Improving Survival for Stage IV Non-small Cell Lung Cancer

A Surveillance, Epidemiology, and End Results Survey from 1990 to 2005

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Background: Although there has been a significant survival improvement for patients with metastatic NSCLC enrolled in randomized trials, it is not clear whether a similar benefit is seen in an unselected group of patients. Therefore, we conducted a study to evaluate for survival changes in a large national cancer registry database.

Patients and Methods: The Surveillance, Epidemiology, and End Results (SEER) registry was queried for patients with NSCLC stage IV, aged 21 years or older, and diagnosed between 1990 and 2005. We analyzed four equally divided time periods between 1990 and 2005 (1990 to 1993 or period 1, 1994 to 1997 or period 2, 1998 to 2001 or period 3, and 2002 to 2005 or period 4) to determine changes in overall survival for all patients and according to histology.

Results: We identified 129,337 patients meeting eligibility criteria. There was a significant improvement in overall survival since period 1. One-year and 2-year overall survival increased from 13.2 and 4.5%, respectively, in period 1 to 19.4% and 7.8%, respectively, in period 4. On multivariate analysis, survival for adenocarcinoma was increased compared with squamous cell carcinoma only in period 4 ($p = 0.02$).

Conclusions: There has been a modest but statistically significant improvement in overall survival for stage IV NSCLC over the past 16 years. The recent differences in outcomes based on histology observed in period 4 may reflect the increased activity of epidermal growth factor receptor tyrosine kinase inhibitors in adenocarcinoma compared with squamous cell carcinoma.

Key Words: Non-small cell lung cancer, Survival, SEER.

Lung cancer is the most common cause of cancer-related death in the United States, with 161,840 deaths estimated by the American Cancer Society for the year 2008.[1] Non-small cell lung cancer (NSCLC) currently constitutes approximately 87% of the lung cancer cases.[2] Approximately 40% of patients with newly diagnosed NSCLC present with metastatic disease.[3]

Survival improvement for NSCLC in the past 2 decades has been modest. Breathnach et al.[4] performed a combined analysis of the Surveillance, Epidemiology, and End Results (SEER) database and 33 North American phase III trials from 1973 to 1994. The SEER database showed improved 3-year overall survival for patients with NSCLC, including all stages, from 14.4% between 1972 and 1973 to 18.1% between 1993 and 1994. In patients with distant disease (according to SEER historical staging system), which also includes patients with subtypes of T4 such as malignant pleural effusion and direct extension into the sternum, vertebra, and skeletal muscle, there was also a slight improvement in median survival from 6.9 to 7.3 months during the same time period. Among patients with stage III or IV treated in the randomized clinical trials, median survival improved from 5.2 months between 1973 and 1983 to 5.8 months between 1984 and 1994.

Since 1990, there have been several changes in the management of advanced NSCLC, including the development of new chemotherapy agents and regimens,[5] increasing use of salvage chemotherapy,[6,7] and the introduction of molecularly targeted therapies, specially the epidermal growth factor tyrosine kinase inhibitors (TKIs).[8] Although these advances have been associated with improved response rates and survival in clinical trials, there are only limited data regarding the extent of this benefit in an unselected patient population. Therefore, we performed an analysis of the SEER database to evaluate for trends in survival for patients with stage IV NSCLC over the last 16 years.

PATIENTS AND METHODS

Since its establishment in 1973, the National Cancer Institute-funded SEER program has been collecting data on demographics, pathologic, and clinical characteristics including stage, initial treatment, and survival for newly diagnostic cancer cases. The database expanded from nine registries covering approximately 10% of the U.S. population from 1973 to 1991 (SEER-9) to 14% from 1992 to 1999 and 26% since the year 2000 (SEER-17).

We searched the April 2008 release of the SEER-17 registry data version 6.4.4,[9] for patients with stage I to IV NSCLC according to the modified AJCC, 3rd edition, aged 21 years or older, with active follow-up, and diagnosed between 1990 and 2005. Patients with nonmetastatic disease were evaluated only for the calculations of stage migration, whereas the remaining of the study was focused on patients with stage IV. Because there was no access to patient identity, it was not necessary to obtain informed consent. The histology was coded according to the International Classification of Diseases for Oncology (0-3) into adenocarcinoma (8140–8147, 8255, 8260, 8310, 8323, 8480, 8481, 8490, 8550, and 8572), squamous cell carcinoma (8050–8052 and 8070–8078), large cell carcinoma (8012 and 8014), and other histologies, including undifferentiated tumors (8020–8022) and carcinomas not otherwise specified or not defined as one of the three most common histologies (8010, 8015, 8030–8036, and 8046). Large cell neuroendocrine carcinomas and bronchioloalveolar carcinoma were excluded, the former due to different behavior and lack of data before the year 2000 and the latter due to a more indolent clinical course, distinct from other subtypes of adenocarcinoma and NSCLC in general.

