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Determinants of Survival in Advanced Non-Small Cell Lung Cancer (NSCLC) in the Era of Targeted Therapies

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Abstract

Introduction—Molecular profiling of NSCLC samples has a profound impact on choice of therapy. It is less clear, however, whether *EGFR* and *KRAS* mutations are prognostic outside of a trial-based treatment paradigm.

Methods—We performed a retrospective chart review of 513 NSCLC patients undergoing *EGFR* and *KRAS* mutational analysis at the Hospital of the University of Pennsylvania between May 2008 and November 2011. Survival analysis was based upon the 376 patients who received systemic treatment and their survival was determined from date of initiation of systemic therapy.

Results—The median overall survival was 30.8 months (95%CI 24.7–36.9 months). Neither *EGFR* mutational status ($p=0.09$) nor *KRAS* mutational status ($p=0.69$) was associated with overall survival. Female sex ($p<0.001$), never smoker status ($p=0.01$), better PS ($p<0.001$), lower Charlson Comorbidity Index ($p<0.001$) and lower age-weighted Index ($p<0.001$) were associated with prolonged survival. The presence of bone metastases ($p=0.001$) and liver metastases ($p=0.004$) were also associated with a shortened survival. In a multivariable regression that adjusted for stage, we demonstrated that male gender ($p=0.002$), worse ECOG PS ($p=0.01$), metastases to bone ($p=0.03$) and higher age-weighted co-morbidity Index ($p=0.001$) were independent prognostic factors for shorter survival. *EGFR* mutation status was not prognostic ($p=0.85$).

Conclusion—*EGFR* and *KRAS*, in our series, do not function as prognostic determinants for NSCLC.

Keywords

EGFR; *KRAS*; prognosis; NSCLC

Introduction

Non-Small Cell Lung Cancer (NSCLC) is a prevalent disease with a high mortality rate. It is the leading cause of cancer death in America.(1) The advent of drugs targeting molecular abnormalities in *EGFR*, *EML4-ALK*, and *ROS1* has changed the face of systemic therapy for NSCLC.(2–6) It is not clear, however, whether the presence of such molecular abnormalities portends *a priori* an independently better prognosis. *EGFR* mutations have been shown to occur more frequently in never smokers,(7) women,(8) those with adenocarcinoma, and well differentiated tumors(9), each of which is associated with a better prognosis among patients with NSCLC.(10–12) By contrast, *KRAS* mutations are more commonly found in smokers,(13) a group which appears to have an impaired prognosis. No study to date has incorporated an assessment of comorbidity, which is an important confounding factor for survival in patients with cancer.(14, 15)

Materials and Methods

After acquiring approval from our institutional review board and in conjunction with our Molecular Pathology laboratory (MP) we reviewed every *EGFR* mutation analysis for a diagnosis of NSCLC performed at Hospital of the University of Pennsylvania from May 2008 through November 2011. MP also provided us with the results of *KRAS* mutational analysis when performed on the same patients during this time period. May 2008 was when molecular test results began being stored in a centralized database at our institution, and data abstraction for this project began in November 2011. Results that were indeterminate or inconclusive were excluded from further analysis.

Once the list of patient names was made available, a retrospective chart review was performed using our electronic medical record (EMR) to acquire demographic, treatment and tumor related data. Stage was determined using our internal tumor registry and the EMR. In addition, a Charlson Comorbidity Index as well as an age-weighted Index(16) were calculated for each patient using an online calculator (<http://www.medal.org/OnlineCalculators/ch1/ch1.13/ch1.13.01.php>) based on medical history data extracted from the EMR.

For mutation analysis, DNA was extracted from formalin fixed paraffin embedded tissue using conventional methods. *EGFR* mutation analysis for exon 19 deletions and the L858R point mutation (*EGFR* NM_005228.3:c.2573T>G) was performed as previously described. (17) *KRAS* mutation analysis was performed using multiplex PCR coupled with analysis on a liquid bead array. Primers designed to detect the seven most common point mutations in nucleotides c.34G, c.35G and c.38G in codons 12 and 13 of *KRAS* (NM_004985.3) were used to amplify the target sequence. Amplified products were then hybridized to a liquid bead array and analyzed with a Luminex 100. The analytical sensitivity of both methods is approximately 5%.

