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Survival trends of metastatic lung cancer in California by age at diagnosis, sex, race/ethnicity and histology, 1990–2014

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Abstract

Background: We analyzed the survival trends for patients with metastatic lung cancer in California.

Methods: We identified patients first diagnosed with primary lung cancer at distant (metastatic) stage in the California Cancer Registry (CCR) between 1990 and 2014, with follow-up through end of 2015. Race/ethnicity was categorized into non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, and Asian/Pacific Islander (API). One-year and five-year relative survival rates

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Authors' contributions

TL and RDC contributed to the conception and design of the study. AKE and RDC contributed to accessing data and analysis. TL and KP contributed to analyzing and interpreting the data and drafted the manuscript. All authors participated in revising and approving the final manuscript.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and supplemental data.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Declarations:

Competing interests

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were calculated overall and by age at diagnosis, sex, race/ethnicity, and histology during the study period. Joinpoint regression was used to evaluate the trends and to calculate the annual percentage changes (APCs).

Results: A total of 186,156 adults were identified for analysis. Between 1990 and 2014, one-year relative survival significantly improved from 18.4% to 29.4%, with most improvement observed between 1993 and 2012 (APC=2.60%, 95% CI: 2.41–2.79, p<0.01). Five-year relative survival significantly improved from 2.2% to 5.0%, with an APC of 4.05% (95% CI: 3.47–4.64, p<0.01). All age groups experienced an improvement in survival rates. The greatest increases in relative survival were observed among females, APIs, and patients with adenocarcinoma. Yearly survival rates increased for all histologic types over the study period, with adenocarcinoma having the most improvement after 2000.

Conclusions: Survival for patients with metastatic lung cancer in California steadily improved during the 1990–2014 period, before the era of lung cancer screening and cancer immunotherapy. The greatest increase in relative survival was observed in those patients who have the most clinical benefit from the history- and biomarker-based precision oncology drugs during the study period.

MicroAbstract

We analyzed the survival trends for 186,156 adult patients first diagnosed with primary lung cancer at distant (metastatic) stage in the California Cancer Registry between 1990 and 2014, with follow-up through end of 2015. We found that one-year relative survival significantly improved from 18.4% to 29.4%, with most improvement observed between 1993 and 2012. Relative survivals had the greatest increases in females, Asian/Pacific Islanders, and patients with adenocarcinoma who have the most clinical benefit from the history- and biomarker-based precision oncology drugs over a 24-year period in California. This period is right before the era of lung cancer screening and cancer immunotherapy.

Keywords

Lung cancer; metastatic; California Cancer Registry; relative survival rate; annual percentage change

INTRODUCTION

Lung cancer causes significant disease burden in the United States and worldwide [1]. From 1988 to 2014, lung cancer incidence rates in California decreased by 40% [2], while rates in the rest of the country dropped by only 19% during the period [1]. The decrease in the incidence of lung cancer has been attributed to the dramatic decrease in the number of smokers from the successful Tobacco Control Program in California, which includes banning public advertisements, mandates smoke-free environments, increases the price of cigarettes, and prohibits the sale of cigarettes to minors [3]. This is a remarkable achievement given that the global burden of smoking and lung cancer is still rising in many developing countries [4]. Despite steady declines in incidence, lung cancer remains the leading cause of cancer-related death in California.

The combined cancer mortality rates steadily decreased for both women and men from 1991 to 2015 by a total of 26% in the United States, translating to approximately 2,378,600 fewer cancer deaths than would have been expected if death rates had remained at their peak [1]. Survival from lung cancer varies by geographic location, histologic subtype, stage at diagnosis, and treatment [1, 4]. From 1988 to 2014, lung cancer death rates in California decreased 2.8% per year in men and 1.5% per year in women, with a total decline in mortality of 30% [2]. For all stages combined, the five-year survival rate of lung cancer was 18.2% in California in 2004–2013. By stage, five-year survival rates were 57.2% for localized, 28.9% for regional, 4.6 % for distant (or metastatic) lung cancer [5], which were similar to those of national rates of 56% for localized, 29% for regional, 5% for distant lung cancer [1]. The majority of lung cancer patients are diagnosed with distant stage and contribute to the majority of lung cancer deaths [2]. Given that recent advances in the diagnosis and treatment have revolutionized cancer care for patients with metastatic lung cancer, the purpose of this study was to analyze the survival trends in patients with metastatic lung cancer by age at diagnosis, sex, race/ethnicity and histology in California between 1990 and 2014.

