

# EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer

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A small subset of patients with nonsmall cell lung cancer (NSCLC) harbors mutations in the epidermal growth factor receptor (*EGFR*) that predict unique sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs). The characteristics and behavior of brain metastases (BMs) in these patients have not been well described. The longitudinal records of all NSCLC patients who underwent *EGFR* mutation screening at our center from August 2004 to November 2008 were reviewed for eligibility, and 93 patients were identified who developed BM during the course of their disease. Survival was estimated using the Kaplan–Meier method and the log-rank test. Multivariable predictors were assessed via the Cox proportional hazards model. Among the 93 patients with BM, 41 (44%) had mutations in *EGFR*, including 13 exon 19 deletions and 12 L858R mutations. Eighty-three percent of patients with BM were treated initially with whole brain radiation, either alone (53%) or in combination with craniotomy for neurosurgical resection (22%) or stereotactic radiosurgery (8%). Median survival from the time of BM was 11.7 months and was longer for patients with an *EGFR* mutation (14.5 vs 7.6 months,  $P = .09$ ). On multivariable analysis, *EGFR* mutation (HR: 0.50, 95% CI: 0.30–0.82), age (HR: 1.03, 95% CI: 1.00–1.05), and active extracranial disease (HR: 3.30, 95% CI: 1.70–6.41) were independently associated with survival. In NSCLC patients with BM, *EGFR* mutation status is associated with

improved survival, independent of age, functional status, extracranial disease status, and number of BMs.

**Keywords:** brain metastasis, *EGFR* (epidermal growth factor receptor), nonsmall cell lung cancer.

Nonsmall cell lung cancer (NSCLC) is the leading cause of cancer-related deaths in the United States and the most frequent site of origin for brain metastases (BMs).<sup>1</sup> Despite advances in systemic therapy and improvements in survival for advanced NSCLC, BMs remain an important cause of morbidity and mortality. Nearly 50% of patients with metastatic NSCLC will be affected by BM during the course of their disease.<sup>2</sup> Historically, survival after diagnosis of BM in NSCLC has been poor, with a median overall survival (OS) of only 4.5 months in patients treated with standard whole brain radiation therapy (WBRT).<sup>3</sup>

Although the majority of lung cancers overexpress the epidermal growth factor receptor (*EGFR*), it is now known that somatic *EGFR* mutations present in about 10% of US NSCLC patients predict increased response and survival with the *EGFR* oral tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib.<sup>4–8</sup> Patients with *EGFR* mutation-positive advanced NSCLC treated with first-line TKIs have response rates of 55%–82%, median progression-free survival (PFS) of 8.9–13.3 months, and median OS of 17.5 months—approximately 2-fold greater than the typical results with cytotoxic regimens in unselected NSCLC populations.<sup>9–15</sup>

Patients with BM harboring *EGFR* mutations may have higher response rates to WBRT compared those with wild-type tumors.<sup>16</sup> Moreover, multiple case reports have described favorable outcomes with new or recurrent BM to *EGFR* TKI therapy, particularly in

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those harboring *EGFR* mutations.<sup>17–30</sup> In this study, we sought to systematically examine a large cohort of consecutive patients with BM from NSCLC to determine the impact of *EGFR* mutation status on response to treatment and survival.

## Materials and Methods

### Case Identification

EGFR mutation testing has been performed for clinically selected NSCLC patients as part of routine care at Massachusetts General Hospital (MGH) since 2004.<sup>31</sup> We reviewed the 443 patients screened between August 2004 and November 2008. Patients were excluded if they did not receive the majority of their care at MGH or if they had more than 1 primary cancer. Medical records of the remaining 373 patients were reviewed to determine all patients who developed BM, defined as the presence of 1 or more intra-axial enhancing lesions on gadolinium-enhanced brain magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) felt by the radiologist and treating physicians to represent metastatic disease. Patients with leptomeningeal metastases (LMs) were also included. A total of 93 patients with BM were identified. This study was approved by our institutional review board.

