Supplementary

Table S1 The association of systemic treatment and subsequent BM occurrence among 231 patients with *EGFR*-mutated NSCLC without BM at diagnosis

Covariate[†]	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (<60/≥60)	2.63 (1.48–4.68)	0.001*	3.22 (1.68-6.15)	<0.001*
Gender (male/female)	0.79 (0.44–1.41)	0.429		
ECOG PS (≥2/0–1)	1.09 (0.44–2.66)	0.851		
Smoking (current-former/never)	1.30 (0.64–2.63)	0.460		
Histology (non-ADC/ADC)	1.38 (0.37–5.04)	0.626		
Stage at diagnosis (M1/M0)	1.85 (0.88–4.87)	0.101	1.58 (0.71-3.53)	0.257
No. metastatic site (≥3/<3)	0.82 (0.40–1.68)	0.599		
EGFR subtype (Del19/L858R)	1.21 (0.68–2.14)	0.517		
EGFR subtypes (others/common)	1.39 (0.47–4.06)	0.547		
T790M status (negative/positive)[‡]	1.48 (0.65–3.35)	0.350		
No. lines of treatment (≥3/1–2)	2.84 (1.58–5.12)	<0.001*	1.82 (0.89-3.73)	0.101
TKIs (no/yes)	1.55 (0.73–3.27)	0.251		
TKIs as first treatment (no/yes)	2.30 (1.25–4.23)	0.007*	1.77 (0.86-3.67)	0.119
Generation of TKIs(first/others)	2.32(0.65–8.34)	0.197		
First generation of TKIs (gefitinib/erlotinib)	1.02 (0.52–2.01)	0.955		
Subsequent 3rd generation TKIs (no/yes)^	1.14(0.18–7.40)	0.889		

[†], Category after the slash (/) was set as reference category. [‡], Only 101 patients who progressed after *EGFR*-TKIs treatment were further tested for secondary T790M mutation. *, P<0.05; ^, 58 patients received 3rd generation of *EGFR* TKIs as subsequent treatment. BM, brain metastasis; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ADC, adenocarcinoma; M1, metastatic disease; M0, recurrent disease; OR, odds ratio.

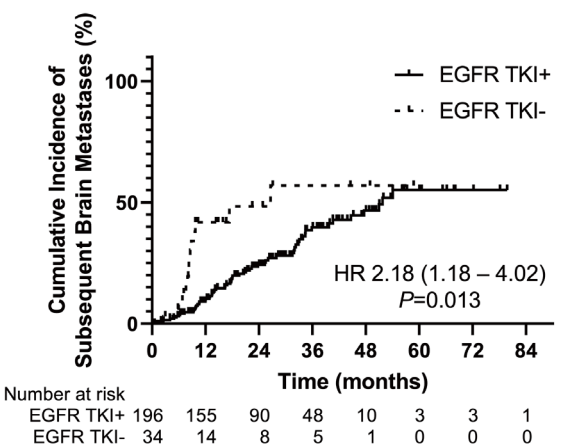

Figure S1 Estimated cumulative incidence curves illustrating subsequent brain metastasis over time according to *EGFR* TKIs treatment. EGFR, epidermal growth factor receptor.

http://dx.doi.org/10.21037/tlcr-20-1020

Table S2 Factors associated with time to subsequent BM (TTSBM) among 231 patients with *EGFR*-mutated NSCLC without BM at diagnosis

Covariate[†]	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (<60/≥60)	1.89 (1.21–2.97)	0.005*	1.66 (1.03–2.66)	0.036*
Gender (male/female)	1.41 (0.89–2.26)	0.147		
ECOG PS (≥2/0–1)	1.57 (0.74–3.31)	0.237		
Smoking (current-former/never)	1.77 (0.99–3.15)	0.053		
Histology (Non-ADC/ADC)	1.62 (0.59–4.46)	0.352		
Stage at diagnosis (M1/M0)	2.37 (1.24–4.50)	0.009*	2.51 (1.31–4.79)	0.006*
No. metastatic site (≥3/<3)	1.13 (0.62–2.06)	0.695		
EGFR subtype (Del19/L858R)	0.83 (0.52–1.32)	0.430		
EGFR subtypes (others/common)	2.26 (0.97–5.27)	0.059		
T790M status (negative/positive)[‡]	1.60 (0.81–3.13)	0.173		
No. lines of treatment (≥3/1-2)	1.43 (0.90–2.25)	0.127		
TKIs (no/yes)	2.45 (1.37–4.41)	0.003*	2.18 (1.18–4.02)	0.013*
TKIs as first treatment (no/yes)	1.27 (0.79–2.04)	0.323		
Generation of TKIs (first/others)	1.74 (0.70–4.37)	0.235		
First generation of TKIs (gefitinib/erlotinib)	1.04 (0.59–1.85)	0.886		
Subsequent 3rdgeneration TKIs (no/yes)^	1.19 (0.85–1.68)	0.304		