Demographic variables were defined as age at diagnosis, gender, and race (white, black, and other). Follow-up cutoff was on December 31, 2005. Diagnostic periods were subdivided into four groups as follows: 1990–1993 (period 1), 1994–1997 (period 2), 1998–2001 (period 3), and 2002–2005 (period 4).

To evaluate for possible effects of the new SEER registries, we performed a subset analysis including only patients from registries available before the study, including Atlanta, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle (Puget Sound), and Utah.

Statistical Analysis

Overall survival was defined as time from diagnosis to death from any cause and patients alive were censored at the time of last recording. Data analyses were performed according to diagnostic period, with comparisons between consecutive periods, and subset analysis for each histologic subtype. Overall survival was estimated using the Kaplan-Meier product limit method and compared by log-rank test. Multivariate Cox models were also fitted to evaluate whether diagnostic period was an independent risk factor, while adjusting for age, gender, race, and histologic subtypes. Statistical analyses were performed using the standard package SAS version 9 (SAS institute, Cary, NC). A *p* value less than 0.05 was considered significant, and all statistical tests were two sided.

RESULTS

Demographics

Among the 346,023 patients diagnosed in the four periods, 37,347 (10.7%) had unknown stage. The percentages of patients with unknown stage for periods 1 to 4 were 14.2%, 11.3%, 7.9%, and 11.2% respectively. Among those with known stage classification, the proportions of patients with

TABLE 1. Patient Demographics

Parameter	Variables	Number (%)
Age	21–30	124 (0.1)
	31–40	1579 (1.2)
	41–50	9570 (7.4)
	51–60	24,100 (18.6)
	61–70	39,165 (30.3)
	71–80	39,675 (30.7)
	81–90	14,132 (10.9)
	>91	992 (0.8)
Gender	Male	75,078 (58.0)
	Female	54,259 (42.0)
Race	White	105,731 (81.7)
	Black	15,178 (11.7)
	Other	8428 (6.6)
Histology	Adenocarcinoma	53,300 (41.2)
	Squamous	22,944 (17.7)
	Large cell	8842 (6.9)
	Other	44,251 (34.2)
Diagnostic period	1990–1993	17,763 (13.8)
	1994–1997	21,131 (16.3)
	1998–2001	36,975 (28.6)
	2002–2005	53,468 (41.3)

metastatic disease from periods 1 to 4 were 39.3%, 38.9%, 41.2%, and 44.6%, respectively.

The demographics for the 129, 337 patients with stage IV at presentation are described in Table 1. The median age was 67.2 ± 11.4 years (range, 21–105). There were 75,058 men (58%) and 54,259 women (42%). Whites represented the majority of patients (82%), followed by African Americans (12%) and others (6%). Adenocarcinoma was the most common histology (41%), followed by other histologies (34%), squamous cell carcinoma (17%), and large cell carcinoma (8%). The median follow-up time was 4 months (range, 1–191). Approximately 8% of the subjects were censored. As reflected by the expanding SEER coverage, the number of patients with the diagnosis of NSCLC entered in the registry increased according to the year and period of diagnosis.

