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Authors

Lara, Matthew S
Brunson, Ann
Wun, Ted
et al.

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Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): A California Cancer Registry analysis

Matthew S. Lara[a], Ann Brunson[b], Ted Wun[b], Ben Tomlinson[b], Lihong Qi[b,c], Rosemary Cress[b,c], David R. Gandara[b], Karen Kelly[b,*]

[a] Davis Senior High School, Davis, CA, United States
[b] Division of Hematology Oncology, and University of California Davis Comprehensive Cancer Center, UC Davis School of Medicine Sacramento, CA, United States
[c] UC Davis Department of Public Health Sciences, UC Davis School of Medicine, Davis, CA, United States

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ABSTRACT

Background: Non-small cell lung cancer (NSCLC) is uncommonly diagnosed in patients younger than 50 years of age. We analyzed the California Cancer Registry (CCR) to describe epidemiologic characteristics and outcomes in this patient subset and to identify factors prognostic for cause-specific survival (CSS).
Methods: Patients diagnosed with NSCLC between 1/1/98 through 12/31/09 and reported to the (CCR) as of October 2011 were included. The primary outcome measure was CSS. Cox regression models were used to evaluate predictors of CSS in young patients with NSCLC, adjusted for potential confounders. Interaction analysis was performed between age groups (<50 vs. ≥50) and specific demographic and tumor covariates.
Results: We identified 132,671 lung cancer cases, of which 114,451 (86.3%) had NSCLC. Of these, 6389 (5.6%) were < 50 years of age (median, 46 years). The most common histology was adenocarcinoma (3697, 57.9%). Most patients had stage III (1522, 23.8%) or IV (3655, 57.2%) disease. Fewer young patients were diagnosed in recent years (*n*, % of total NSCLC population of that era): 1998–2001 (2355, 6.0), 2002–2005 (2182, 5.7), and 2006–2009 (1852, 5.0), $P < 0.001$. Multivariate analysis showed that age <50 years was an independent predictor of improved CSS (HR 0.827, $P < 0.001$). Significant predictors of better CSS in patients <50 years included female sex, Asian or Hispanic ethnicity, lower stage, later year of diagnosis, and higher socioeconomic status, among others. Adenocarcinoma histology was not associated with improved CSS in this patient subset (HR 0.987, $P = 0.78$). Interaction analysis revealed that Hispanic race and bronchioloalveolar histology had differential CSS outcomes dependent on age group.
Conclusions: This large registry study found that age <50 years is an independent predictor of improved CSS. Variables prognostic for CSS differed somewhat from those in older patients.

1. Background

Lung cancer will be diagnosed in approximately 200,000 Americans in 2013 and unfortunately remains the leading cause of cancer-related death in both men and women in the United States [1]. Among the subtypes of lung cancer, non-small cell lung cancer (NSCLC) is the most prevalent, accounting for 85% of all new cases. Lung cancer is more common in older individuals, with an average age at diagnosis of 68 years and about a third of patients over 70 years of age [2]. Recent reports have suggested that there may be a rise in the number of young patients with NSCLC, particularly females [3,4].

There have been numerous papers focused on young NSCLC patients, each with varying definitions of "young" [5–8]. Some of these studies attempted to compare outcomes between younger and older NSCLC patients. Results have thus far been conflicting. For example, in a small study of patients less than 40 years of age, the authors concluded that "... young patients tend to present with advanced disease at diagnosis, resulting in an extremely poor survival" [9]. A Greek study of NSCLC patients <45 years of

* Corresponding author at: UC Davis School of Medicine, UC Davis Comprehensive Cancer Center, 4501 X Street, Suite 3016, Sacramento, CA 95817, United States. Tel.: +1 916 734 3771; fax: +1 916 734 7946.
E-mail address: Karen.kelly@ucdmc.ucdavis.edu (K. Kelly).

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Table 1
Patient characteristics.