For overall survival (OS) analysis, dates of death were confirmed either from death certificates scanned into the EMR or the Social Security Death Index (SSDI). For those patients without a documented death, the censor date was established by the most recent date of clinical encounter in the EMR. Survival was calculated from the date of first systemic therapy administration. This date was chosen to be consistent with clinical trials, which define survival time from chemotherapy administration date.

Descriptive statistics were employed to describe characteristics of the study population and subgroups of patients who were included or excluded from the survival analysis population. Categorical variables were summarized by frequency and percentage. Continuous variables were summarized by mean and standard error. Patients who were positive for either an exon

19 deletion or L858R mutation were classified as *EGFR* mutation positive, while patients who were negative for both mutations were classified as *EGFR* mutation negative or wild type. Patients who were positive (or negative) for one mutation but were indeterminate or inconclusive for the other mutation were classified as non-informative. Prevalences of *EGFR* or *KRAS* mutations were described by frequencies and percentages based on informative cases only. Associations between patient characteristics and either inclusion/exclusion from the survival analysis population or *EGFR* or *KRAS* mutation status were tested by Fisher's exact test, from systemic therapy, as outlined above. Median overall survival was estimated by the Kaplan-Meier method and 95% confidence interval by Greenwood's formula. Univariate Cox regression analysis was employed to estimate the magnitude of association with survival, using the hazard ratio and 95% confidence interval. Multivariable Cox regression analysis was utilized to identify significant independent determinants of overall survival. Statistical significance was assessed by the Wald test. The variables considered for model building exhibited univariate significance of $p < 0.10$. These included gender, smoking status, PS, *EGFR* mutational status, liver metastases, bone metastases, age, Charlson Comorbidity Index and age-weighted Index. Backward selection was employed to construct the optimal multivariable model. Stage was included in multivariable models to adjust for timing and impact of chemotherapy, regardless of achieved significance. A p-value less than or equal to 0.05 was considered statistically significant. All statistical analyses were produced in SPSS 19 (SPSS Inc., Chicago, IL) or StatXact (Cytel Corp, Cambridge, MA).

Results

Patient Characteristics

Our initial list of *EGFR* test requests numbered 543, but after eliminating patients who had a diagnosis other than NSCLC as well as patients whose primary cancer was tested twice, our cohort was reduced to 513 NSCLC patients (CONSORT diagram, Figure 1). When data on initial chemotherapy ($n=37$) or chemotherapy start date ($n=3$) were incomplete, patients were excluded from analysis. Missing data generally occurred when patients received their chemotherapy at another institution. Absence of systemic therapy ($n=97$) often occurred due to patient refusal or impaired functional status. After the exclusions documented in the CONSORT, 376 patients were included in the survival analysis population.

Not surprisingly, there were significantly more patients with Stage I disease excluded from survival analysis ($p<0.001$, Table 1). There were fewer patients with any *EGFR* mutation excluded from analysis ($p=0.001$), although this was not true individually for L858R mutations ($p=0.10$) or exon 19 deletions ($p=0.22$).

Patients included in the analysis were younger ($p=0.001$) but had a higher Charlson Comorbidity Index (more comorbidity, $p<0.001$) and age-weighted Index ($p=0.008$).

EGFR mutations were more likely in women ($p=0.002$), Asian Americans ($p<0.001$), and never smokers ($p<0.001$, Table 2). Patients with *EGFR* mutation had a significantly lower Charlson Comorbidity Index ($p=0.002$) as well as a lower age-weighted Index ($p=0.02$), indicating less comorbidity (Table 3). *KRAS* mutations were more common among smokers ($p<0.001$). One patient's tumor harbored mutations in both *EGFR* and *KRAS*.