Univariate Survival Analysis

Overall survival at 1 and 2 years improved consistently during each succeeding period (Figure 1 and Table 2). Overall survival at 1 and 2 years were 13.2% and 4.5% for period 1, 14.0% and 4.9% for period 2, 17.2% and 6.5% for period 3, and 19.4 and 7.8% for period 4, respectively. All the improvements were statistically significant, including period 2 compared with period 1 ($p = 0.006$), period 3 compared with period 2 ($p < 0.0001$), and period 4 compared with period 3 ($p < 0.0001$). A similar pattern was observed for the four histologies, with modest improvement from periods 1 to 2 and more significant survival gains in subsequent periods. However, median survival for all histologies remained stable at approximately 4 months. Overall survival at 1 and 2 years was significantly higher in adenocarcinoma and squamous cell carcinoma compared with large cell carcinomas and other histologies.
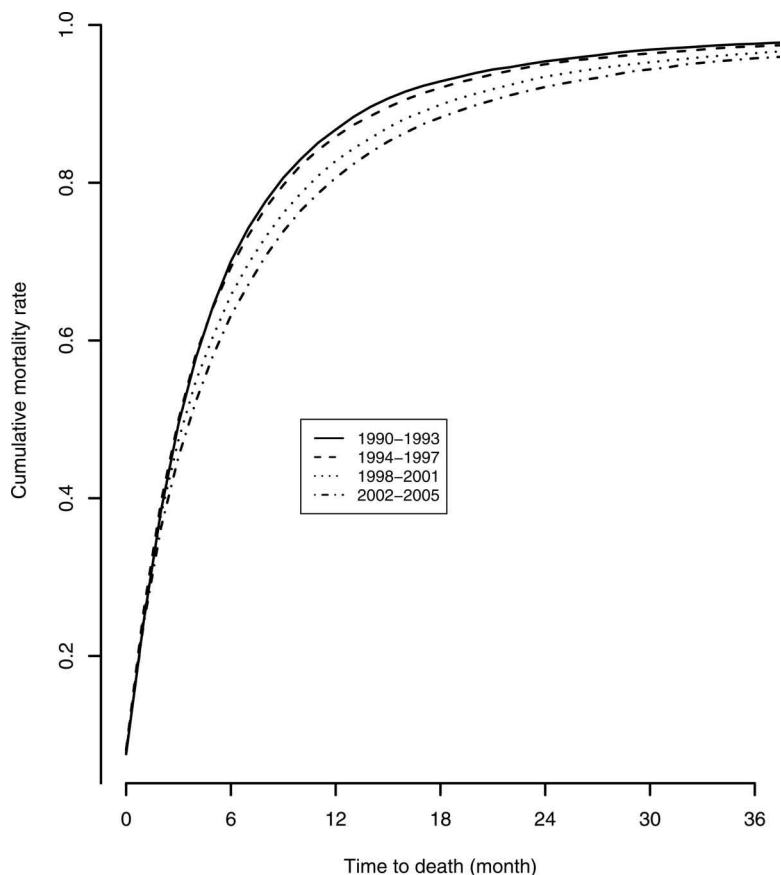
FIGURE 1. Cumulative mortality rate according to diagnostic period.

TABLE 2. Overall Survival According to Histology

Histology	Period	Median Survival (mo)	1-yr OS (%)	2-yr OS (%)
All histologies	1990–1993	4	13.2	4.6
	1994–1997	4	14.1	4.9
	1998–2001	4	17.2	6.5
	2002–2005	4	19.3	7.8
Adenocarcinoma	1990–1993	4	15.5	5.4
	1994–1997	4	16.1	5.7
	1998–2001	4	20.4	7.9
	2002–2005	5	23.3	9.9
Squamous	1990–1993	4	13.5	4.3
	1994–1997	4	14.3	4.9
	1998–2001	4	17.1	6.4
	2002–2005	4	19.9	7.2
Large cell	1990–1993	3	11.5	4.3
	1994–1997	3	12.5	3.8
	1998–2001	4	14.8	5.7
	2002–2005	4	16.6	6.6
Other	1990–1993	3	10.3	3.4
	1994–1997	3	11.8	4.2
	1998–2001	3	14	5.1
	2002–2005	3	16.2	6.3

OS, overall survival.

Multivariate Survival Analysis

Factors associated with better survival in multivariate analysis included younger age, female gender, ethnicity other than whites or African Americans, adenocarcinoma or squamous cell carcinoma histology, and successive diagnostic periods (Table 3). Survival improvement was statistically significant for all histology groups (Table 4). Survival was significantly better for adenocarcinoma and squamous cell carcinoma compared with large cell carcinoma or other histologies in all diagnostic periods (Table 5). However, increased survival for adenocarcinoma compared with squamous cell was not observed until the fourth period.

Subset Analysis of Patients from Registries Available Before 1990

Among the 129,337 patients, 69,130 (53.4%) were enrolled from the SEER registries available before 1990. In this subset, the overall survival at 1 and 2 years were 13.4% and 4.6% for period 1, 14.3% and 5.1% for period 2, 17.2% and 6.6% in period 3, and 20.1% and 7.9% in period 4, respectively. In a multivariate analysis, there was a statistically significant difference in survival for all diagnostic periods. Comparing with period 1, used as reference, the hazard ratios for periods 2, 3, and 4 were 0.975 (95% confidence interval [CI]: 0.954–0.998), 0.902 (95% CI: 0.883–0.922), and 0.824 (95% CI: 0.806–0.843), respectively.

