group of cancers with varying clinical behavior.
- Little is known about the epidemiology of lung NETs or predictors of survival beyond disease-related factors like histology (typical vs atypical) and stage.
- We investigated associations between sociodemographic, clinicopathologic, geographic, and treatment factors with survival for patients with lung NETs in the diverse state of California.
- CCR is a uniquely complete data source encompassing nearly all cancer diagnoses within the state.

Objectives

- To compare overall survival of patients with lung NETs in California and evaluate for survival differences by sociodemographic and geographic characteristics, along with clinicopathologic and and treatment factors.

Research methods

Study Design:

- Population-based, prospective study of Californians with an incident diagnosis of a lung NET in the California Cancer Registry (CCR).

Study population:

- Californians age ≥18 years in the CCR with an incident diagnosis of a lung NET (typical or atypical histology) from 1992-2017.
- Cases selected based on ICD-O-3 histology codes rom typical carcinoid (8240) or atypical carcinoid (8249) histology with an ICD-10 primary site code of bronchus or lung.
- Poorly-differentiated histologies (small or large cell neuroendocrine carcinomas) were excluded.

Covariates: 1) sex; 2) race/ethnicity; 3) county of residence, classified as rural, suburban, or urban; 4) neighborhood socioeconomic status (nSES); 5) marital status; 6) year of diagnosis; 7) first course of treatment within 12 months of diagnosis; 8) insurance payer (for cases diagnosed after 1995).

Primary Outcome: All-cause mortality. CCR follows patients until confirmation of their death using linkages to state and national vital statistics databases.

Statistical methods:

- Patient characteristics were compared by stage at diagnosis using Kruskal-Wallis test for continuous variables or chi-square test for categorical variables.
- We used time-to-event survival analysis by Kaplan-Meier method and compared univariate survival among demographic and disease factors by the log-rank test.
- Sequential multivariable survival analyses were performed using Cox proportional hazard models. Models were adjusted sequentially for possible confounders, including previously published predictors and our sociodemographic variables of interest.
- Because the assumption of proportional hazards was violated for age, Cox models were age-stratified to allow baseline hazards to vary.

This work is supported by a **NETRF Mentored Award**.

Results

Table 1. Demographic and Clinical Characteristics of Lung NET Population in California from 1992-2017 by Stage at Diagnosis

Variable	Level	Local/Regional Disease (n=4,345)	Metastatic Disease (n=609)	p value[a]
Age at diagnosis	Median [IQR]	63 [52, 72]	68 [58, 77]	<0.001
Sex[b]	Male	1,319 (88.0%)	180 (12.0%)	0.86
	Female	3,025 (87.6%)	429 (12.4%)	
Diagnosis decade	1992-2000	1,107 (90.9%)	111 (9.1%)	<0.001
	2001-2009	1,506 (87.7%)	212 (12.3%)	
	2010-2017	1,732 (85.8%)	286 (14.2%)	
Histology	Typical carcinoid	4,087 (88.4%)	534 (11.6%)	<0.001
	Atypical carcinoid	258 (77.5%)	75 (22.5%)	
Race/Ethnicity[b]	NH White	3,269 (88.8%)	414 (11.2%)	<0.001
	NH Black	208 (80.3%)	51 (19.7%)	
	Hispanic	655 (86.3%)	104 (13.7%)	
	Asian/Pacific Islander	176 (84.6%)	32 (15.4%)	
	Native American	21 (87.5%)	3 (12.5%)	
County	Urban	3,109 (87.9%)	428 (12.1%)	0.62
	Suburban	1,120 (87.0%)	167 (13.0%)	
	Rural	116 (89.2%)	14 (10.8%)	
Marital status[b]	Single (never married, separated, divorced, widowed)	1,738 (87.3%)	252 (12.7%)	0.41
	Partnered (married or domestic)	2,503 (88.1%)	338 (11.9%)	
nSES	Quartile 1	592 (84.1%)	112 (15.9%)	<0.001
	Quartile 2	974 (85.6%)	164 (14.4%)	
	Quartile 3	1,222 (88.9%)	153 (11.1%)	
	Quartile 4	1,387 (90.5%)	145 (9.5%)	
Insurance[b,c]	Private only	2,156 (90.1%)	237 (9.9%)	<0.001
	Medicare	1,202 (85.2%)	208 (14.8%)	
	Medicade/Military/Other Public	462 (81.6%)	104 (18.4%)	
	None/Self Pay	46 (80.7%)	11 (19.3%)	