### Variables

The inpatient and outpatient medical records of all patients were reviewed, and data were collected regarding the demographic and clinical characteristics including patient age; TNM classification of the primary tumor;<sup>32</sup> treatment history; date of first metastasis; date of first BM; symptoms, organ involvement, and extracranial disease activity at BM diagnosis; distribution and imaging characteristics of BM; BM treatment, response, and time to recurrence; survival; and cause of death. Follow-up took place through December 31, 2009.

Systemic disease activity at the time of BM diagnosis was considered active if chest, abdomen and pelvis CT, positron emission tomography, and/or bone scan within 4 weeks of the BM diagnosis demonstrated new sites of extracranial metastatic disease or progression at previously known sites of disease. Time to neurological progression was measured from the day of the initial diagnostic CT or MRI until the day of radiological progression. Responses were categorized per standard RECIST criteria.<sup>33</sup>

Death was attributed to central nervous system (CNS) progression if the patient had radiological progression or worsening neurological symptoms at the time of last follow-up and had radiological documentation of stable extracranial disease within 3 months of death. Death was attributed to systemic progression if the patient had active and symptomatic extracranial disease at last follow-up and had no clinical or radiological evidence of CNS progression within 3 months of

death. In all other cases, death was attributed to both CNS and systemic progression, unless death occurred greater than 3 months after last follow-up, in which case the cause of death was considered indeterminate, or death was unrelated to cancer.

### Statistical Analysis

Frequencies and descriptive statistics of demographic and clinical variables were obtained. Categorical variables were compared using the Fisher exact test and chi-square test, and continuous variables were compared using the Student's *t*-test or the Wilcoxon rank-sum test, as appropriate. Survival from the time of BM to death or last follow-up was estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Multivariable predictors of survival were determined using the Cox proportional hazards model. A 2-sided *P* < .05 was considered significant. All analyses were conducted using SAS statistical software version 9.1 (SAS Institute).

## Results

### Patient Characteristics

A total of 93 NSCLC patients who were clinically selected for *EGFR* mutation screening and developed BM at any point in their disease course were identified. Patient characteristics at initial diagnosis of NSCLC according to *EGFR* mutation status are listed in Table 1. The mean age at diagnosis was  $60.9 \pm 11$  years and did not vary by *EGFR* status. The majority of patients were Caucasian, consistent with the demographics of our clinic population. Sixty-seven percent of patients were female and 43% were lifetime nonsmokers; the proportion of females and smokers was higher in the *EGFR* wild-type group (75% and 75%, respectively) compared with the *EGFR*-mutant group (56% and 34%, respectively). The majority of patients had stage IV adenocarcinoma, reflecting the type of patient most likely to receive a clinical recommendation for *EGFR* screening. Among the 26 patients with nonstage IV disease at diagnosis, the majority were treated with surgery (*n* = 20) plus chemotherapy (*n* = 17) and radiation (*n* = 11). The most common *EGFR* mutations identified were in-frame exon 19 deletions and the exon 21 point mutation L858R, comprising 28% and 25%, respectively (Table 2).

The mean age at diagnosis of BM was  $61.9 \pm 12$  years (Table 3). BMs were synchronous with the primary lung cancer diagnosis in 44 (47%) patients and metachronous in 49 (53%). In those with metachronous BM, median time from initial diagnosis to first BM was 17 months (range 1–88 months) and was longer in patients with *EGFR*-mutant cancers (19 vs 14 months, *P* = .27). Brain was a first site of metastasis in 59% and accompanied by other sites of metastatic disease in the majority. Nineteen (20%) patients had solitary BM with no sites of extracranial metastatic disease at the time of brain involvement; this was significantly more