Survival analysis

At a median follow up of 32 months (21 months in 178 living patients), the median overall survival was 30.8 months (95% CI 24.7–36.9 months). Univariate results are listed in Table 4. Female sex ($p<0.001$), never smoker status ($p=0.01$), better PS ($p<0.001$), lower Charlson Comorbidity Index ($p<0.001$) and lower age-weighted Index ($p<0.001$) were associated with

a prolonged survival (Figures 2A–2D). In addition, older age ($p=0.01$) and the presence of bone metastases ($p=0.001$, Figure 2E) and liver metastases ($p=0.004$) were associated with a shortened survival. *EGFR* mutational status was not associated with a statistically significant overall survival advantage (median OS 46.8 vs 29.6 months for *EGFR* positive vs negative patients, $p=0.09$, Figure 3A), and neither *EGFR* mutation individually was associated with survival. *KRAS* mutation was also not associated with survival (median OS 32.7 vs 33.0 months for *KRAS* mutant vs wildtype patients, $p=0.69$, Figure 3B). Stage was not associated with survival in this analysis ($p=0.10$), since our sample had a relatively small number of patients with early stage cancer due to our elimination of any patients who did not receive systemic therapy.

Nine candidate factors were selected for multivariable survival analysis based upon univariate significance. Given the expected differences in prognosis based upon stage inherent in choosing the date of first systemic therapy administration, stage was included in the model. The multivariable model demonstrated that gender ($p=0.002$), ECOG PS ($p=0.01$) metastases to bone ($p=0.03$) and higher age-weighted co-morbidity Index ($p=0.001$) were significant independent prognostic factors for shorter survival (Table 5). Smoking status nearly reached statistical significance ($p=0.055$). Based upon our interest in testing *EGFR* as a potentially important factor, we specifically included it in a separate model.

Discussion

In this era of targeted therapy, characterization of the prognostic impact of mutations is crucial to appropriate patient consultation. The survival documented in our analysis is significantly longer than that previously reported in the literature for patients with NSCLC, but is similar to prior reports evaluating patients tested for *EGFR* mutation (18, 19). This likely indicates a selection bias in such studies. The patients who historically would be tested more frequently for *EGFR* mutation include those with demographic traits associated with a higher incidence of such mutation. This cohort by its very nature would include never or light smokers and would more likely be female. It has been widely reported that these groups have a significantly better prognosis than the average patient with NSCLC. (7, 8)

The main criteria for exclusion were missing data or failure to receive systemic therapy. As expected, stage and metastatic status differed between those included and those excluded from analysis. Patients excluded from the analysis were more likely to have early stage disease and less likely to have liver or bone metastases, consistent with current guidelines. The patients included in our survival analysis were significantly younger than those excluded, likely secondary to lower frequency of administration of chemotherapy in the elderly (22). The higher Charlson Comorbidity Index in included patients, by contrast, was likely due to generally sicker patients with more advanced disease. This reflects the main indications for withholding chemotherapy – early disease and poor medical health. Patients included in the survival analysis were more likely to have tumors harboring an *EGFR* mutation, though this was not true of the individual mutations.

Data conflict on the contribution of *EGFR* mutations to the prognosis of patients with NSCLC independent of the therapy they receive (Table 6). While many studies have shown no difference in the prognosis of patients with *EGFR* mutation (9, 20–23), three large studies have shown an improved survival in those patients with *EGFR* mutation compared to those whose tumors are wild type. In 2005, Eberhard et al (24) performed a univariate subgroup analysis of the TRIBUTE trial. Of the original 1079 patients in the trial, mutational data were available for 274 patients. When combining the treatment arms, patients with tumors harboring an *EGFR* mutation had a prolonged median survival. In 2007, Sequist et al (18)