[†], Category after the slash (/) was set as reference category. [‡], Only 101 patients who progressed after *EGFR*-TKIs treatment were further tested for secondary T790M mutation. *, P<0.05; ^, 58 patients received 3rd generation of *EGFR* TKIs as subsequent treatment. BM, brain metastasis; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ADC, adenocarcinoma; M1, metastatic disease; M0, recurrent disease; HR, hazard ratio.

http://dx.doi.org/10.21037/tlcr-20-1020

Table S3 Baseline characteristics for the 190 available tumor specimens for vimentin expression by IHC according to *EGFR* mutation status

Characteristics	*EGFR* mutation (N=121)	*EGFR* wild type (N=69)
Age at diagnosis, median (IQR)	63.8 (55.3–73.1)	61.1 (54.4–67.5)
Gender, n (%)		
Male	36 (29.8%)	47 (68.1%)
Female	85 (70.2%)	22 (31.9%)
ECOG PS, n (%)		
0–1	93 (80.9%)	56 (84.8%)
≥2	22 (19.1%)	10 (15.2%)
Missing	6	3
Smoking status, n (%)		
Never	84 (80.0%)	21 (35.0%)
Current/former	21 (20.0%)	39 (65.0%)
Missing	16	9
Histology, n (%)		
Adenocarcinoma	117 (96.7%)	59 (85.5%)
Non adenocarcinoma	4 (3.3%)	10 (14.5%)
Stage at diagnosis, n (%)		
Recurrent	31 (25.6%)	33 (47.8%)
Metastatic	90 (74.4%)	36 (52.2%)
Number of metastatic site(s), n (%)		
1–2 sites	92 (76.0%)	60 (89.6%)
≥3 sites	29 (24.0%)	31 (10.4%)
EGFR mutation subtypes, n (%)		
Del19	62 (51.2%)	N/A
L858R	50 (41.3%)	
Others	9 (7.4%)	
Number of systemic treatment(s), n (%)		
Supportive care	0	20 (29%)
1–2 regimens	85 (70.2%)	38 (55.1%)
3 regimens or more	36 (29.8%)	11 (15.9%)
Brain metastases, n (%)		
Brain metastases	63 (52.1%)	34 (49.3%)
No brain metastases	58 (47.9%)	35 (50.7%)
Vimentin expression, n (%)		
Positive	49 (40.5%)	34 (49.3%)
Negative	72 (59.5%)	35 (50.7%)

EGFR, epidermal growth factor receptor; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

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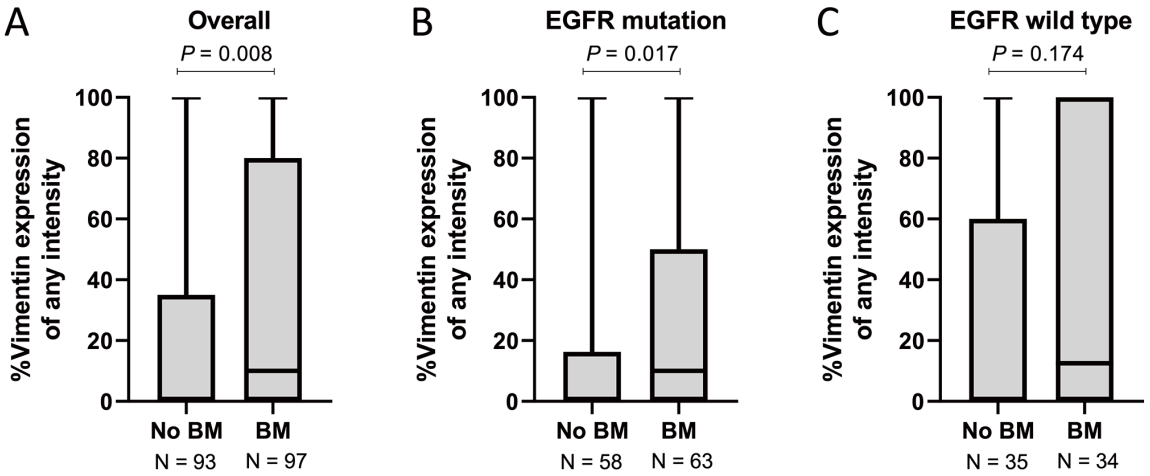

Figure S2 Distribution of vimentin expression according to BM status and *EGFR* mutation status in patients with NSCLC. BM, brain metastasis; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

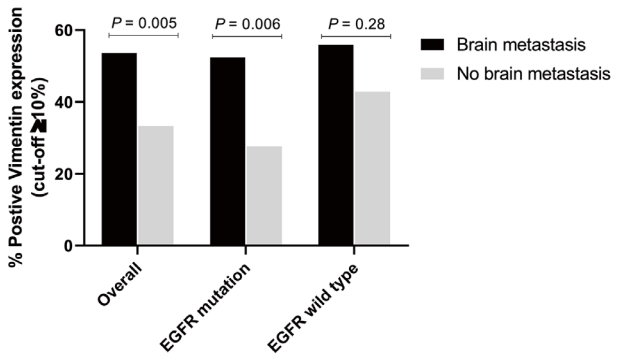

Figure S3 Correlation between vimentin expression according to BM status and *EGFR* mutation status in patients with NSCLC. BM, brain metastasis; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

http://dx.doi.org/10.21037/tlcr-20-1020

Table S4 Vimentin expression is associated with occurrence of BM in patients with wild-type *EGFR* (N=69)