TABLE 3. Predictors for Improved Survival in Multivariate Analysis

Parameter	Variables	Hazard Ratio (95% CI)	p
Age (yr)	18–30	0.709 (0.580–0.866)	0.0008
	31–40	0.787 (0.746–0.829)	<0.0001
	41–50	0.837 (0.818–0.857)	<0.0001
	51–60	0.905 (0.890–0.920)	<0.0001
	61–70	Reference	
	71–80	1.167 (1.150–1.184)	<0.0001
	81–90	1.440 (1.411–1.469)	<0.0001
	>90	1.641 (1.538–1.751)	<0.0001
Gender	Female	Reference	
	Male	1.128 (1.115–1.141)	<0.0001
Race	Other	Reference	
	White	1.146 (1.119–1.174)	<0.0001
	Black	1.187 (1.154–1.221)	<0.0001
Histology	Adenocarcinoma	Reference	
	Squamous	1.015 (0.999–1.032)	0.074
	Large cell	1.129 (1.104–1.156)	<0.0001
	Others	1.194 (1.178–1.210)	<0.0001
Period	1990–1993	Reference	
	1994–1997	0.973 (0.953–0.992)	0.006
	1998–2001	0.887 (0.871–0.903)	<0.0001
	2002–2005	0.823 (0.808–0.838)	<0.0001

CI, confidence interval.

TABLE 4. Multivariate Analysis for Survival Differences among Histology Types According to Diagnostic Period

Histology	Period	Hazard Ratio (95% CI)	p
Adenocarcinoma	1990–1993	Reference	
	1994–1997	0.974 (0.944–1.004)	0.09
	1998–2001	0.887 (0.862–0.912)	<0.0001
	2002–2005	0.810 (0.788–0.833)	<0.0001
Squamous	1990–1993	Reference	
	1994–1997	0.993 (0.949–1.038)	0.74
	1998–2001	0.902 (0.867–0.940)	<0.0001
	2002–2005	0.853 (0.820–0.887)	<0.0001
Large cell	1990–1993	Reference	
	1994–1997	0.974 (0.915–1.036)	0.39
	1998–2001	0.884 (0.834–0.937)	<0.0001
	2002–2005	0.847 (0.796–0.902)	<0.0001
Other	1990–1993	Reference	
	1994–1997	0.961 (0.924–0.999)	0.04
	1998–2001	0.881 (0.851–0.912)	<0.0001
	2002–2005	0.823 (0.796–0.851)	<0.0001

CI, confidence interval.

TABLE 5. Multivariate Analysis for Survival Differences According to Histology Subtype Within Each Diagnostic Period

Period	Histology	Hazard Ratio (95% CI)	p
1990–1993	Adenocarcinoma	Reference	
	Squamous	0.990 (0.952–1.030)	0.62
	Large cell	1.121 (1.068–1.177)	<0.0001
	Other	1.203 (1.159–1.250)	<0.0001
1994–1997	Adenocarcinoma	Reference	
	Squamous	1.007 (0.969–1.046)	0.72
	Large cell	1.117 (1.063–1.173)	<0.0001
	Other	1.178 (1.140–1.217)	<0.0001
1998–2001	Adenocarcinoma	Reference	
	Squamous	0.997 (0.968–1.027)	0.85
	Large cell	1.106 (1.060–1.153)	<0.0001
	Other	1.172 (1.144–1.200)	<0.0001
2002–2005	Adenocarcinoma	Reference	
	Squamous	1.033 (1.004–1.062)	0.02
	Large cell	1.171 (1.117–1.240)	<0.0001
	Other	1.214 (1.189–1.240)	<0.0001

CI, confidence interval.

DISCUSSION

The role of chemotherapy in previously untreated patients with advanced NSCLC was debatable until nearly 15 years ago.[10–13] Before 1990, few drugs had consistent activity against NSCLC, defined as response rate ≥15%, including cisplatin, mytomicin C, vinblastine, vindesine, and ifosfamide. Since then, several novel chemotherapy agents have been approved by the Food and Drug Administration for the treatment of advanced NSCLC. Vinorelbine, paclitaxel, gemcitabine, and docetaxel were approved between 1994 and 1999, whereas gefitinib, erlotinib, and pemetrexed were approved between 2003 and 2004.[14] In a meta-analysis of 19 randomized clinical trials reported between 1994 and 2004, Baggstrom et al.[15] compared the efficacy of third-generation agents with best supportive care or second-generation agents, defined as platinum alone or in combination with etoposide, vindesine, ifosfamide, or mitomycin. One-year survival with single-agent third-generation agents was similar to second-generation platinum-based combination therapy but significantly improved when compared with best supportive care. In a comparison between second and third generation platinum-based regimens, both response rate and 1-year survival favored the third-generation combinations.