performed the first analysis of this kind in the United States. Using a multivariable model, they showed an association of *EGFR* with longer survival. They defined survival from date of diagnosis, did not control for smoking or comorbidity, and their mutational frequency indicates a marked referral bias. In 2012 Johnson et al(19) reviewed patients with stage IV adenocarcinoma of the lung at Sloan Kettering. While they found a prolonged survival associated with *EGFR* mutation, the incidence of mutation indicated a referral bias and they did not control for comorbidity. Additionally, given the high prevalence of *EGFR* targeted clinical trials at that institution, it is questionable whether their response rate was indicative of currently available therapies. Our study showed no association between *EGFR* mutation and survival on multivariable analysis. The trend seen on univariate analysis was obviously due to strong collinearity with gender and smoking and not an issue of power. In addition, given that 99.9% of patients received a first line systemic therapy consistent with current guidelines and 95.1% of patients with tumors harboring an *EGFR* mutation received erlotinib or gefitinib in the first or second line, failure to identify an association with survival is unlikely to be due to inappropriate therapy administration in either group.

The prognostic impact of *KRAS* mutation upon patients with NSCLC has been similarly controversial. A full evaluation of all studies to date is beyond the scope of this paper. Multiple studies, however, indicate that patients whose tumors harbor *KRAS* mutations have a worse prognosis(13, 25–27), while others suggest that it is associated with a similar prognosis.(11, 28–30) In 2005 Mascaux(31) et al performed a meta-analysis of markedly heterogeneous studies evaluating *KRAS* mutation status in lung cancer, showing a worse prognosis associated with *KRAS* mutation. There were more than twice as many studies in the meta-analysis that found no significant difference as a function of *KRAS* than those that noted a shortened survival with *KRAS* mutation. Johnson et al(19) noted no difference in survival with *KRAS* mutation on univariate analysis, but on multivariable analysis a statistically significant difference was seen. Our study showed no significant association between *KRAS* mutation and survival (Figure 3B) and no difference was seen on multivariable analysis (data not shown).

The lack of a strong association between OS and age in the multivariable model is at first surprising, since there are multiple other studies which indicate that age is an important prognostic variable in NSCLC and other cancers.(32–34) However, more modern data clearly show that elderly patients gain at least equivalent benefit from systemic therapy compared to younger patients.(35, 36) Since our cohort excluded those patients who were too ill to receive systemic therapy and focused on patients actively undergoing therapy, we are very likely including a group of relatively healthy older patients. The association of impaired survival with male gender, smoking, bone metastasis and liver metastasis has been previously reported, (10) (12) (37) (38) (39–41) and our data are consistent with these findings.(Figure 2A, 2B, 2E)

Few prior studies have evaluated the impact of comorbidity on survival in patients with NSCLC receiving systemic therapy.(42, 43) Frasci et al studied chemotherapy in elderly patients with advanced NSCLC and found that more severe comorbidity was associated with impaired survival. Firat et al evaluated patients receiving XRT for NSCLC and noted that comorbidity and PS were associated with OS. While PS provides some insight into a patient's health status, it is an enormously subjective measure and does not fully characterize a patient's comorbidity. In our analysis population, for example, there was no association between Charlson Comorbidity Index and PS (Spearman rank correlation = 0.08, $p=0.20$, data not shown). Our analysis is the largest to date evaluating this association, and it confirms the findings of these smaller studies (Figure 2C–2D). In addition, our effort is amongst the first to include “real world” population outside the confines of a clinical trial.

This indicates that differences in comorbidity are important at all levels of health, not only in our clinical trial populations who tend to be the healthiest.

Our study suffers from several obvious limitations. First, not every patient seen in our thoracic oncology program underwent *EGFR* mutational testing. That being said, our mutational frequency appears similar to prior North American studies. Additionally, the retrospective nature of our analysis increases the likelihood of missing clinical data and limits definitive conclusions. The population was only evaluated for the two most common *EGFR* mutations in NSCLC. (44) The clinical impact of other mutations, both within the *EGFR* gene and in other genes, not detected in this study is uncertain but could be important, as seen in leukemia. (45)

Yet our study also exhibits a number of important strengths. With increased utilization of molecular profiling, it is becoming more important to know the prognostic implications of each mutation for which we are testing. Our study had a substantial sample size, and it is the largest study to date to include “real world” clinical options and referral patterns. During the time period of our study, no clinical trials were open at our institution using agents targeted at *EGFR* mutation, and our *EGFR* mutational frequency was similar to that reported in the North American population studies.

