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

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Introduction

- Typical and atypical lung neuroendocrine tumors (NETs) are a relatively rare, heterogeneous group of cancers with a wide spectrum of clinical behavior and limited data regarding risk factors.
- Like other primary sites, the incidence of lung NETs has increased over the last 40 years.[1-3] This contrasts with the declining incidence of non-small cell and small cell lung carcinomas, which are largely smoking related, and suggests distinct underlying risk factors.[4]
- Little is known about the epidemiology of lung NETs or predictors of survival beyond disease-related factors like histology (typical vs atypical) and stage.

Objectives

- To characterize the burden of lung NETs (typical or atypical histology) in California.
- 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: Observational, population-based study of Californians with an incident diagnosis of a lung NET in the California Cancer Registry (CCR). CCR is a uniquely rich data source encompassing nearly all cancer diagnoses within the diverse state of California.

Study population: Californians age ≥18 years in the CCR with an incident diagnosis of a lung NET (typical or atypical histology) from 1992-2017.

Predictors: 1) sex; 2) race/ethnicity; 3) county of residence, classified as rural, suburban, or urban; 4) neighborhood socioeconomic status (nSES); 5) marital status

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

Statistical methods:

- Kaplan-Meier time-to-event survival analysis and compared univariate survival among demographic and disease factors by log-rank test.
- Multivariable Cox proportional hazard models were used to estimate associations of sociodemographic and disease-related factors with all-cause mortality.
- Models adjusted sequentially for possible mediators including tumor and patient characteristics, first treatment, and diagnosis year.
- Because the assumption of proportional hazards was violated for age, Cox models were age-stratified to allow baseline hazards to vary.

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Results

Table 1. Demographics of N=5,127 Lung NET Cases in California from 1992-2017

Variable	Level	N (%)
Histology	Typical carcinoid	4,784 (93.3%)
	Atypical carcinoid	343 (6.7%)
Age at diagnosis	Median [IQR]	64 [52,73]
Diagnosis decade	1992-2000	1,289 (25.1%)
	2001-2009	1,767 (34.5%)
	2010-2017	2,071 (40.4%)
Sex	Female	3,574 (69.7%)
Race/Ethnicity[a]	NH White	3,804 (74.2%)
	NH Black	271 (5.3%)
	Hispanic	785 (15.3%)
	Asian/Pacific Islander	216 (4.2%)
	Native American	25 (0.5%)
	Unknown	26 (0.5%)
County	Urban	3,649 (71.2%)
	Suburban	1,344 (26.2%)
	Rural	134 (2.6%)
Marital status[a]	Single (never married, separated, divorced, widowed)	2,066 (40.3%)
	Partnered	2,921 (57.0%)
	Unknown	140 (2.7%)
nSES quartile[a]	Quartile 1 (lowest)	743 (14.5%)
	Quartile 2	1,185 (23.1%)
	Quartile 3	1,409 (27.5%)
	Quartile 4 (highest)	1,575 (30.7%)
	Unknown	215 (4.2%)
Stage[a]	Localized	3,427 (66.8%)
	Regional	918 (17.9%)
	Distant	609 (11.9%)
	Missing or unknown	173 (3.4%)

Abbreviations: NETs, neuroendocrine tumor; IQR, interquartile range; NH, non-Hispanic; nSES, neighborhood socioeconomic status.

Figure 1. Kaplan-Meier Overall Survival Curves by Disease Characteristics

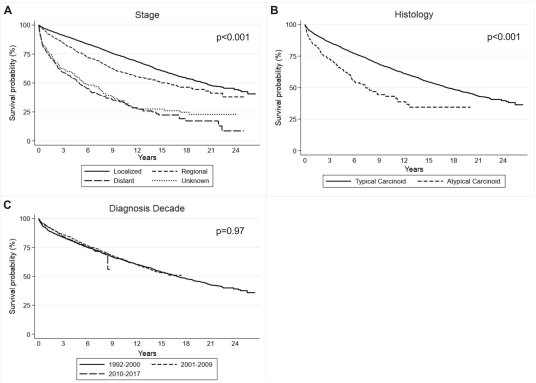
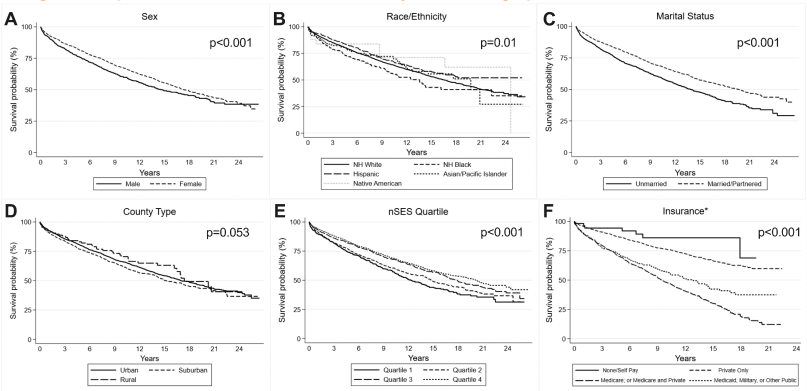