	Age < 50		Age ≥ 50		*P*-value
	N	%	*N*	%	
	6389	100	108,062	100	N/A
Sex					
Males	3284	51.4	57,023	52.8	*0.03
Females	3105	48.6	51,039	47.2	*0.03
Race/Ethnicity					
NH White	3557	55.7	77,685	71.9	*<0.001
NH African American	831	13.0	8014	7.4	*<0.001
Hispanic	953	14.9	10,342	9.6	*<0.001
Asian/PI	1003	15.7	11,251	10.4	*<0.001
NH American Indian	24	0.4	352	0.3	0.49
Other/unknown	21	0.3	418	0.4	0.46
Histology categories					
Carcinoma (NOS)	1562	24.4	26,899	24.9	0.42
Large cell	285	4.5	4878	4.5	0.84
Squamous Cell	781	12.2	23,922	22.1	*<0.001
Adenocarcinoma (BAC only)	291	4.6	5493	5.1	0.06
Adenocarcinoma (papillary, mucinous, adenosquamous, w/metaplasia)	3406	53.3	45,294	41.9	*<0.001
Other	64	1.0	1576	1.5	*0.003
Year of diagnosis					
1998–2001	2355	36.9	36,859	34.1	*<0.001
2002–2005	2182	34.2	35,936	33.3	0.14
2006–2009	1852	29.0	35,267	32.6	*<0.001
AJCC stage					
I	674	10.5	20,763	19.2	*<0.001
II	187	2.9	3961	3.7	*0.002
III	1,522	23.8	27,999	25.9	*<0.001
IV	3,655	57.2	46,012	42.6	*<0.001
Unknown	351	5.5	9327	8.6	*<0.001
Primary treatment					
Surgery					
Yes	1418	22.2	25,693	23.8	*0.004
No	4968	77.8	82,257	76.1	*0.003
Unknown	3	0.0	112	0.1	0.16
Chemo					
Yes	3922	61.4	39,279	36.3	*<0.001
No	2310	36.2	66,229	61.3	*<0.001
Unknown	157	2.5	2554	2.4	0.63
Radiation					
Yes	3134	49.1	38,502	35.6	*<0.001
No	3254	50.9	69,478	64.3	*<0.001
Unknown	1	<0.1	82	0.1	0.0823
Rural vs. Urban residence					
Rural	444	6.9	8781	8.1	*<0.001
Urban	5945	93.1	99,281	91.9	
Socioeconomic status (SES)					
Lowest SES (quinyost 1, 2)	2639	41.3	38,796	35.9	*<0.001
Mid SES (quinyost 3)	1439	22.5	24,509	22.7	0.77
Highest SES (quinyost 4, 5)	2311	36.2	44,757	41.4	*<0.001

The asterisk (*) refers to statistically significant *p* values.

age suggested that outcomes are no different between younger and older patients [10]. Some community-based and national registry analyses of all forms of bronchogenic carcinoma have found improved outcomes in younger cohorts [18,19]. A more recent surveillance, epidemiology, and end results (SEER) study of NSCLC patients <40 years of age concluded that "despite presenting with stage IV disease more often, the overall and cancer-specific survivals are better in (the) younger than in the older cohort" [7].

Many of these prior studies attempted to define clinical characteristics predictive of outcome for young NSCLC patients. However, most of these papers had very limited sample sizes and/or were derived from single institution databases, hence limiting their generalizability [6,9,11].

In order to provide a more modern context of the epidemiologic characteristics and survival outcomes of younger patients with NSCLC while employing a more robust sample size, we analyzed the California Cancer Registry (CCR), a large database of all cancer cases diagnosed in California since 1988. We hypothesized that baseline variables predictive of outcome would be identified in young patients (here defined as <50 years of age) that differ from older patients, and that these patients will have better survival outcomes compared to those 50 years or older.

2. Methods

The objectives of the present study are (1) to describe the demographic characteristics and epidemiologic trends in the NSCLC population in the CCR from 1998 to 2008 with a focus on younger patients (<50 years of age); (2) to assess cause-specific survival (CSS, the primary outcome measure) in this younger cohort, and (3) to develop multivariate logistic regression survival models

(adjusted for relevant variables) in order to identify baseline features prognostic CSS in younger patients with NSCLC.

We collected data from the CCR, a statewide cancer surveillance database that obtains information on every cancer patient in California from eight different regional registries [12]. Hospitals and other facilities that provide treatment and care for any cancer patients residing in California report to the Chronic Disease Surveillance & Research Branch of the California Department of Public Health. The cases included in these analyses were any stage NSCLC diagnosed between January 1, 1998 and December 31, 2009, and were reported to the Cancer Surveillance Program as of October 2011. Lung cancer was defined using the relevant International Classification of Diseases – Oncology (ICDO)-2 and ICDO-3 site codes. The version of CCR utilized in this study had all personal health identifiers removed, and therefore institutional review board approval was not necessary per CCR and UC Davis policy.