In conclusion, among patients with NSCLC receiving systemic therapy who had *EGFR* mutational testing performed at our institution, neither *EGFR* nor *KRAS* mutation was associated with overall survival. As oncologists move more towards targeted therapies for cancer, it becomes increasingly important and relevant to understand the prognostic impact of our test results. On multivariable analysis, shorter survival was associated with a worse ECOG PS, metastases to bone and higher age-weighted co-morbidity Index.

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Clinical Practice Points

- Molecular profiling of NSCLC samples is now standard of care.
- *EGFR* mutations are more common among populations with a more favorable prognosis.
- *KRAS* mutations are more common among populations with more adverse risk factors.
- In our study, neither *EGFR* nor *KRAS* mutational status was independently associated with prognosis.
- Strong collinearity was seen between *EGFR*, smoking status, and gender, which may account for the clinical impression that patients with tumors harboring *EGFR* mutations fare better.
- In counseling patients, we can use *EGFR* as a predictive marker but not as a prognostic marker.
- The impact of *KRAS* mutational status in modern clinical care remains unclear.

Figure 1.
CONSORT Diagram

Figure 2.

Figure 3.

Table 1

Characteristics of NSCLC Patients with EGFR testing

Variable	Entire Study Population, n=513		Patients included in survival analysis, n=376		Patients excluded from survival analysis, n=137		Comparison of included and excluded patients Fisher's exact P value
	#	%	#	%	#	%	
Gender							0.36
Female	303	59.1	227	60.4	76	55.5	
Male	210	40.9	149	39.6	61	44.5	
Race							0.05
Caucasian	399	79.0	295	79.5	104	77.6	
African American	67	13.3	51	13.7	16	11.9	
Asian American	17	3.4	13	3.5	4	3.0	
Hispanic	3	0.6	0	0.0	3	2.2	
Other	19	3.8	12	3.2	7	5.2	
Unknown	8	—	5	—	3	—	
Smoking status							0.80
Never smoker	104	20.4	78	20.9	26	19.3	
Ever smoker	405	79.6	296	79.1	109	80.7	
Unknown	4	—	2	—	2	—	
ECOG PS							0.55 ⁺
0	165	40.5	125	40.6	40	40.4	
1	192	47.2	149	48.4	43	43.4	
2+	50	12.3	34	11.0	16	16.2	
Unknown	106	—	68	—	38	—	
Histology							0.29
AdenoCA	405	79.6	298	79.9	107	78.7	
Squamous	46	9.0	30	8.0	16	11.8	
Adenosquamous	16	3.1	14	3.8	2	1.5	
NOS*	30	5.9	20	5.4	10	7.4	
Large Cell	9	1.8	8	2.1	1	0.7	

Variable	Entire Study Population, n=513		Patients included in survival analysis, n=376		Patients excluded from survival analysis ^a , n=137		Comparison of included and excluded patients Fisher's exact P value
	#	%	#	%	#	%	
Other ^b	3	0.6	3	0.8	0	0.0	
Unknown	4	—	3	—	1	—	
Stage							<0.001 ⁺
I	112	21.8	43	11.4	69	50.4	
II	44	8.6	33	8.8	11	8.0	
III	137	26.7	121	32.2	16	11.7	
IV	220	42.9	179	47.6	41	29.9	
EGFR Mutation (any)							0.01
Positive	69	13.5	60	16.0	9	6.6	
Negative	428	83.4	303	80.6	125	91.2	
Indeterminate/inconclusive	16	3.1	13	3.5	3	2.2	
EGFR Exon 19 Mutation							0.22
Positive	45	8.8	38	10.1	7	5.1	
Negative	456	88.9	329	87.5	127	92.7	
Indeterminate/inconclusive	12	2.3	9	2.4	3	2.2	
EGFR L858R Mutation							0.10
Positive	24	4.7	22	5.9	2	1.5	
Negative	475	92.6	343	91.2	132	96.4	
Indeterminate/inconclusive	14	2.7	11	2.9	3	2.2	
KRAS Mutation status							0.72
Mutant	105	27.5	83	27.9	22	25.9	
Wild type	269	70.4	207	69.7	62	72.9	
Indeterminate/inconclusive	8	2.0	7	2.4	1	1.2	
Unknown	131	—	79	—	52	—	
Brain Metastases							0.13
No	398	79.0	290	77.3	108	83.7	
Yes	106	21.0	85	22.7	21	16.3	