**Table 1.** Patient characteristics at the time of initial lung cancer diagnosis

Characteristics	EGFR mutant (n = 41) (n [%])	EGFR wild-type (n = 52) (n [%])	Total (n = 93) (n [%])
Mean age $\pm$ SD (yrs)	60.4 $\pm$ 14.1	61.3 $\pm$ 10.1	60.9 $\pm$ 12.0
Gender			
Male	18 (44)	13 (25)	31 (33)
Female	23 (56)	39 (75)	62 (67)
Race			
Caucasian	37 (90)	49 (94)	86 (93)
African American	0 (0)	0 (0)	0 (0)
Asian	2 (5)	3 (6)	5 (5)
Other	2 (5)	0 (0)	2 (2)
Histology			
Adenocarcinoma	40 (98)	47 (90)	87 (94)
Squamous	0 (0)	1 (2)	1 (1)
Large Cell	1 (2)	0 (0)	1 (1)
Other	0 (0)	4 (8)	4 (4)
Stage			
I	4 (10)	5 (10)	9 (10)
II	2 (5)	2 (4)	4 (4)
IIIA	4 (10)	5 (10)	9 (10)
IIIB	1 (2)	3 (6)	4 (4)
IV	30 (73)	37 (71)	67 (72)
Smoking history			
Ever	14 (34)	39 (75)	53 (57)
Never	27 (66)	13 (25)	40 (43)
Sites of metastatic disease <sup>a</sup>			
Brain	20 (67)	24 (65)	44 (66)
Lung	22 (73)	15 (41)	37 (55)
Liver	11 (37)	6 (16)	17 (25)
Bone	18 (60)	11 (30)	29 (43)
Other	6 (20)	9 (24)	15 (22)

<sup>a</sup>In patients with stage IV disease at diagnosis, rows do not necessarily total 100%, as all sites of disease were categorized for each patient.

**Table 2.** EGFR mutations identified in 41 patients

Mutation <sup>a</sup>	Exon number	Frequency (n [%])
Exon 19 deletion	19	13 (28)
L858R	21	12 (25)
G719X	18	5 (11)
L861Q	21	4 (8)
Other		7 (17)

<sup>a</sup>Five patients had a second mutation in addition to the primary mutation; 2 of these were T790M.

common in patients with *EGFR* wild-type tumors (31% vs 7%,  $P = .03$ ). In *EGFR*-mutant patients, active systemic disease was very common at the time of BM, with 83% of patients having either new or progressive disease outside of the brain within 1 month of BM diagnosis. In *EGFR* wild-type patients, this proportion was significantly lower (62%,  $P = .001$ ). The most common sites of extracranial metastasis were contralateral lung (57%), bone (43%), liver (27%), and lymph nodes (27%). According to the recursive partitioning analysis (RPA) prognostic classification system,<sup>34</sup> 3 patients were in RPA Class 1, 79 patients were in RPA

Class 2, and 11 patients were in RPA Class 3 at the time of BM diagnosis.

A minority of patients had received an *EGFR* TKI prior to diagnosis of BM, including 12 (29%) with an *EGFR* mutation and 6 (12%) without a mutation. Of these, 7 were actively receiving *EGFR* TKI therapy at the time of BM diagnosis (4 patients with a mutation and 3 without). The median number of prior chemotherapy regimens for all patients was 0 (range 0–5).

### Lesion Characteristics

BM's were single in 23 patients (25%) and multiple in the remaining 60 patients. *EGFR* wild-type patients were significantly more likely to present with a single BM (35% vs 12%,  $P = .02$ ). Approximately half of patients were symptomatic at the time of BM diagnosis, and the remaining patients were diagnosed on the basis of a screening brain MRI. The proportion of patients diagnosed by screening MRI did not vary by *EGFR* mutation status. The size of the largest BM ranged from 3 mm to 5 cm, with a median of 1.4 cm. A minority of patients (17%) had evidence of blood products within 1 or

**Table 3.** Patient characteristics at the time of brain metastasis

Characteristics	EGFR mutant ( <i>n</i> = 41) ( <i>n</i> [%])	EGFR wild-type ( <i>n</i> = 52) ( <i>n</i> [%])	Total ( <i>n</i> = 93) ( <i>n</i> [%])
Mean age ± SD (yrs)	61.5 ± 14.3	62.2 ± 10.3	61.9 ± 12.1
Karnofsky performance status			
≥70	35 (85)	47 (90)	82 (88)
<70	6 (15)	5 (10)	11 (12)
Prior chemotherapy			
0	25 (61)	29 (56)	54 (58)
1	6 (15)	13 (25)	19 (20)
2	3 (7)	4 (8)	7 (8)
3 or more	7 (17)	6 (11)	13 (14)
Prior EGFR TKI			
Yes	12 (29)	6 (12)	18 (19)
No	29 (71)	46 (88)	75 (81)
Status of primary tumor			
Active	29 (71)	35 (67)	64 (69)
Inactive or absent	12 (29)	17 (33)	29 (31)
Status of extracranial disease			
Active	34 (83)	32 (61)	66 (71)
Inactive	4 (10)	4 (8)	8 (9)
Absent	3 (7)	16 (31)	19 (20)
Brain metastases			
1	5 (12)	18 (35)	23 (25)
2–3	13 (32)	18 (35)	31 (33)
>3	22 (54)	15 (29)	37 (40)
Unknown	1 (2)	1 (2)	2 (2)
Hemorrhagic brain metastases			
Yes	6 (15)	10 (19)	16 (17)
No	33 (80)	41 (79)	74 (80)
Unknown	2 (5)	1 (2)	3 (3)