Descriptive statistics were used to describe the demographic variables of the cohort. In univariate analysis, continuous variables were compared using the Student's *t*-test, while categorical variables were compared using the Chi-square test. The primary outcome variable was CSS. The Kaplan–Meier method was used to determine survival, and the Log-rank test to compare survival proportions between groups. Multivariate analysis was performed with Cox proportional hazards models that evaluated predictors of CSS in young NSCLC patients. In order to formally determine differential effects of predictive covariates between the two age groups, tests for interaction were performed between age and each of the predictive covariates in the Cox model (e.g., age * histology, age * stage, age * race, etc). If significant interactions were identified, specific hazard ratios, confidence intervals, and *P*-values only for those interactions were calculated. All the analyses were performed using SAS 9.3 (SAS, Cary, NC) and all *P*-values were two-sided.

3. Results

3.1. Patient characteristics

A total of 132,671 lung cancer patients were identified for this study, 114,451 with NSCLC (Table 1). Of these, 6389 (5.5% of all NSCLC patients) were <50 years of age. Median age of this younger subset was 46 years (range: 6–49). Most younger patients were White (3557 patients, or 55.7% of the group), which was a lower percentage than the age-over-50 cohort. The most prevalent histology was adenocarcinoma, which accounted for 57.9% of all young patients and was of a higher proportion than in older patients. Of this young patient population, 57.2% were diagnosed with Stage IV disease compared to 42.6% of older patients ($P < 0.0001$). The proportion of lung cancer patients under 50 years of age decreased in recent years: 6.0% of patients were identified in the 1998–2001 year group, 5.7% of patients in the 2002–2005 group, but only 5% of NSCLC patients were younger than 50 in the 2006–2009 group ($P < 0.001$). Incidence rates (per 100,000 person years) declined as well in this subset, as follows: 3.65 (1998–2001), 3.23 (2002–2005), and 2.92 (2005–2009).

3.2. Univariate analysis

Cause specific survival for each baseline clinical variable in patients under age 50 was evaluated; these results are summarized in Table 2. Female sex was associated with better median CSS (16 vs. 11 months, $P < 0.0001$ Fig. 1). Differential CSS was also seen with regard to race and ethnicity, with Asians having the highest median CSS estimate of 17 months. Patients diagnosed in later years (2006–2009) had a higher median CSS of 17 months: this was significantly different ($P < 0.0001$) when compared to earlier eras (1998–2001, 2002–2005) where median CSS was only 12 months. Expectedly, patients whose initial treatment consisted of potentially curative procedures such as surgery or radiation therapy had higher median CSS times. Similarly, patients with lower stage (i.e., potentially curable) disease also had higher median CSS compared to those with higher stage: stage IV – 8 months, stage III – 17 months, stage II – 29 months, and stage I – median CSS not reached (Fig. 2). Patients in the highest socioeconomic status quintiles (4 and 5) also had higher median CSS (16 months), as compared to those with the lowest quintiles (1 and 2: 11 months), with a *P*-value of <0.001. Finally, patients in the urban setting had a modest median CSS advantage over those in the rural setting (13 vs. 10 months, $P = 0.0139$).

Table 2
Univariate analysis (Patients < 50 years of age).

Variable	Median cause specific survival (months)	95% CI	*P*-value (Log Rank)
Sex			
Males	11	(10–12)	<0.001
Females	16	(15–17)	
Race/Ethnicity			
NH White	12	(12–13)	<0.001
NH African American	11	(10–12)	
Hispanic	14	(12–16)	
Asian/PI	17	(15–19)	
Other/unknown	8	(5–17)	
Year of diagnosis			
1998–2001	12	(11–12)	<0.001
2002–2005	12	(12–13)	
2006–2009	17	(15–18)	
Primary treatment			
Surgery			
Yes	93	N/A	<0.001
No	9	(9–10)	
Chemotherapy			
Yes	14	(13–14)	<0.001
No	12	(10–13)	
Radiation			
Yes	12	(11–12)	<0.001
No	15	(14–17)	
AJCC Stage			
I	Not reached	N/A	<0.001
II	49	(39–70)	
III	17	(16–19)	
IV	8	(8–9)	
Unknown	17	(13–19)	
Socioeconomic status (SES)			
Lowest SES (quinyost 1, 2)	11	(10–12)	<0.001
Mid SES (quinyost 3)	12	(11–14)	
Highest SES (quinyost 4, 5)	16	(15–17)	
Rural vs. Urban			
Rural	10	(8–12)	0.014
Urban	13	(12–14)	

3.3. Multivariate analysis

Variables associated with improved CCS for the entire population of NSCLC patients and those under age 50 were evaluated using separate Cox models. Tests for interactions for predictive variables were performed between the two age groups. These results are summarized in Table 3. Within the younger patient cohort, most trends seen in the univariate analysis were still present after adjustment. The primary exception was that a trend for worse outcomes for patients from rural areas was no longer statistically significant for those under 50 years.