Variable	Entire Study Population, n=513		Patients included in survival analysis, n=376		Patients excluded from survival analysis ^a , n=137		Comparison of included and excluded patients Fisher's exact P value
	#	%	#	%	#	%	
Unknown	9	—	1	—	8	—	
Liver Metastases							0.01
No	455	90.6	333	88.8	122	96.1	
Yes	47	9.4	42	11.2	5	3.9	
Unknown	10	—	1	—	11	—	
Subcutaneous Metastases							1.00
No	495	98.6	370	98.7	125	98.4	
Yes	7	1.4	5	1.3	2	1.6	
Unknown	11	—	1	—	10	—	
Bone Metastases							0.001
No	373	74.3	265	70.7	108	85.0	
Yes	129	25.7	110	29.3	19	15.0	
Unknown	11	—	1	—	10	—	
	Mean	SE	Mean	SE	Mean	SE	t test P value
Age	64.2	0.5	63.2	0.6	67.0	1.0	0.001
Charlson Comorbidity Index	5.5	0.1	5.8	0.1	4.7	0.2	<0.001
Age-weighted Comorbidity Index	7.5	0.1	7.7	0.1	7.0	0.2	0.008

^a Excluded due to missing data on initial treatment.

[†] Exact trend test P value

Table 2

Associations between Patient Characteristics and EGFR and KRAS Mutation Status

Variable	EGFR Mutation Status			KRAS Mutation Status		
	# positive/# tested	%	Fisher's exact P value	# positive/# tested	%	Fisher's exact P value
Gender			0.002			0.03
Female	47/220	21.4		58/173	33.5	
Male	13/143	9.1		25/117	21.4	
Race			<0.001			0.05
Caucasian	47/287	16.4		72/224	32.1	
African American	3/47	6.4		8/40	20.0	
Asian American	9/12	75.0		0/11	0.0	
Other	0/12	0.0		2/10	20.0	
Smoking status			<0.001			<0.001
Never smoker	36/75	48.0		4/56	7.1	
Ever smoker	24/286	8.4		78/232	33.6	
ECOG PS			0.54 ⁺			0.52 ⁺
0	20/121	16.5		25/99	25.3	
1	24/143	16.8		36/125	28.8	
2+	3/32	9.4		8/26	30.8	
Histology			0.15			0.42
AdenoCA ±BAC	53/287	18.5		70/228	30.7	
Squamous	6/28	21.4		3/22	13.6	
Adenosquamous	0/14	0.0		4/11	36.4	
NOS [*]	1/20	5.0		3/17	17.6	
Large Cell	0/8	0.0		2/7	28.6	
Other [§]	0/3	0.0		0/2	0.0	
Stage			0.73 ⁺			0.23 ⁺
I	9/43	20.9		11/29	37.9	
II	5/33	15.2		9/27	33.3	

Variable	EGFR Mutation Status			KRAS Mutation Status		
	# positive/# tested	%	Fisher's exact P value	# positive/# tested	%	Fisher's exact P value
III	17/115	14.8		25/93	26.9	
IV	29/172	16.9		38/141	27.0	
Brain Metastases			0.50			0.37
No	49/281	17.4		66/219	30.1	
Yes	11/81	13.6		17/70	24.3	
Liver Metastases			0.04			0.18
No	58/323	18.0		76/252	30.2	
Yes	2/39	5.1		7/37	18.9	
Subcutaneous Metastases			0.60			0.07
No	60/357	16.8		80/285	28.1	
Yes	0/5	0.0		3/4	75.0	
Bone Metastases			0.28			0.15
No	39/257	15.2		65/208	31.2	
Yes	21/105	20.0		18/81	22.2	