METHODS

The California Cancer Registry (CCR) is the single largest population-based state cancer registry in the US, which contains demographic, diagnosis, and treatment information on all reportable cancers diagnosed in California residents since January 1988 [3]. Patients who were at least 20 years old when diagnosed with a first primary remote lung cancer in California between January 1, 1990 and December 31, 2014 were included in this study. Because staging systems used by population based cancer registries have changed over time, stage was defined by the Surveillance, Epidemiology, and End Results (SEER) Summary Stage [6] in this study to provide consistent staging over time. Patients diagnosed at autopsy or by death certificate only were excluded.

Variables of interest included age at diagnosis, sex, race/ethnicity and histology. Race/ethnicity was categorized into non-Hispanic white (NHW), non-Hispanic black (NHB), Hispanic, and Asian/Pacific Islander (API). Histologic subtype was coded using the International Classification of Diseases for Oncology, third edition [7], and was categorized into: small cell lung cancer (SCLC:8041-8045 and 8246), squamous cell carcinoma (LUSC: 8051, 8052, 8070–8078, 8083, and 8084), adenocarcinoma (LUAD: 8050, 8140–8147, 8201, 8230, 8250–8255, 8260, 8263, 8290, 8310, 8320, 8323, 8220, 8350, 8441, 8460, 8470, 8471, 8480, 8481, 8490, 8500, 8503, 8507, 8550, and 8570 to 8576), large cell carcinoma (LCC: 8011–8015, 8082, and 8123), non-small cell lung cancer, not otherwise specified (NSCLC, NOS: 8010, 8020–8022, 8030–8035, 8046, 8094, 8120, 8130, 8170, 8200, 8240–8245, 8247–8249, 8340, 8430, 8525, 8551, 8560, 8562, 8580, 8940, 8972, and 8980), and other/unknown (all remaining codes), as previously reported [8].

Relative survival, defined as the ratio of the observed survival rate among metastatic lung cancer patients divided by the expected survival rate of a comparable set of cancer-free persons in the general population of California [9], was calculated using SEER*Stat version 8.3.5. One- and five-year relative survival were calculated overall and by age at diagnosis,

sex, race/ethnicity, and histology for each year in the study period. Survival information was complete for all patients through December 31, 2015 (Table S1). To allow for enough follow-up time, five-year survival was only determined for patients diagnosed through 2010, while one-year survival was calculated for all patients through 2014. Joinpoint Regression Program version 4.6.0 was used to evaluate trends and the estimated annual percentage rate change (APC) of relative survival. To smooth the fluctuations in relative survival for histologic subtypes, we divided the study period into five consecutive, five-year periods (i.e., 1990–1994, 1995–2004, 2000–2004, 2005–2009, and 2010–2014). Given relative yearly survival rates have been used to measure treatment outcomes [10], we assessed one-, two-, three-, four-, and five-year relative survival for each interval and lung cancer type. Due to insufficient follow-up time, two- through five-year relative survival were not computed for the 2010–2014 period. Statistical significance was set at two sided with an alpha of 0.05 for all analysis. Graphs were made using the GraphPad Prism 8 software (San Diego, CA).

RESULTS

A total of 186,156 patients with distant (metastatic) lung cancer were identified for analysis. Table 1 summarizes the characteristics of study population. The distribution of age at diagnosis was about one-third each for ages 20–64, 65–74, and greater than or equal to 75 years. Most patients were male (55.3%) and NHW (71.3%). LUAD constituted the highest proportion of cases at 36.9%, followed by NSCLC, NOS (23.7%), SCLC (17.0%), SCC (14.0%), LCC (4.4%), and other/unknown (4.0%).