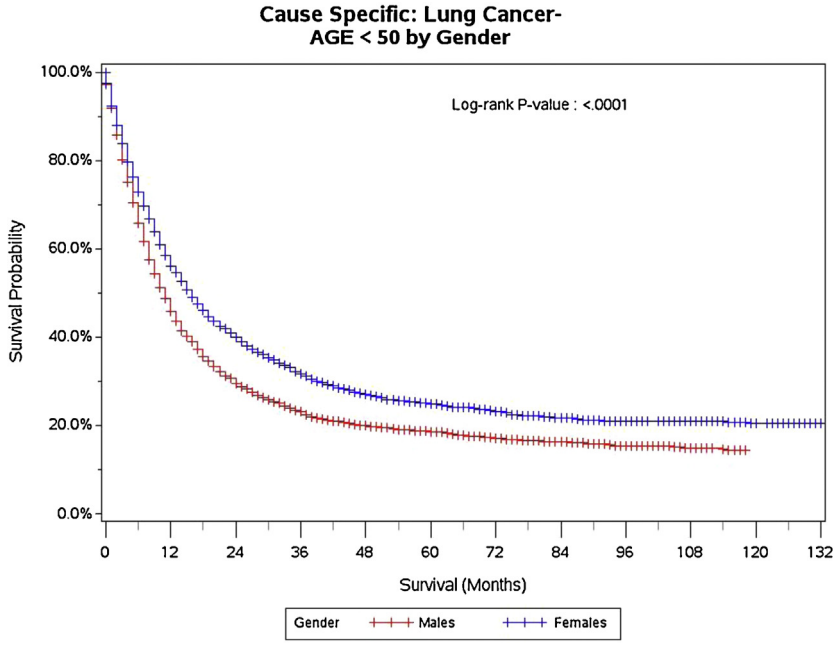
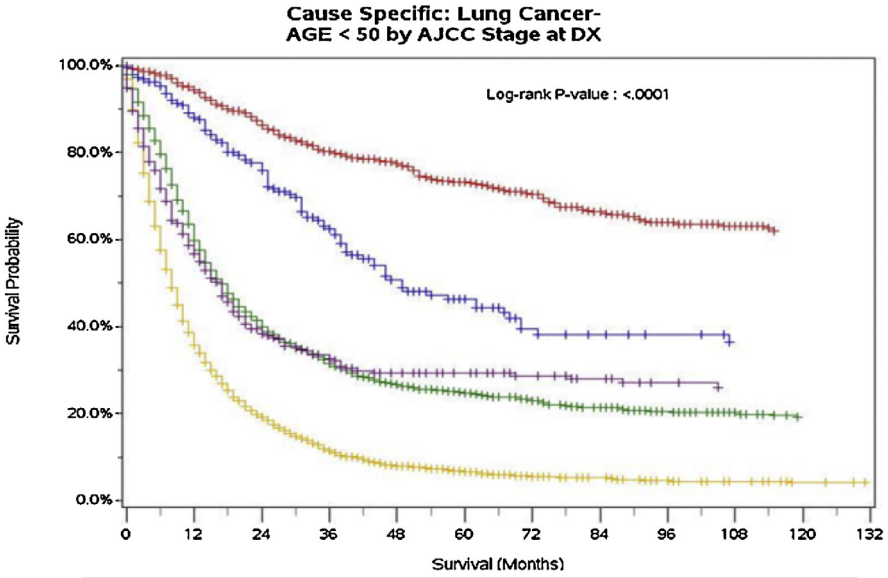


Fig. 1. Kaplan Meier cause specific survival for patients less than 50 years of age categorized by gender (male vs. female).



Stage	Months	Proportion Alive	95% CI	
Stage I	6	0.977	0.963	0.986
	12	0.944	0.923	0.959
	24	0.863	0.834	0.888
Stage II	6	0.952	0.909	0.975
	12	0.880	0.824	0.920
	24	0.758	0.688	0.815
Stage III	6	0.797	0.776	0.816
	12	0.597	0.571	0.622
	24	0.398	0.372	0.424
Stage IV	6	0.576	0.560	0.593
	12	0.358	0.342	0.374
	24	0.192	0.178	0.206
Unknown	6	0.717	0.665	0.762
	12	0.566	0.510	0.619
	24	0.383	0.327	0.437

Fig. 2. Kaplan Meier cause specific survival for patients less than 50 years of age categorized by stage.