[†] Exact trend test P value

^{*} Not Otherwise Specified (Poorly Differentiated)

[§] Other Histology includes Sarcomatoid (1), Pleotropic (1), NOS (1)

Table 3
Associations between Patient Characteristics and EGFR and KRAS Mutations

Variable		EGFR Mutation Status				t test P value
		Positive		Negative		
		#	Mean ± SE	#	Mean ± SE	
Age		60	65.1 ± 1.4	303	62.9 ± 0.7	0.18
Charlson Comorbidity Index		60	5.1 ± 0.3	303	5.9 ± 0.1	0.002
Age-weighted Comorbidity Index		60	7.1 ± 0.3	303	7.9 ± 0.1	0.02

Variable		KRAS Mutation Status				t test P value
		Mutant		Wild Type		
		#	Mean ± SE	#	Mean ± SE	
Age		83	62.3 ± 1.1	207	62.6 ± 0.9	0.82
Charlson Comorbidity Index		83	6.0 ± 0.2	206	5.8 ± 0.1	0.31
Age-weighted Comorbidity Index		83	7.9 ± 0.2	206	7.7 ± 0.2	0.46

Table 4

Univariate Survival Analysis

Variable	N	Kaplan-Meier Analysis		Univariate Cox Regression		
		Median OS months	95% CI	H.R.	95% CI	Wald test P value
All Patients	376	30.8	24.7 – 36.9			
Gender						<0.001
Female	227	39.1	27.2 – 51.0	1.00		
Male	149	23.0	17.8 – 28.2	1.68	1.26 – 2.25	
Race						0.65
Caucasian	295	33.0	25.9 – 40.0	1.00		
African American	51	23.7	18.3 – 29.0	1.27	0.85 – 1.89	
Asian American	13	33.2	18.6 – 47.8	1.07	0.47 – 2.42	
Other	12	17.9	ND	1.33	0.55 – 3.26	
Smoking status						0.01
Never smoker	78	53.0	24.4 – 81.6	1.00		
Ever smoker	296	28.8	23.2 – 34.4	1.66	1.11 – 2.46	
ECOG PS						<0.001
0	125	43.0	30.0 – 55.9	1.00		
I	149	24.4	16.1 – 32.8	1.33	0.94 – 1.90	
2+	34	14.9	13.2 – 16.6	2.57	1.64 – 4.04	
Histology						0.20
AdenoCA	298	34.1	26.8 – 41.4	1.00		
Squamous	30	22.1	9.0 – 35.2	1.64	1.03 – 2.60	
Adenosquamous	14	17.9	14.6 – 21.2	1.51	0.77 – 2.97	
NOS*	20	49.0	0.0 – 104.1	0.93	0.49 – 1.77	
Large cell	8	26.2	9.8 – 42.6	1.44	0.53 – 3.89	
Original Stage						0.10
I	43	39.7	18.8 – 60.6	1.00		
II	33	49.7	25.2 – 74.3	0.88	0.41 – 1.87	
III	121	27.1	22.2 – 31.9	1.36	0.76 – 2.44	

Variable	N	Kaplan-Meier Analysis		Univariate Cox Regression		
		Median OS months	95% CI	H.R.	95% CI	Wald test P value
IV	179	28.8	19.7 – 38.0	1.60	0.91 – 2.80	
EGFR Mutation (any)						0.09
Positive	60	46.8	26.4 – 67.3	1.00		
Negative	303	29.6	22.9 – 36.3	1.48	0.95 – 2.32	
EGFR Exon 19 Mutation						0.09
Positive	38	46.8	26.1 – 67.6	1.00		
Negative	329	29.6	23.2 – 36.1	1.59	0.93 – 2.69	
EGFR L858R Mutation						0.70
Positive	22	ND	—	1.00		
Negative	343	30.8	24.5 – 37.0	1.16	0.54 – 2.48	
KRAS Mutation status						0.69
Mutant	83	32.7	20.3 – 45.1	0.93	0.64 – 1.34	
Wild type	207	33.0	25.0 – 41.0	1.00		
Brain Metastases						0.52
No	290	32.7	25.0 – 40.4	1.00		
Yes	85	28.8	19.7 – 37.9	1.11	0.80 – 1.54	
Liver Metastases						0.004
No	333	35.4	28.6 – 42.2	1.00		
Yes	42	20.3	15.3 – 25.4	1.79	1.20 – 2.67	
Subcutaneous Metastases						0.79
No	370	30.8	24.5 – 37.0	1.00		
Yes	5	16.8	0.0 – 64.9	1.15	0.42 – 3.11	
Bone Metastases						0.001
No	265	39.1	26.7 – 51.5	1.00		
Yes	110	24.4	17.2 – 31.7	1.62	1.20 – 2.18	
Age						0.01
Charlson Comorbidity Index						<0.001
Age-weighted Comorbidity Index						<0.001