One-year relative survival rates are illustrated in Figure 1, and APCs in one-year relative survival for patients with metastatic lung cancer in California between 1990 and 2014 are summarized in Table 2. One-year relative survival significantly improved from 18.4% in 1990 to 29.4% in 2014, with the most improvement observed between 1993 and 2012 (APC=2.60%, 95% CI: 2.41–2.79, $p<0.01$) (Figure 1A). One-year relative survival was higher among younger age groups, though all ages had statistically significant improvements with APCs of 2.51–2.74 over the study period (Figure 1B). Females had significantly better one-year relative survival than males, and relative survival increased more quickly for females than males (Figure 1C). Males' relative survival steadily rose from 17.5% in 1990 to 25.7% in 2014 (APC=2.12%, 95% CI: 1.88–2.35, $p<0.01$). Females' relative survival steadily rose from 19.9% in 1990 to 33.3% in 2014. The greatest increase in females' relative survival occurred from 1996–2011 (APC=2.96%, 95% CI: 2.66–3.26, $p<0.01$).

Relative survival rates improved in all four major racial/ethnic groups in California during the study period (Figures 1D). APIs had the most favorable prognosis at one year, and they also exhibited the greatest improvement in one-year relative survival, with an APC of 3.28% over the study period (95% CI: 2.84–3.72%, $p<0.01$). NHWs and NHBs had the lowest observed survival rates, but both groups experienced annual improvements in one-year survival of about 2.0% over the study period (respectively, APC=1.91, 95% CI: 1.77–2.06, $p<0.01$ and APC=2.05, 95% CI: 1.63–2.48, $p<0.01$). Hispanics initially saw a nonsignificant decline in one-year survival from between 1990–1995, followed by a significant improvement from 1995–2014 (APC=2.92, 95% CI: 2.15–3.68, $p<0.01$). Increases in survival rates varied across histological subtypes (Figures 1E). While one-year survival rates

remained stable in SCLC (APC=0.04%, 95% CI: −0.26–0.33, P=0.79), survival improved for all other subtypes. The greatest increase was observed for LUAD between 1990–2009 (APC=3.90%, 95% CI: 3.59–4.21, P<0.01), followed by NSCLC, NOS between 1990–2006 (APC=3.32%, 95% CI: 2.83–3.81, p<0.01). Both LCC and LUSC had steady and significant improvement in survival throughout the entire study period (respectively, APC= 2.31%, 95% CI: 1.55–3.06, p<0.01 and APC=1.31%, 95% CI: 0.95–1.66, p<0.01).

Similar findings overall and by age at diagnosis, sex, and race/ethnicity were observed for five-year relative survival (Figure S1**)**. APCs for five-year relative survival between 1990 and 2010 are summarized in Table 3. Five-year relative survival for patients with metastatic lung cancer in California increased from 2.2% in 1990 to 5.0% in 2010 (Figure S1A), with an APC of 4.05% (95% CI: 3.47–4.64, p<0.01). Five-year survival increased for all histologic subtypes (Table 3), with LUAD having the greatest improvement from 2.3% in 1990 to 6.2% in 2010 (APC 5.66, 95% CI: 4.73–6.60, p<0.01).

The one-, two-, three-, four-, and five-year relative survival trends for consecutive five-year intervals by histology are depicted in Figure 2. There were significant and steady increases in survival rates for all lung cancer types combined over the study period (Figure 2A). However, the improvement of survival rates varied across NSCLC histological subtypes. While the yearly survival rates remained stable in SCLC (Figure 2B) and LUSC (Figure 2C), the greatest improvement in relative survival rates occurred in LUAD during the 2005–2009 period compared to previous periods (Figure 2D). Between 1990–1994, there were no significant differences in survival among different histology subtypes (Figure 2E). Between 2005–2009, LUAD had the highest survival rates compared to other histology subtypes (Figure 2F).

DISCUSSION

In this study, we analyzed the survival trends in adults diagnosed with metastatic lung cancer in California between 1990 and 2014. Our results are consistent with those reported recently by Howlader et al. [11] who conducted an analysis of incidence-based mortality for lung cancer cases in the SEER 18-registry database. The authors of this study reported a decline in lung cancer mortality that exceeded the decline in incidence from 2001 to 2016. They also reported an increase in 2-year relative survival among men with NSCLC (all stages) from 26% in 2001 to 35% in 2014, and among women of 35% to 44% in the same time period. These results are comparable to our findings of an increase in 1-year relative survival among men with metastatic lung cancer from 18% in 1990 to 26% in 2014 and among women from 20% to 33% in the same time period. This consistency in results is reassuring but not surprising given that patients from California composed about 50% of the SEER database. Our results enhance the Howlader analysis by focusing on patients with metastatic cancer and reporting on relative survival trends for the four major race/groups in California as well as for NSCLC histologic subtypes.