more BM, and none had symptomatic intracranial hemorrhage. Most patients had BMs located in the supratentorial compartment (66%); 3 (3%) patients had isolated cerebellar metastases and 29 (32%) patients had both supra- and infratentorial BMs.

### Treatment

The majority of patients (82%) were treated initially with WBRT, either alone (*n* = 49), in combination with stereotactic radiosurgery (SRS) boost (*n* = 7), or craniotomy for resection of a single or dominant lesion (*n* = 20). Five patients were treated with SRS alone (*n* = 4) or craniotomy with SRS boost to the surgical cavity (*n* = 1). Five patients with *EGFR*-mutant tumors and asymptomatic multiple BM were treated with erlotinib as primary therapy. Of these, 2 had complete and sustained responses for 7 and 32 months, respectively; 1 had stable disease but progressed in the CNS after 4 months; 1 had progressive CNS disease after 2 months; and 1 had an unknown response and died within 1 month of diagnosis from progressive systemic disease. One patient with an *EGFR* wild-type tumor was treated with an EGFR TKI first-line and progressed in the CNS at the first restaging scan 2 months later. Two patients received supportive care alone.

Seventy-eight percent of patients with an *EGFR* mutation received an EGFR TKI after the diagnosis of BM, as did 19% of patients without an *EGFR* mutation.

Among 70 patients with evaluable CNS disease who had at least 1 post-treatment MRI, the best response obtained from first-line CNS therapy was complete in 17 patients (24%), partial in 18 (25%), stable disease in 22 (31%), and progressive disease in 13 (19%). Among 42 evaluable patients treated with WBRT only as first-line therapy, the response rate was higher in *EGFR*-mutant patients (67% vs 50%, *P* = .23).

### Recurrence

Recurrence or progression in the brain before death was diagnosed by CT or MRI in 56% of evaluable patients (45 of 85) at a median of 11.2 months (95% CI: 8.4–14.7) from the date of BM diagnosis. Time to progression (TTP) in the brain was longer in mutant patients compared with wild type (12.4 vs 8.4 months, *P* = .39). In patients with an *EGFR* mutation, TTP in the brain was significantly longer in those who received EGFR TKI therapy after initial brain-directed therapy (*n* = 31) compared with those who did not (17.5 vs 9.6 months, *P* = .03). Eight patients (9%) developed LMs, 2 at initial presentation of BM and 6 at relapse.

**Table 4.** Predictors of survival after diagnosis of brain metastasis

Variable <sup>a</sup>	Unadjusted hazards ratio (95% CI)	P value	Adjusted hazards ratio (95% CI)	P value
Age	1.03 (1.01–1.05)	0.02	1.03 (1.00–1.05)	0.02
KPS	0.42 (0.22–0.81)	0.01	0.65 (0.32–1.29)	0.21
Number of BM	1.33 (0.83–2.12)	0.24	0.88 (0.52–1.51)	0.65
Extracranial disease	2.41 (1.39–4.16)	0.002	3.30 (1.70–6.41)	0.0004
Primary tumor	1.09 (0.67–1.80)	0.73	0.94 (0.55–1.63)	0.84
EGFR mutation	0.67 (0.42–1.07)	0.09	0.50 (0.30–0.82)	0.006

<sup>a</sup>Reference groups: KPS, Karnofsky performance status; KPS < 70; 1–3 BM; controlled or absent extracranial disease; controlled or absent primary tumor; no EGFR mutation.