Figure 2. Kaplan-Meier Overall Survival Curves by Sociodemographic Variables



*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**	0.63 [0.57, 0.70]	**<0.001**	0.62 [0.55, 0.69]	**<0.001**
Race/ethnicity	NH White	1	-	1	-	1	-	1	-
	NH Black	1.18 [0.96, 1.46]	0.12	1.14 [0.92, 1.41]	0.23	0.98 [0.79, 1.21]	0.83	0.92 [0.74, 1.16]	0.50
	Hispanic	0.94 [0.81, 1.11]	0.47	0.95 [0.81, 1.11]	0.50	0.91 [0.77, 1.06]	0.22	0.92 [0.77, 1.09]	0.32
	Asian/Pacific Islander	0.95 [0.73, 1.24]	0.71	0.94 [0.73, 1.23]	0.67	0.81 [0.62, 1.05]	0.11	0.71 [0.53, 0.95]	**0.022**
	Native American	0.79 [0.39, 1.62]	0.52	0.77 [0.38, 1.70]	0.56	0.77 [0.37, 1.68]	0.54	1.18 [0.52, 2.66]	0.69
County	Urban	1	-	1	-	1	-	1	-
	Suburban	1.11 [0.99, 1.23]	0.071	1.09 [0.98, 1.22]	0.12	1.07 [0.96, 1.19]	0.25	1.03 [0.91. 1.16]	0.66
	Rural	0.80 [0.59, 1.09]	0.16	0.79 [0.58, 1.07]	0.13	0.79 0.58, 1.07]	0.13	0.78 [0.55, 1.11]	0.17
Marital status	Single	1	-	1	-	1	-	1	-
	Married	0.78 [0.70, 0.86]	**<0.001**	0.77 [0.70, 0.85]	**<0.001**	0.80 [0.72, 0.89]	**<0.001**	0.81 [0.72, 0.91]	**<0.001**
nSES	Quartile 1 (lowest nSES)	1	-	1	-	1	-	1	-
	Quartile 2	0.87 [0.75, 1.02]	0.084	0.86 [0.74, 1.00]	0.051	0.89 [0.76, 1.04]	0.13	0.94 [0.79, 1.11]	0.45
	Quartile 3	0.73 [0.63, 0.86]	**<0.001**	0.73 [0.63, 0.86]	**<0.001**	0.73 [0.63, 0.85]	**<0.001**	0.76 [0.64, 0.91]	**0.002**
	Quartile 4 (highest nSES)	0.64 [0.55, 0.75]	**<0.001**	0.63 [0.54, 0.74]	**<0.001**	0.65 [0.59, 0.76]	**<0.001**	0.70 [0.58, 0.83]	**<0.001**
Stage	Local	1	-	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**	1.35 [1.16, 1.56]	**<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**	2.06 [1.76, 2.41]	**<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**	1.35 [1.04, 1.74]	**0.022**
Diagnosis decade	1992-2000	1	-	1	-	1	-	1	-
	2001-2009	0.78 [0.70, 0.88]	**<0.001**	0.74 [0.66, 0.83]	**<0.001**	0.72 [0.64, 0.81]	**<0.001**	0.76 [0.66, 0.87]	**<0.001**
	2010-2017	0.71 [0.61, 0.83]	**<0.001**	0.65 [0.55, 0.76]	**<0.001**	0.63 [0.54, 0.74]	**<0.001**	0.67 [0.56, 0.80]	**<0.001**
Histology	Typical carcinoid			1	-	1	-	1	-
	Atypical carcinoid			2.03 [1.67, 2.45]	**<0.001**	1.91 [1.57, 2.32]	**<0.001**	1.92 [1.58, 2.33]	**<0.001**
Treatment	Surgery (yes)					0.48 [0.42, 0.55]	**<0.001**	0.49 [0.43, 0.56]	**<0.001**
	Radiation (yes)					1.54 [1.28, 1.85]	**<0.001**	1.52 [1.24, 1.87]	**<0.001**
	Chemo (yes)					1.82 [1.50, 2.21]	**<0.001**	1.89 [1.54, 2.33]	**<0.001**
	Chemo (unknown)					2.23 [1.41, 3.51]	**0.001**	2.67 [1.62, 4.39]	**<0.001**
	Hormone treatment (yes)					0.58 [0.24, 1.41]	0.23	0.58 [0.24, 1.42]	0.24
	Immune treatment (yes)					2.40 [1.34, 4.30]	**0.003**	2.33 [1.19, 4.58]	**0.014**
Insurance	Private only							1	-
	None/Self Pay							0.61 [0.29, 1.29]	0.19
	Medicare only or Medicare + Private							1.27 [1.11, 1.45]	**0.001**
	Medicaid/Military/Other Public							1.54 [1.29, 1.84]	**<0.001**

Multivariable Cox regression models of survival stratified by age. Model 1 adjusted for sex, race/ethnicity, county, marital status, nSES. stage, and decade of diagnosis. Model 2 adjusted for the variables in Model 1, plus histology. Model 3 adjusted for the variables in Model 2, plus treatment variables. Model 4 adjusted for the variables in Model 3, plus insurance payer. *Model 4 includes only the N=4,621 cases diagnosed after 1995, when insurance payer collection was mandated in the CCR. Hazard ratios for treatment variables are given relative to no treatment. Abbreviations: HR, hazard ratio; CI, confidence interval.

Conclusions

- 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 overall survival. Race/ethnicity was associated with survival in univariate models, but not in our multivariable models.
- These results can guide future research into the pathogenesis of lung NETs and help identify opportunities for interventions to reduce survival disparities.