During this period, the proportion of patients in the metastatic stage remained stable, as there had not been an uptake of lung cancer screening that improves lung cancer-specific survival by stage shift [12]. We found that both one-year and five-year relative survival rates

had significantly improved for almost all patients, though the magnitude of improvement varied across age at diagnosis, sex, race/ethnicity and NSCLC histologic subtypes. Histology and molecular biomarkers became the two most important factors for prognosis and treatment selection for patients with metastatic lung cancer [13], which is the key factor driving the increased survival during the study period [13, 14]. Figure 3 summarizes the major milestones in systemic therapy for metastatic lung cancer according to the updated American Society of Clinical Oncology Clinical Practice Guideline based on the clinical data collected before 2015 [10]. Treatment advances for patients with metastatic LUAD include the first line platinum-based combination chemotherapy, second line single agent chemotherapy or unselected molecularly targeted therapy, histology-directed chemotherapy, tumor genotyping, and first-, second- and third-generation molecularly targeted therapies in the United States. For patients with metastatic SCLC, the platinum and etoposide combination as the first line systemic therapy after 1991 [15, 16] and topotecan monotherapy as a second line therapy in 2007 [17, 18] only marginally improved survival during the study period. Furthermore, the uptake and impact of these advances vary significantly among regions and countries [19]. Consistent with these milestones, we found that the relative yearly survival rates in metastatic lung cancer patients of all histological subtypes had steady improvements over each 5-year period between 1990 and 2010, with the most improvement observed in patients with LUAD in the 2005–2009 period, followed by LCC and NSCLC NOS (Figure 2). In contrast, there was no significant improvement in yearly survival rates for patients with SCLC or LUSC over the study period.

We found that the greatest increases in relative survival were observed among females, APIs, and patients with adenocarcinoma. Differential survival outcomes in these patient groups have been reported before using national registries [20–24]. Nationally, the five-year relative survival rate for lung cancer is 15% for men and 21% for women [1]. A previous study showed that patients with adenocarcinoma had the best 1-year survival among all metastatic NSCLC cases diagnosed in 2000–2011 using the SEER database [23]. Asian patients with adenocarcinoma have higher prevalence of unique biologic features such as a higher incidence of oncogene-driven NSCLC (mainly EGFR-mutant and ALK-rearranged tumors), and the majority of Asian women with lung cancer are never-smokers [24–26]. Additional factors, such as timely access to health care, area of residence, immigration status, and other biologic differences can also contribute to differential incidence and mortality by race [27].

Our data have important clinical implications. The study was conducted in a period right before the new era of lung cancer screening and cancer immunotherapy starting in 2015. The recent development of new generation of molecularly targeted therapies and immune checkpoint inhibitors (ICIs) targeting programed cell-death protein 1 (PD-1) or its ligand PD-L1, has further improved the survival for patients with metastatic lung cancer after 2014 [33, 34]. Recent updates on the 5-year survival for these patients with metastatic NSCLC who received nivolumab exceed 15% [35, 36]. Even for patients with metastatic SCLC, PD-L1 inhibitor has recently been shown to improve the efficacy of standard chemotherapy as first line therapy [37]. Our analysis of annual relative survival rates over the 24-year period in Californian patients with metastatic lung cancer before 2015 could serve as historical controls for new studies using cancer immunotherapy and other novel targeted therapy in California.

Our study has several limitations. First, our study is focused on survival of metastatic lung cancer patients in California and thus may not be generalizable. Secondly, we lacked clinical detail for individual patients because our analysis was based on cancer registry data. For example, we did not have information on factors such as comorbid illness that can influence both treatment and survival. Most importantly we did not have information on tumor molecular biomarkers or detailed information on treatment. Only first course of treatment is reported to population- based registries, and registry data do not contain detailed information about the type or duration of each cancer therapy administered. Efforts to integrate molecular biomarker and treatment information into cancer registry databases are ongoing. Novel methods, such as artificial intelligence using natural language processing (NLP), have been explored to extract the relevant information from e-path reports in the electronic medical records for outcome research [38]. Recently text mining was used to extract information about systemic therapy for patients with metastatic lung cancer [39]. Thirdly, survival rates could be affected by the increase of new immigrants with different race/ethnicity backgrounds, various tumor biology features, and unique lifestyle factors. Fourthly, we did not analyze the impacts of socioeconomic status, access to health care, education levels, and geographic regions within California on survival for patients with metastatic lung cancer. Strengths of our study include high quality registry data with long-term follow up for survival, and our ability to evaluate survival for a large diverse population.