Abbreviations; IQR, interquartile range; NH, non-Hispanic; nSES, neighborhood socioeconomic status. Demographic and clinical characteristics for the 4,954 patients with stage at diagnosis information available..a) p value for difference between local/regional disease and distant metastatic disease at diagnosis obtained from chi-square test for categorical variables or Kruskal-Wallis test for age at diagnosis. b) Counts do not add up to 4,954 due to missing data. c) Payer/insurance carrier reporting was not mandatory in the California Cancer Registry prior to 1996, so insurance data is presented for the N=4,621 cases diagnosed after 1995.

Figure 1. Kaplan-Meier OS Curves by Disease Characteristics

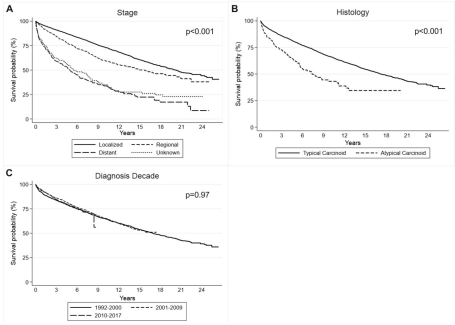
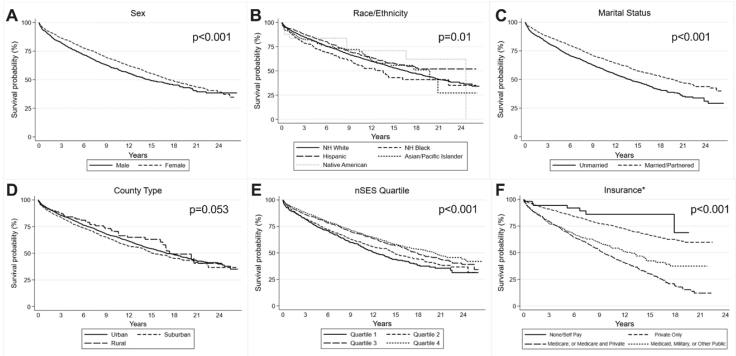


Figure 2. Kaplan-Meier OS Curves by Sociodemographic Variables



*Reporting payer/insurance carriers was not mandatory in CCR prior to 1996, so insurance data is presented for the N=4,621 cases diagnosed from 1996 onwards.

Table 2. Associations between Sociodemographic and Clinicopathologic Factors and All-Cause Mortality in Age-Stratified Models Among N=5,127 Lung NETs, 1992-2017