**Table 5.** Survival by RPA class

RPA class	EGFR mutation negative		EGFR mutation positive	
	Survival (mos)	95% CI	Survival (mos)	95% CI
1	Not yet reached	9.0–.	Not yet reached	–.
2	7.4	5.7–11.7	17.9	12.0–27.6
3	3.7	1.5–19.9	5.9	3.9–10.5

The proportion of patients with LMs was higher in patients with an *EGFR* mutation compared with those without (9.8% vs 7.7%,  $P = \text{NS}$ ).

### Survival

Seventy-four patients (79%) had died by the end of follow-up. Median survival from the date of initial NSCLC diagnosis was 23 months and was longer for *EGFR*-mutant patients (30.2 vs 17.9 months,  $P = .12$ ). Median OS from the time of BM diagnosis was 11.7 months and was also longer for *EGFR*-mutant patients (14.5 vs 7.6 months,  $P = .09$ ). Significant predictors of survival on univariate analysis (Table 4) were controlled vs active extracranial disease (23.6 vs 7.9 months,  $P = .001$ ) and receipt of an *EGFR* TKI post-BM (19.1 vs 7.3 months,  $P = .001$ ). On multivariable analysis, the presence of an *EGFR* mutation (HR: 0.50, 95% CI: 0.30–0.82), age (HR: 1.03, 95% CI: 1.00–1.05), and active extracranial disease (HR: 3.30, 95% CI: 1.70–6.41) were independently associated with survival. Receipt of an *EGFR* TKI was not included in the multivariable model because it was highly collinear with *EGFR* mutation status. Survival did not vary significantly by specific *EGRF* mutation as categorized in Table 2.

Using the traditional RPA classification system, median survival was not yet reached for the 3 patients (3%) in RPA Class 1; 11.8 months for the 79 patients (85%) in RPA Class 2; and 4.0 months for the 11 patients (12%) in RPA Class 3 ( $P = .01$ ). Survival was longer for *EGFR*-mutant patients in every RPA class (Table 5).

### Cause of Death

Cause of death could be determined in 62 (84%) patients. A minority of patients (11%) had isolated CNS progression with stable systemic disease at the time of death. This proportion did not vary according

to *EGFR* status. Over half of all *EGFR* mutation carriers (54%) died from systemic disease progression with stable CNS disease, compared with 1/3 of patients without a mutation. The remaining patients had active disease in both CNS and extracranial sites at the time of death.

## Discussion

We retrospectively analyzed a large consecutive cohort of NSCLC patients tested for *EGFR* mutations and found that among those with BMs, *EGFR* mutation status strongly influenced survival after diagnosis of BM (adjusted HR: 0.50, 95% CI: 0.30–0.82). Despite significant differences in active extracranial disease (82% in *EGFR*-mutants vs 62% in wild-type patients,  $P = .001$ ) and detection of multiple BM (86% in *EGFR* mutants vs 64% in wild-type patients,  $P = .02$ ), those with *EGFR*-mutant NSCLC had a doubling of their median survival compared with wild-type patients (14.5 vs 7.6 months,  $P = .09$ ). Our results suggest that this difference is mediated through both intracranial and extracranial disease control after diagnosis of BM, since patients with *EGFR*-mutant cancers had improved intracranial disease control and were more likely to die from systemic than CNS causes (54% of *EGFR* mutants died from systemic progression compared with 33% of wild-type patients).

To our knowledge, this is the largest study to date systematically examining the impact of *EGFR* mutation status on patients with BM and the first of its kind in a US patient cohort. In a prior study, Gow et al.<sup>16</sup> retrospectively analyzed 63 NSCLC patients with BM, all of whom were treated with WBRT, and found that the 46 patients carrying an *EGFR* mutation had a median survival of 17.3 months, compared with 6.6 months among wild-type patients. Additionally, 54% of patients with *EGFR* mutations experienced a response from WBRT,



compared with only 24% in the wild-type group. In our cohort, there was no large difference in response rates between patients with and without *EGFR*-mutant disease (67% and 50%,  $P = .23$ ). However, for *EGF*-mutant patients, the median time to CNS progression (12.4 months) and OS (14.7 months) were prolonged compared with internal control patients, as well as historical estimates for unselected NSCLC patients.<sup>3</sup> This is consistent with the notion that *EGFR*-mutant cancer may have increased radiosensitivity compared with wild-type disease, even though this does not necessarily translate into an early radiographic tumor response.