To the best of our knowledge, our study is the first report showing improved survival in California patients with metastatic lung cancer over a 24-year period before the era of lung cancer screening and cancer immunotherapy. In this large, diverse population, we demonstrated that improvements in survival were not experienced equally by all groups and that disparities by race and ethnicity persist. Further studies are needed to better understand the survival disparity by sex, ethnicity and histology, and to improve the treatment of histologic subtypes other than adenocarcinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- Between 1990 and 2014, one-year relative survival significantly improved from 18.4% to 29.4%, and five-year relative survival significantly improved from 2.2% to 5.0%.
- All age groups and histologic types experienced improvements in survival rates. The greatest increase in relative survival was observed in females, Asian/Pacific Islanders, and patients with adenocarcinoma who have the most clinical benefit from the history- and biomarker-based precision oncology drugs during the study period.
- Survival for patients with metastatic lung cancer in California steadily improved during the 1990–2014 period, before the era of lung cancer screening and cancer immunotherapy.

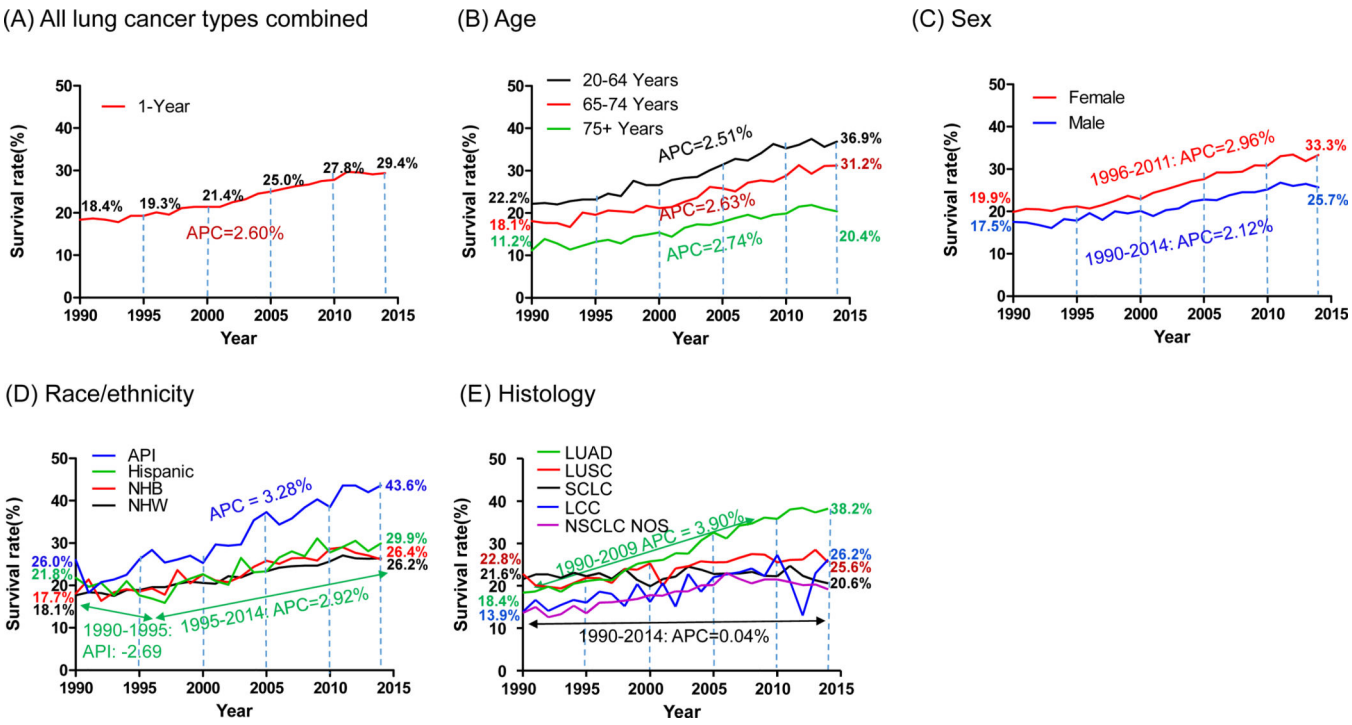

Figure 1. Trends in one-year survival rates in patients with metastatic lung cancer in California, 1990 to 2014.