		Model 1		Model 2		Model 3		Model 4	
Variable	Level	HR [95% CI]	p value	HR [95% CI]	p value	HR [95% CI]	p value	HR [95% CI]	p value
Sex	Male	1	-	1	-	1	-	1	-
	Female	0.60 [0.54, 0.67]	<0.001	0.60 [0.54, 0.67]	**<0.001**	0.60 [0.54, 0.67]	**<0.001**	0.63 [0.57, 0.70]	**<0.001**
Race/ethnicity	NH White	1	-	1	-	1	-	1	-
	NH Black	1.40 [1.14, 1.73]	**0.002**	1.18 [0.96, 1.46]	0.12	1.14 [0.92, 1.41]	0.23	0.98 [0.79, 1.21]	0.83
	Hispanic	0.99 [0.85, 1.16]	0.89	0.94 [0.81, 1.11]	0.47	0.95 [0.81, 1.11]	0.50	0.91 [0.77, 1.06]	0.22
	Asian/Pacific Islander	1.01 [0.78, 1.31]	0.92	0.95 [0.73, 1.24]	0.71	0.94 [0.73, 1.23]	0.67	0.81 [0.62, 1.05]	0.11
	Native American	0.66 [0.32, 1.35]	0.25	0.79 [0.39, 1.62]	0.52	0.77 [0.38, 1.70]	0.56	0.77 [0.37, 1.68]	0.54
County	Urban	1	-	1	-	1	-	1	-
	Suburban	1.11 [1.00, 1.24]	0.051	1.11 [0.99, 1.23]	0.071	1.09 [0.98, 1.22]	0.12	1.07 [0.96, 1.19]	0.25
	Rural	0.74 [0.54, 1.01]	0.056	0.80 [0.59, 1.09]	0.16	0.79 [0.58, 1.07]	0.13	0.79 0.58, 1.07]	0.13
Marital status	Single	1	-	1	-	1	-	1	-
	Married	0.80 [0.73, 0.89]	**<0.001**	0.78 [0.70, 0.86]	**<0.001**	0.77 [0.70, 0.85]	**<0.001**	0.80 [0.72, 0.89]	**<0.001**
nSES	Quartile 1 (lowest nSES)	1	-	1	-	1	-	1	-
	Quartile 2	0.86 [0.74, 1.00]	0.057	0.87 [0.75, 1.02]	0.084	0.86 [0.74, 1.00]	0.051	0.89 [0.76, 1.04]	0.13
	Quartile 3	0.69 [0.59, 0.80]	**<0.001**	0.73 [0.63, 0.86]	**<0.001**	0.73 [0.63, 0.86]	**<0.001**	0.73 [0.63, 0.85]	**<0.001**
	Quartile 4 (highest nSES)	0.58 [0.50, 0.68]	**<0.001**	0.64 [0.55, 0.75]	**<0.001**	0.63 [0.54, 0.74]	**<0.001**	0.65 [0.59, 0.76]	**<0.001**
Diagnosis decade	1992-2000	1	-	1	-	1	-	1	-
	2001-2009	0.85 [0.76, 0.95]	**0.005**	0.78 [0.70, 0.88]	**<0.001**	0.74 [0.66, 0.83]	**<0.001**	0.72 [0.64, 0.81]	**<0.001**
	2010-2017	0.77 [0.66, 0.90]		0.71 [0.61, 0.83]	**<0.001**	0.65 [0.55, 0.76]	**<0.001**	0.63 [0.54, 0.74]	**<0.001**
Stage	Local			1	-	1	-	1	-
	Regional			1.61 [1.41, 1.83]	**<0.001**	1.57 [1.38, 1.80]	**<0.001**	1.42 [1.24, 1.62]	**<0.001**
	Distant			3.42 [3.00, 3.90]	**<0.001**	3.42 [3.00, 3.90]	**<0.001**	2.14 [1.84, 2.48]	**<0.001**
	Unknown			2.43 [1.98, 2.99]	**<0.001**	2.39 [1.95, 2.94]	**<0.001**	1.44 [1.15, 1.80]	**0.001**
Histology	Typical carcinoid					1	-	1	-
	Atypical carcinoid					2.03 [1.67, 2.45]	**<0.001**	1.91 [1.57, 2.32]	**<0.001**
Treatment	Surgery (yes)							0.48 [0.42, 0.55]	**<0.001**
	Radiation (yes)							1.54 [1.28, 1.85]	**<0.001**
	Chemo (yes)							1.82 [1.50, 2.21]	**<0.001**
	Chemo (unknown)							2.23 [1.41, 3.51]	**0.001**
	Hormone treatment (yes)							0.58 [0.24, 1.41]	0.23
	Immune treatment (yes)							2.40 [1.34, 4.30]	**0.003**

Abbreviations: HR, hazard ratio; CI, confidence interval.
Multivariable Cox regression models of survival stratified by age. Model 1 adjusted for sex, race/ethnicity, county, marital status, nSES. and decade of diagnosis. Model 2 adjusted for variables in Model 1 plus age. Model 3 adjusted for the variables in Model 2, plus histology. Model 4 adjusted for the variables in Model 3, plus treatment variables. Hazard ratios for treatment variables are given relative to no treatment. An additional fully-adjusted that also included insurance payer as a covariate, only for cases diagnosed after 1995 when insurance payer collection was mandated in the CCR, did not change overall associations in fully-adjusted model (data not shown).

Conclusions

- There were sociodemographic differences by stage at diagnosis. Compared with patients with locoregional disease, patients with metastatic disease were older, more likely to be diagnosed in most recent decade, more likely to have atypical carcinoid histology, less likely to be NH White, more likely to come from lowest nSES quartile, and more likely to not have insurance.
- Beyond disease-related factors, sociodemographic factors are independently associated with overall survival in lung NETs. Sex, nSES, marital status, age, health insurance, stage, and receipt of surgery, radiation, chemotherapy, and immune treatments were all independently associated with survival. Race/ethnicity was associated with survival in univariate models, but not in multivariable models.
- These results can guide future research into the pathogenesis of lung NETs and help identify opportunities for interventions to reduce survival disparities.