Overall BM occurrence covariate[†]	Univariate	
	OR (95% CI)	P value
Age (<60/≥60)	0.66 (0.26–1.71)	0.394
Gender (Male/female)	1.64 (0.59–4.58)	0.343
ECOG PS (≥2/0–1)	2.69 (0.63–11.49)	0.181
Smoking (current-former/never)	2.88 (0.95–8.72)	0.062
Histology (Non-ADC/ADC)	1.66 (0.42–6.50)	0.466
Stage at diagnosis (M1/M0)	0.84 (0.33–2.17)	0.722
No. metastatic site (≥3/<3)	0.40 (0.07–2.23)	0.295
Vimentin (positive/negative)	1.68 (0.65–4.37)	0.281

[†], Category after the slash (/) was set as reference category. BM, brain metastasis; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ADC, adenocarcinoma; M1, metastatic disease; M0, recurrent disease; OR, odds ratio.

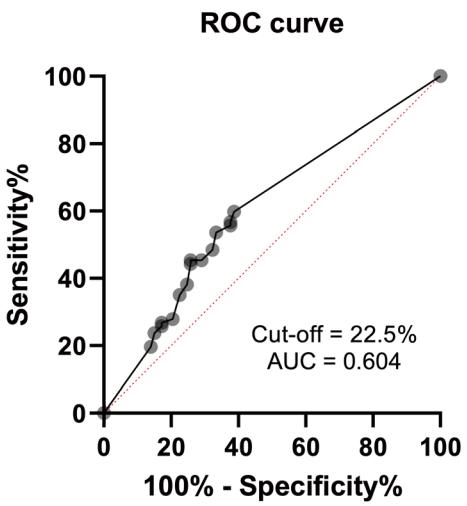

Figure S4 The cut-off value of vimentin expression using ROC curve analysis. ROC, receiver operating characteristic.

http://dx.doi.org/10.21037/tlcr-20-1020

Table S5 Vimentin expression and occurrence of BM using the cut-off value of vimentin expression by ROC analysis

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Overall populations covariate†				
Age (<60/≥60)	1.46 (0.81–2.62)	0.210		
Gender (Male/female)	1.49 (0.84–2.65)	0.177		
ECOG PS (≥2/0–1)	2.21 (1.00–4.91)	0.051	2.31 (0.92–5.79)	0.076
Smoking (current-former/never)	1.73 (0.91–3.28)	0.095	1.82 (0.92–3.60)	0.085
Histology (Non-ADC/ADC)	1.80 (0.58–5.59)	0.309		
Stage at diagnosis (M1/M0)	1.56 (0.85–2.85)	0.152		
No. metastatic site (≥3/<3)	0.97 (0.93–4.17)	0.078	2.42 (1.03–5.69)	0.042*
Vimentin (positive/negative)	2.39 (1.29–4.41)	0.005*	2.39 (1.21–4.70)	0.012*
Mutant *EGFR* covariate†				
Age (<60/≥60)	2.51 (1.15–5.48)	0.021*	2.93 (1.25–6.86)	0.013*
Gender (Male/female)	1.68 (0.76–3.73)	0.197		
ECOG PS (≥2/0–1)	2.03 (0.77–5.31)	0.147		
Smoking (current-former/never)	1.46 (0.55–3.84)	0.436		
Histology (Non-ADC/ADC)	2.85 (0.28–28.20)	0.370		
Stage at diagnosis (M1/M0)	2.48 (1.06–5.80)	0.035*	1.71 (0.69–4.26)	0.250
No. metastatic site (≥3/<3)	3.12 (1.25–7.77)	0.014*	3.27 (1.21–8.80)	0.019*
Vimentin (positive/negative)	3.07 (1.37–6.87)	0.006*	2.92 (1.22–6.98)	0.016*
Wild-type *EGFR* covariate†				
Age (<60/≥60)	0.66 (0.26–1.71)	0.394		
Gender (Male/female)	1.64 (0.59–4.58)	0.343		
ECOG PS (≥2/0–1)	2.69 (0.63–11.49)	0.181		
Smoking (current-former/never)	2.88 (0.95–8.72)	0.062		
Histology (Non-ADC/ADC)	1.66 (0.42–6.50)	0.466		
Stage at diagnosis (M1/M0)	0.84 (0.33–2.17)	0.722		
No. metastatic site (≥3/<3)	0.40 (0.07–2.23)	0.295		
Vimentin (positive/negative)	1.70 (0.65–4.49)	0.282		

†, Category after the slash (/) was set as reference category. *, P<0.05. BM, brain metastasis; ROC, receiver operating characteristic; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ADC, adenocarcinoma; M1, metastatic disease; M0, recurrent disease; EGFR, epidermal growth factor receptor; OR, odds ratio.

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