One-year survival rates and prominent APCs for all lung cancer types combined (**A**) and by age (**B**), sex (**C**), race/ethnicity (**D**), and histology (**E**) between 1990 and 2014 are illustrated.

Abbreviation: APC, annual percent change.

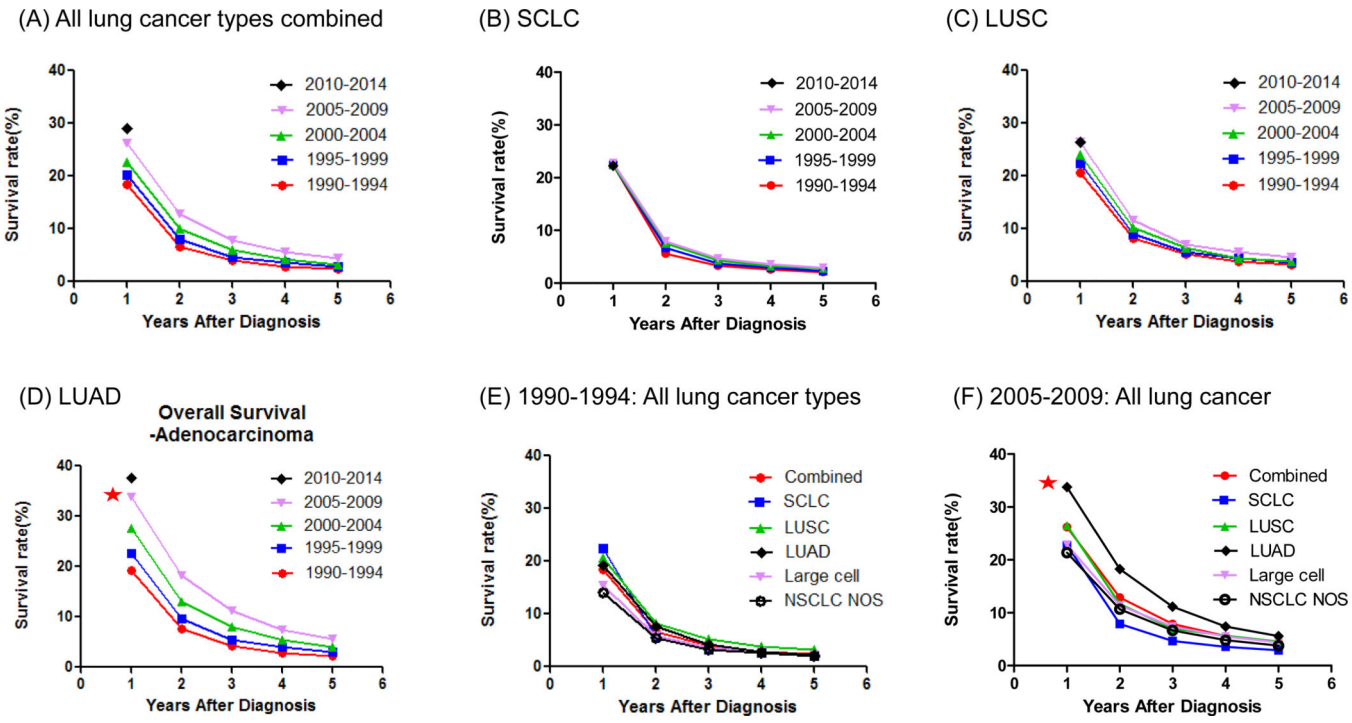

Figure 2. Trends in yearly cancer specific survival rates by lung cancer types in California, 1990 to 2014.

