

Table SI. Demographics of patients with lung adenocarcinoma.

Variable	With BMs (n=401)	Without BMs (n=214)	P-value
Age (median, range), years			
All	61 (24,88)	60 (30,93)	0.635 ^a
≥45 years	62 (45,88)	61 (45,93)	0.797 ^a
Sex, n (%)			0.168 ^b
Male	222 (55.4)	106 (49.5)	
Female	179 (46.7)	108 (50.5)	
Smoking, n (%)	37 (9.2)	20 (9.3)	0.961 ^b
Pathologic stage (AJCC eight edition), n (%)			<0.001 ^b
IA-B	-	58 (27.1)	
IIA-B	-	14 (6.5)	
IIIA-C	-	51 (23.8)	
IVA-B	401	91 (42.5)	
Primary tumor, n (%)			<0.001 ^b
T1	32 (8.0)	78 (36.4)	
T2	52 (13.0)	31 (14.5)	
T3	41 (10.2)	9 (4.2)	
T4	276 (68.8)	96 (44.9)	
Lymph node metastasis, n (%)			<0.001 ^b
N0	28 (7.0)	92 (43.0)	
N1	34 (8.5)	24 (11.2)	
N2	163 (40.6)	51 (23.8)	
N3	176 (43.9)	47 (22.0)	
Number of BMs, n (%)			-
One	123 (30.7)	-	
Multiple	278 (69.3)	-	
Other tissues metastasis, n (%)	217 (54.1)	47 (22.0)	<0.001 ^b
Gene mutation, n (%)			0.999 ^b
EGFRm	208 (51.9)	111 (51.9)	
EGFRnm	193 (48.1)	103 (48.1)	

^aMann-Whitney test; ^bChi-square test. BM, bone metastasis.

Table SII. EGFR genotypes in patient of lung adenocarcinoma.

Variable	19del (n=142, 23.09%)	21L858R (n=150, 24.39%)	Other EGFR genotypes (n=323, 52.52%)
Age (median, range), years			
All	58 (33,93)	62 (30,84)	61 (24,88)
≥45 years	59 (45,93)	62 (45,84)	62 (45,88)
Sex, n (%)			
Male	65 (45.8)	68 (45.3)	195 (60.4)
Female	77 (54.2)	82 (54.7)	128 (39.6)
Pathologic stage (AJCC eight edition), n (%)			
IA-B	12 (8.5)	17 (11.3)	29 (9.0)
IIA-B	2 (1.4)	4 (2.7)	8 (2.5)
IIIA-C	4 (2.8)	18 (12.0)	29 (9.0)
IVA-B	124 (87.3)	111 (74.0)	257 (79.6)
Primary tumor, n (%)			
T1	32 (22.5)	31 (20.7)	47 (14.6)
T2	16 (11.3)	20 (13.3)	47 (14.6)
T3	10 (7.0)	14 (9.3)	26 (8.0)
T4	84 (59.2)	85 (56.7)	203 (62.8)
Lymph node metastasis, n (%)			
N0	25 (17.6)	31 (20.7)	64 (19.8)
N1	12 (8.5)	18 (12.0)	28 (8.7)
N2	47 (33.1)	62 (41.3)	105 (32.5)
N3	58 (40.8)	39 (26.0)	126 (39.0)
Number of BMs, n (%)			
One	19 (18.1)	30 (33.7)	74 (35.7)
Multiple	86 (81.9)	59 (66.3)	133 (64.3)
Other tissues metastasis, n (%)	66 (46.5)	56 (37.3)	142 (44.0)
Brain metastasis ^a , n (%)	105 (26.2)	89 (22.2)	-

^aP-values determined with the chi-square test were P=0.013 for 19del vs. pooled non-19del group and P=0.083 for 21L858R vs. pooled non-21L858R group.

Table SIII. Logistic regression analysis about factors related to brain metastasis in lung adenocarcinoma.

Variable	Univariate analysis		Multivariate analysis	
	P-value	OR (95%CI)	P-value	OR (95%CI)
Age	0.43	0.99 (0.97,1.01)	-	-
Sex (male vs. female)	0.168	1.26 (0.91,1.76)		
Primary tumor				
T1	Ref.	-	Ref.	-
T2	<0.001	3.73 (1.77,7.86)	0.534	1.34 (0.52,3.51)
T3	<0.001	7.25 (2.81,18.73)	0.231	2.04 (0.64, 6.54)
T4	<0.001	5.80 (3.20,10.51)	0.418	1.39 (0.63, 3.05)
Lymph node metastasis				
N0	Ref.	-	Ref.	-
N1	<0.001	4.24 (1.89,9.51)	0.027	2.90 (1.13, 7.44)
N2	<0.001	10.01 (5.28,18.96)	<0.001	5.66 (2.66, 12.05)
N3	<0.001	12.31 (6.45,23.47)	<0.001	4.54 (2.06, 9.97)
Other tissues metastasis	<0.001	3.46 (2.25,5.32)	0.144	1.48 (0.88, 2.50)
EGFR 19del	0.005	2.10 (1.25,3.51)	0.009	2.35 (1.24, 4.49)
EGFR 21L858R	0.055	0.65 (0.42,1.01)	-	-
NSE >18.18 ng/ml	<0.001	5.09 (3.29,7.86)	0.009	2.07 (1.20, 3.56)
CEA >6.01 ng/ml	<0.001	4.97 (3.24,7.63)	0.007	2.06 (1.22, 3.46)
CA125 >19.59 U/ml	<0.001	4.54 (3.00,6.87)	0.119	1.54 (0.90, 2.64)
CA153 >14.82 U/ml	<0.001	3.97 (2.63,5.99)	0.164	1.46 (0.86, 2.49)
CYFRA21-1 >4.17 ng/ml	<0.001	6.06 (3.93,9.34)	0.007	2.11 (1.23, 3.63)

OR, odds ratio; NSE, neuron-specific enolase; CYFRA21-1, cytokeratin 19 fragment; 19del, exon 19 deletion.

Table SIV. The 10 validated ROCs in 10-fold cross validation.

Resample	AUC	Sensitivity	Specificity	Brier score
Fold01	0.85	0.733	0.906	0.135
Fold02	0.84	0.533	1	0.13
Fold03	0.84	0.571	0.844	0.148
Fold04	0.6	0.333	0.844	0.22
Fold05	0.83	0.533	0.906	0.143
Fold06	0.88	0.733	0.906	0.123
Fold07	0.72	0.6	0.844	0.171
Fold08	0.83	0.333	1	0.145
Fold09	0.9	0.733	0.903	0.126
Fold10	0.86	0.533	0.906	0.144
Average	0.81	0.564	0.906	0.149

ROC, receiver operating characteristic; AUC, area under the ROC curve.