Data from randomized clinical trials have shown improved 1-year survival from approximately 20% in early 1990s[16] to approximately 38% in more recent studies using platinum-based doublets.[17–20] We conducted this study to determine whether the survival improvement over the past 2 decades reported in controlled clinical trials is seen in unselected representative patient population from the large SEER database, possibly reflecting the true impact of recent advances on patients with NSCLC.

In keeping with published literature, we observed better outcomes for women[21] and younger patients.[22] The effect of race remains incompletely understood, and our dataset did not show significant differences in outcomes between whites and African Americans in the multivariate analysis. Decreased access to optimal care, mostly surgical resection in early stage,[23] and higher percentage of advanced stage[24] have been postulated as possible causes for worse outcomes in this population. When similar therapies were used, there were no differences in outcomes according to race.[25] Because our large

database included only patients with stage IV disease, it eliminated the biases caused by differences in stage at presentation.

The impact of histology on survival for patients with advanced NSCLC has not been well delineated. Large retrospective studies have shown decreased survival for large cell carcinoma[26,27] and improved outcomes in squamous carcinoma.[27,28] In a recent review, Hirsch et al.[29] evaluated the role of histology in advanced NSCLC. Among the 408 publications surveyed between 1982 and 2007, 32 studies reported a statistically significant associated between histology and NSCLC outcomes. Results from chemotherapy trials showed inconsistent results but among patients treated with TKIs; however, adenocarcinoma was associated with improved response rates and survival. Histology, in fact, became an important factor for outcomes in NSCLC following the results from Iressa Dose Evaluation in Advanced Lung Cancer 1[30] and 2[31] trials, both showing increased response rates for adenocarcinoma compared with other histologies. This finding was confirmed in subsequent phase III studies using gefitinib[32] or erlotinib.[33] Among patients treated with pemetrexed, outcomes are better for adenocarcinoma compared with squamous cell carcinoma.[34] Although no significant differences in survival between adenocarcinoma and squamous cell carcinoma were observed on a multivariate analysis in our study between periods 1 and 3, survival was significantly better for patients with adenocarcinoma in period 4 compared with patients with other histologies, possibly due to the increased use of epidermal growth factor receptor TKIs. However, it should be noted that the difference remains small, perhaps due to the very poor outcomes in both subgroups.

Additional contributing factors for the increased survival in NSCLC include improved supportive therapy over time and stage migration. Positron emission tomography (PET) has been associated with a detection rate of unsuspected distant metastases in approximately 10% of patients with NSCLC.[35] With the Medicare approval for reimbursement in 1998, an increasing number of patients are undergoing PET scan during the staging process.[36,37] Two retrospective studies showed increased percentage of patients diagnosed with stage IV after the introduction of PET scan, with both showing correspondent survival improvement in the arbitrarily defined "PET period."[38,39] The stage migration was confirmed in a large National Cancer Database Study involving 813,312 patients with NSCLC and known stage, which showed increased percentage of stage IV from 35.4 to 38.8% between the years 2000 and 2001, followed by a plateau with minimal subsequent changes.[3] The impact of improved survival by stage migration may be explained by the "Will Rogers phenomenon,"[40] which is characterized by the apparent paradox observed when moving elements from one group to another raises the average for both donor and recipients. In this case, patients with metastatic disease diagnosed only by PET scan are expected to have decreased tumor burden and improved outcome compared with other patients with metastatic disease. Therefore, the inclusion of this subgroup originated from the stage migration is expected to increase the overall survival for stage IV to a certain degree. In our database, there was an increase in the percentage of patients with metastatic disease at presentation between periods 2 to 3 and 3 to 4. It is possible that this change may account at least in part to the survival improvement in stage IV disease.

The possibility of improved survival caused by the addition of SEER registries during the study period was ruled out by the almost identical survival rates observed in the subset analysis restricted to registries available before 1990.

Despite the drawbacks from analyzing retrospective database cohorts, our study provides insight into the changing outcomes in advanced NSCLC over time and the impact of recent advances in diagnosis and therapy beyond what has been learnt studying highly selected group of patients enrolled in prospective studies. Although the development of several new agents led to a statistically significant survival improvement over the last 16 years, it is sobering that the 1-year survival has improved by only 6% during this time. This improvement is certainly modest compared with the extent of 1-year survival improvement reported in recent clinical trials. Real progress can only be achieved with a better understanding of tumor biology and development of novel therapies.

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