The 1-year, 2-year, 3-year, 4-year and 5-year overall survival rates of all lung cancer cases (**A**), SCLC (**B**), LUSC (**C**), and LUAD (**D**) in consecutive five-year periods between 1990 and 2014 are illustrated. Furthermore, the 1-year, 2-year, 3-year, 4-year and 5-year overall survival rates of each subtype and all lung cancer combined in the 1990–1994 and 2005–2009 periods are showed in (**E)** and (**F)**, respectively. Red stars highlight the trends with significant changes in (**D**) and (**F**).

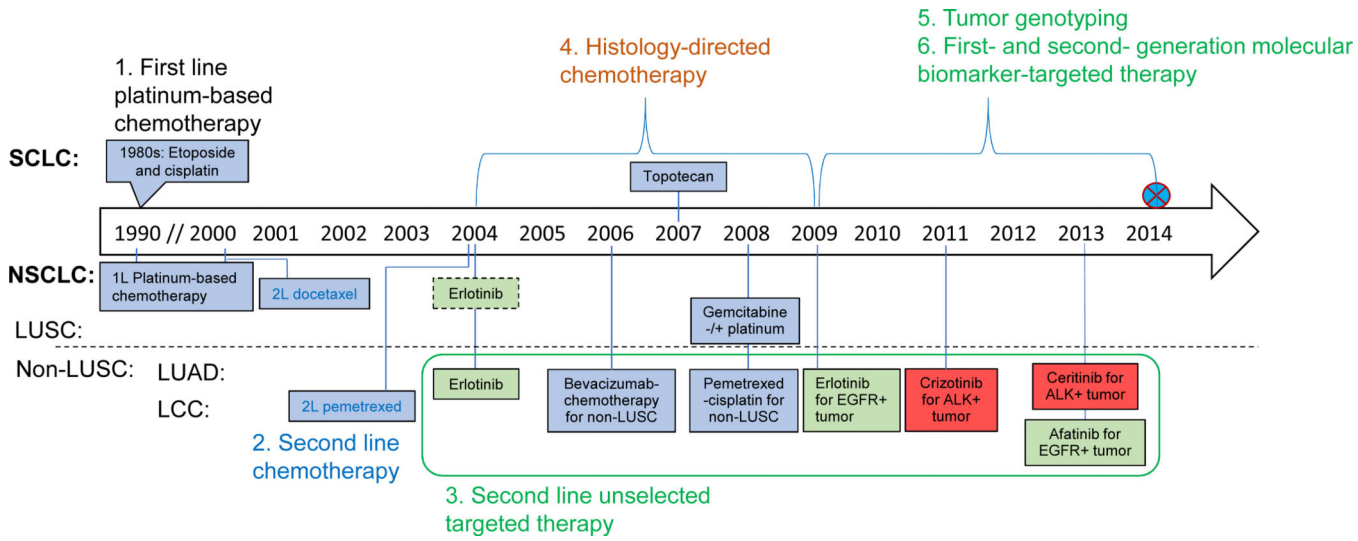

Figure 3. The chronological milestones for metastatic lung cancer.

Over the past 3 decades, many advances have contributed to the improved overall survival for patients with metastatic lung cancer, which includes first line platinum-based combination chemotherapy, second line single agent chemotherapy or unselected molecularly targeted therapy, histology-directed chemotherapy and tumor genotyping for molecular biomarkers, first- and second-generation molecularly targeted therapies in the United States. Notably, patients with metastatic LUAD benefited most from these therapeutic advances. The first generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib was approved in 2004[40], bevacizumab in combination with carboplatin and paclitaxel chemotherapy for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC in October 2006 [36, 41], pemetrexed for non-squamous NSCLC in September 2008 [42], first generation TKI crizotinib for anaplastic lymphoma kinase (ALK)-rearranged tumors 2011 [43], and second generation EGFR TKI afatinib was approved in 2013[44] during the 1990–2014 study period. Patients with LUSC benefited from the docetaxel in 2000 and gemcitabine-containing regimen in 2008 [42].

Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; LUSC, squamous cell lung cancer; Non-LUSC, non-squamous cell lung cancer; LUAD, lung adenocarcinoma; LCC, large cell carcinoma.

Table 1.