HR = Hazard Ratio, CI = Confidence Interval
ND = Not defined
* Not Otherwise Specified (Poorly Differentiated)

Table 5

Multivariable Survival Analysis

Variable	Multivariable Cox Regression 1*			Multivariable Cox Regression 2§		
	H.R.	95% CI	Wald test P value	H.R.	95% CI	Wald test P value
Gender			0.002			0.002
Female	1.00			1.00		
Male	1.70	1.21 – 2.39		1.70	1.21 – 2.38	
Smoking status			0.055			0.09
Never smoker	1.00			1.00		
Ever smoker	1.64	0.99 – 2.71		1.60	0.93 – 2.76	
ECOG PS			0.01			0.01
0	1.00			1.00		
1	1.32	0.90 – 1.92		1.32	0.91 – 1.92	
2+	2.09	1.28 – 3.42		2.09	1.28 – 3.42	
Stage			0.36			0.36
I	1.00			1.00		
II	0.78	0.32 – 1.90		0.78	0.32 – 1.89	
III	1.42	0.74 – 2.74		1.42	0.74 – 2.73	
IV	1.21	0.65 – 2.28		1.21	0.64 – 2.28	
Bone Metastases			0.03			0.03
No	1.00			1.00		
Yes	1.50	1.04 – 2.16		1.49	1.04 – 2.15	
Age-weighted Comorbidity Index	1.16	1.06 – 1.26	0.001	1.16	1.06 – 1.26	0.001
EGFR Mutation (any)						0.85
Positive				1.00		
Negative				1.06	0.59 – 1.92	

* Model 1: Best model by backward elimination based on 293 patients with data on 10 candidate variables selected by univariate significance p 0.10 (see Table 4). Stage was included in the model as an established prognostic factor, regardless of significance.

§ Model 2: EGFR mutation was added to Model 1. Clearly, it was not an independent prognostic factor due to strong collinearity with both smoking status and gender (see Table 2). The significance of smoking status was modified by the presence of EGFR mutation in the model.

HR = Hazard Ratio, CI = Confidence Interval

Table 6Prior Studies Evaluating Survival as a Function of *EGFR*

Author	Population	Patients	Median OS <i>EGFR</i> (+)	Median OS <i>EGFR</i> (-)	p value
Kosaka et al	Surgically resected patients progressing after gefitinib	91	86% 3 year survival	91% 3 year survival	0.993
Shigematsu et al	Patients with NSCLC	617	50 mo *	60 mo *	0.5
Tokuno et al	Surgically resected NSCLC	120	25.1 mo	14 mo	0.153
Eberhard et al	TRIBUTE substudy	274	ND	10 mo	<0.001
Sasaki et al	Surgically resected NSCLC	95	ND *	ND *	0.1824
Sequist et al	All <i>EGFR</i> referrals	278	37.2 months	19.2 months	0.001
Marks et al	AdenoCA, resected at MSKCC	296	ND	ND	0.18
Johnson et al	Stage IV AdenoCA at MSKCC	1036	33.7 months	20.7 months	<0.001

ND = Not defined

* Median estimates were not reported and therefore were approximated from Kaplan-Meier Curve