Table 3
Cause specific survival of patients with NSCLC – cox proportional hazards model.

	ALL AGES			Age < 50		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age < 50	0.827	(0.802–0.852)	<0.001	NA	NA	NA
Female sex	0.863	(0.851–0.875)	<0.001	0.837	(0.788–0.888)	<0.001
Race/Ethnicity						
NH African American	0.93	(0.906–0.955)	<0.001	0.991	(0.905–1.086)	0.850
Hispanic	0.887*	(0.866–0.909)	<0.001	0.76*	(0.694–0.834)	<0.001
Asian/PI	0.77	(0.770–0.788)	<0.001	0.792	(0.727–0.863)	<0.001
Other/Unknown	0.846	(0.779–0.918)	<0.001	0.89	(0.627–1.263)	0.513
Disease stage						
Stage II	1.748	(1.661–1.828)	<0.001	1.936	(1.510–2.483)	<0.001
Stage III	2.242	(2.172–2.300)	<0.001	2.494	(2.107–2.952)	<0.001
Stage IV	3.507	(3.375–3.573)	<0.001	4.373	(3.692–5.180)	<0.001
Stage unknown	1.752	(1.691–1.818)	<0.001	1.744	(1.404–2.167)	<0.001
Treatment						
Chemo and/or radiation (No surgery)	0.531	(0.532–0.541	<0.001	0.533	(0.489–0.581)	<0.001
Surgery	0.221	(0.214–0.227)	<0.001	0.234	(0.206–0.266)	<0.001
Unknown	0.708	(0.678–0.760)	<0.001	0.556	(0.425–0.726)	<0.001
Year of diagnosis						
2002–2005	0.912	(0.898–0.929)	<0.001	0.89	(0.832–0.953)	0.0008
2006–2009	0.819	(0.810–0.839)	<0.001	0.731	(0.677–0.790)	<0.001
Rural	0.988	(0.958–1.010)	0.375	1.086	(0.966–1.220)	0.166
Socio-economic status						
SES-mid level	0.962	(0.944–0.981)	<0.001	0.947	(0.877–1.024)	0.173
SES-high level	0.903	(0.891–0.922)	<0.001	0.832	(0.755–0.894)	<0.001
Histology						
Large cell	1.096	(1.060–1139)	<0.001	1.086	(0.926–1.274)	0.312
Adenocarcinoma	0.928	(0.908–0.944)	<0.001	0.987	(0.897–1.086)	0.788
BAC	0.661*	(0.625–0.682)	<0.001	0.86*	(0.714–1.036)	0.112
Carcinoma, NOS	1.029	(1.010–1.052)	0.005	1.036	(0.935–1.148)	0.497
Other neoplasm, NOS	1.224	(1.157–1.306)	<0.001	1.163	(0.837–1.616)	0.369

Reference groups: Male sex, age ≥ 50, urban residence, stage I, non-hispanic (NH) white, no treatment, 1998–2001, lowest SES (1,2), and squamous histology.
Abbreviations: NH – Non Hispanic; PI – Pacific Islander; SES – socio-economic status; BAC – bronchoalveolar carcinoma; NOS – not otherwise specified; NA – Not applicable
* Yellow cells – highlights only variables where Hazard Ratios between age < 50 and age ≥ 50 were statistically different by interaction test.

For the overall cohort, age under 50 was associated with improved CSS, with a hazard ratio of 0.827 ($P < 0.001$). Trends toward improved survival were noted in groups diagnosed in later years, as compared to 1998–2001 for both the entire population and patients under 50. Female sex and socioeconomic status were predictive of an improved outcome for both cohorts as well. Evaluation of histology found that adenocarcinoma was associated with a modestly improved outcome in the entire population (HR 0.928, $P < 0.001$). This association was not statistically significant in the younger cohort (HR 0.987, $P = 0.788$). Significant interactions were identified between age and Hispanic race as well as between age and bronchioloalveolar carcinoma (BAC) histology. Specifically, young Hispanics had improved outcomes compared to older Hispanics with a HR for CSS of 0.78 vs. 0.90 for older Hispanics. Young patients with BAC had a HR of 0.85 compared to 0.65 in older patients with BAC. These interactions had a *P*-value of <0.001. Thus, BAC was not associated with better prognosis in younger patients, in contrast to older patients.