Characteristics of adults 20 years and older diagnosed with first primary remote lung cancer in California, 1990–2014

Variable	N	%
Total	186,156	
Age at Diagnosis		
20–64 years	66,982	36.0%
65–74 years	60,754	32.6%
≥75 years	58,420	31.4%
Sex		
Male	103,013	55.3%
Female	83,143	44.7%
Race/Ethnicity		
Non-Hispanic White	132,765	71.3%
Non-Hispanic Black	15,309	8.2%
Hispanic	18,719	10.1%
Asian/Pacific Islander	18,394	9.9%
Other/Unknown	969	0.5%
Histology Type		
Small Cell Carcinoma	31,648	17.0%
Squamous Cell Carcinoma	26,033	14.0%
Adenocarcinoma	68,687	36.9%
Large Cell Carcinoma	8,235	4.4%
NSCLC, NOS	44,075	23.7%
Other/Unknown	7,478	4.0%
Year of Diagnosis		
1990–1994	34,843	18.7%
1995–1999	36,563	19.6%
2000–2004	39,455	21.2%
2005–2009	39,253	21.1%
2010–2014	36,042	19.4%

Abbreviation: NSCLC, non-small cell lung cancer; NOS, Not Otherwise Specified

Table 2.

Annual percent change (APC) in one-year relative survival rates for metastatic lung cancer patients in California. (1990–2014)

	One-Year Relative Survival (1990–2014)			
	APC	**95% CI**		**p-value**
Overall ^				
1990–1993	−0.69	−4.22	2.98	0.69
1993–2012	2.60	2.41	2.79	<0.01 *
2012–2014	−0.70	−5.99	4.88	0.79
Age at Diagnosis				
20–64 years	2.51	2.31	2.71	<0.01 *
65–74 years	2.63	2.40	2.87	<0.01 *
≥75 years	2.74	2.40	3.08	<0.01 *
Sex				
Male	2.12	1.88	2.35	<0.01 *
Female ^				
1990–1996	0.85	−0.57	2.29	0.23
1996–2011	2.96	2.66	3.26	<0.01 *
2011–2014	0.17	−2.39	2.80	0.89
Race/ethnicity				
NHW	1.91	1.77	2.06	<0.01 *
NHB	2.05	1.63	2.48	<0.01 *
Hispanic ^				
1990–1995	−2.69	−9.52	4.66	0.44
1995–2014	2.92	2.15	3.68	<0.01 *
API	3.28	2.84	3.72	<0.01 *
Histology				
Small-Cell	0.04	−0.26	0.33	0.79
Squamous	1.31	0.95	1.66	<0.01 *
Adenocarcinoma ^				
1990–2009	3.90	3.59	4.21	<0.01 *
2009–2014	1.17	−0.37	2.74	0.13
Large Cell	2.31	1.55	3.06	<0.01 *
NSCLC NOS ^				
1990–2006	3.32	2.83	3.81	<0.01 *
2006–2014	−0.88	−2.17	0.44	0.18

	One-Year Relative Survival (1990–2014)			
	APC	**95% CI**		**p-value**
Other	−1.04	−1.90	−0.19	0.02 *

^ There were different rates of change over the study period.

* APC is significantly different from 0.

Table 3.

Annual percent change (APC) in five-year relative survival rates for metastatic lung cancer patients in California (1990–2014).

	Five-Year Relative Survival (1990–2010)			
	APC	**95% CI**		**p<0.05**
Overall	4.05	3.47	4.64	<0.01*
Age at Diagnosis				
20–64 years	4.23	3.52	4.95	<0.01*
65–74 years	5.04	3.80	6.29	<0.01*
≥75 years	5.15	3.91	6.41	<0.01*
Sex				
Male	4.04	3.13	4.95	<0.01*
Female	4.35	3.67	5.03	<0.01*
Race/ethnicity				
NHW	4.09	3.46	4.73	<0.01*
NHB	3.58	2.13	5.05	<0.01*
Hispanic^				
1990–1997	−5.42	−14.26	4.32	0.25
1997–2010	5.68	2.74	8.70	<0.01*
API	4.2	2.86	5.56	<0.01*
Histology				
Small-Cell	2.22	0.84	3.62	<0.01*
Squamous	2.29	1.17	3.42	<0.01*
Adenocarcinoma	5.66	4.73	6.60	<0.01*
Large Cell	4.41	2.22	6.65	<0.01*
NSCLC NOS	4.97	3.76	6.20	<0.01*
Other	1.92	−0.92	4.83	0.17