In both the Gow et al. series and ours, patients who received an EGFR TKI at any time after diagnosis of BM survived longer than those who did not. This is particularly interesting in light of 2 recently published large randomized trials of NSCLC patients with advanced disease (not limited to BM) and *EGFR* mutations in which PFS was improved with EGFR TKI therapy compared with chemotherapy, but no OS advantage could be found.<sup>35,36</sup> Although both BM-specific studies are retrospective, limiting firm conclusions, taken together these data suggest that EGFR TKI therapy after the initial diagnosis of BM may provide such a substantial benefit in duration of CNS response that survival is ultimately impacted. It remains unclear to what degree survival differences in patients with *EGFR*-mutant NSCLC and BMs are mediated by radiation or targeted drug therapy. However, there are signals from preclinical and clinical studies suggesting that outcomes with both treatment modalities may be influenced by genotype. Das et al.<sup>37,38</sup> have shown that the majority of mutant *EGFR* NSCLC cell lines exhibit characteristics of a radiosensitive phenotype, demonstrated by delayed DNA repair kinetics, defective radiation-induced arrest in DNA synthesis or mitosis, and pronounced increases in apoptosis. Similarly, the response rates in patients from WBRT in *EGFR*-mutant NSCLC BMs appear to be higher than for nonmutant NSCLC, both in our study and in the Gow et al. series.<sup>16</sup> It is also clear that EGFR TKI therapy alone can elicit CNS responses both in the treatment-naïve and the recurrent BM population,<sup>17–30</sup> providing support that targeted therapy may also be playing a role in achieving CNS control.

In treatment-naïve patients with a known mutation and asymptomatic BM, it may be reasonable to initiate EGFR TKI therapy and defer up front cranial radiation, particularly in those patients with active extracranial disease. Two such patients in our cohort with multiple subcentimeter BM achieved a complete response in the CNS that was sustained for as long as they remained

on drug; 3 others did not respond, for an overall response rate of 40%. In a single-center retrospective study, Kim et al.<sup>23</sup> recently reported a 70% response rate in 23 never-smoker NSCLC patients with synchronous BM treated with first-line EGFR TKI therapy. The Spanish Lung Cancer Group also reported that all 7 patients with BM in its phase II study of gefitinib for chemotherapy-naïve patients with advanced NSCLC and *EGFR* mutations had an objective response in brain.<sup>12</sup> It is important to note, however, that these patients as well as the 2 responders described in our cohort were EGFR TKI naïve at the time of BM. Patients who develop BM while being treated with an EGFR TKI, or who are otherwise heavily pretreated, are unlikely to respond as dramatically and should be considered for radiation therapy.

There are several potential limitations of our study. First, we could not draw conclusions about the efficacy of various treatment modalities because of a limited sample size and the fact that most patients received multimodality therapy. We also cannot exclude the possibility that lead-time bias contributed to differences in survival, although survival did not vary significantly in this cohort according to whether or not the patient had symptoms at diagnosis, and the proportion of asymptomatic patients did not vary by *EGFR* mutation status. Finally, *EGFR* mutation testing was only carried out on a subset of clinically selected patients from our total clinic population and therefore our control group may not be representative of all EGFR wild-type patients. However, since tested patients were younger and more likely to be nonsmokers and females compared with the average NSCLC population, we would predict that our observed differences in response and survival if anything are underestimated rather than overestimated in this study.

In conclusion, this study highlights the importance of *EGFR* mutation status as a prognostic factor in patients with BM from NSCLC, independent of established prognostic factors including age, functional status, number of BM, and systemic disease activity. Future prospective studies should investigate whether selected patients, such as those with minimally symptomatic synchronous BM, can be safely and effectively treated with EGFR TKI therapy and deferred radiotherapy as a potential means by which to minimize treatment-related toxicity without sacrificing CNS disease control.

**Conflict of interest statement.** T.J.L. has paid consulting relationships with Genentech, AZ, Menck, and BIPI and a patent on EGFR mutation testing.

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