4. Discussion

Lung cancer is generally a disease of older patients. Past studies either had conflicting results on the differential survival of young NSCLC patients relative to older patients, or were limited by very small sample sizes. We performed this study to evaluate factors that may influence survival in patients younger than 50 years using a large statewide tumor registry to overcome sample size limitations. We found that several baseline clinical features (including female sex, Asian or Hispanic ethnicity, lower stage, initial treatment with curative intent, high socioeconomic status, but not adenocarcinoma histology) were independently associated with improved CSS in patients <50 years of age. Importantly, we found that age less than 50 years was also strong independent predictor of CSS. We believe that these results provide the most recent large-scale analysis of this specific patient cohort and can therefore serve as a suitable benchmark for future studies.

As noted, we report that age <50 appears to be an independent prognostic factor for better CSS. Similarly, a registry study of Japanese lung cancer patients aged 20–49 diagnosed between 1958 and 2003, and a SEER analysis of lung cancer patients less than age 50 also showed a trend for lower mortality among young adults [4,19]. There are several possible explanations for this emerging observation. Young patients tend to receive more aggressive treatment than their older counterparts, which could have translated into better outcomes [3,7]. There may also have been a higher rate of actionable mutations within the tumors of younger patients for which effective targeted therapy drugs are available. In a recent study of patients less than 40 years of age, driver oncogenes including EGFR activating mutations and EML4-ALK fusion were identified in 75% of cases [14]. It is known that these molecular alterations are particularly sensitive to specific tyrosine kinase inhibitors [14]. Notably, median survival in younger patients increased to 17 months for 2006–2009 as compared to 11 months in 1998–2005: interestingly, erlotinib was approved for refractory NSCLC in 2004.

Our study could not demonstrate that adenocarcinoma histology was a significant predictor of CSS relative to all other histologic groups in young patients, though it was associated with improved CSS for the entire NSCLC cohort. For BAC, a subset of adenocarcinoma, there was an association with improved outcome

in older patients, but this was not present in younger patients. The reasons for this difference are unclear, but it is possible that there may be unseen imbalances in the distribution of molecular features across both age groups and histologic subtypes that could have influenced subsequent prognosis [15].

When compared to other studies, our results show that certain clinical variables were consistently associated with survival, including age < 50 as well as gender and stage [3,6,11]. In a SEER analysis, five-year overall survival was significantly better in a group younger than 50 years of age (16.1% vs. 13.4%; $P < .001$), principally as a result of better survival in patients with presumably curable (localized or early stage) disease (48.7% vs. 35.4%; $P < .001$) [7]. Furthermore, these investigators reported that male sex was also an independent negative prognostic factor.

We also found that the proportion of cases of NSCLC in young patients had marginally decreased over time. This mirrors the observation from registry studies in Japan where the proportion of lung cancer patients aged 40–49 years dropped from 6.9% in 1994 to 4.2% in 2004 [16]. Similarly, in a Korean registry report, the mean age of lung cancer patients increased over successive time intervals (1990–1994, 1995–1999, 2000–2004, and 2005–2009) from 57.8 years to 62.5 years [17].

Our work has several strengths. First, it has a large sample size, representing all lung cancer cases diagnosed in California from 1998 to 2009. By state statute, all cases require mandatory reporting of baseline variables and survival data. In addition, the ethnic diversity of the registry population enhances its potential to be generalizable to the entire NSCLC population and to detect differences between ethnic groups.

There are limitations to this study. Since the CCR is considered a regional (i.e., statewide) registry, it may not be readily applicable to other states that have different demographic features than California. Another limitation is the retrospective nature of the analysis which can introduce certain biases. Finally, the CCR does not collect all relevant clinical information such as molecular phenotypic information (which is becoming critical in systemic treatment selection for NSCLC), detailed treatment data, known risk factors such as smoking, as well other important prognostic variables such as weight loss, functional status, and comorbidity scores.

5. Conclusions

In conclusion, this large registry experience found that age < 50 years is an independent predictor of improved CSS (HR 0.827, $P < 0.001$) in the modern era. In addition, the proportion of young patients with NSCLC has decreased from 6.0% (1998–2001) to 5.0% (2006–2009). Importantly, in young patients BAC histology was not associated with improved survival as it is in the overall population with NSCLC. Finally, clinical variables independently prognostic for CSS were identified in the younger patient subgroup.

Conflict of interest statement

None declared

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