ORIGINAL RESEARCH

Chemotherapy and EGFR tyrosine kinase inhibitors for treatment of brain metastases from non-small-cell lung cancer: survival analysis in 210 patients

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Background: Chemotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors are controversial in the treatment of patients with brain metastases from non-small-cell lung cancer (NSCLC).

Methods: We retrospectively studied the effects of solely localized treatment or localized treatment in combination with chemotherapy and/or EGFR tyrosine kinase inhibitors on outcomes in 210 NSCLC patients with brain metastases. The effects of treatment modality, Karnofsky performance status, age, primary tumor histology, number of brain metastases, and other factors on survival time were analyzed, and the robustness of two prognostic indices, ie, recursive partitioning analysis and graded prognostic assessment, was evaluated.

Results: The median survival time in patients with systemic medication and localized treatments was higher than in those with localized treatments alone (11 versus 3 months, $P=0.000$). Within the systemic medication group, median survival time was significantly longer for EGFR tyrosine kinase inhibitors than for other types of chemotherapy (12 versus 9 months, $P=0.002$). In the EGFR tyrosine kinase inhibitor group, median survival time for patients with *EGFR* gene mutation was 20 months versus 8 months for those with the wild-type *EGFR* gene. The median survival time with pemetrexed was significantly higher than with other chemotherapies (13 versus 7 months, $P=0.006$). In multivariate analysis, the prognosis was significantly correlated with treatment modality ($P=0.000$), Karnofsky performance status ($P=0.000$), number of brain metastases ($P=0.001$), and histologic tumor type ($P=0.007$). In the graded prognostic assessment model, survival curves for the subgroups showed clear separations.

Conclusion: NSCLC patients with brain metastasis benefited from pemetrexed and/or tyrosine kinase inhibitors along with localized treatments, and the graded prognostic assessment index is a robust model for prognostic evaluation.

Keywords: epidermal growth factor receptor, tyrosine kinase inhibitors, brain metastases, non-small-cell lung cancer, pemetrexed, chemotherapy

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Introduction

Brain metastases are a common complication in non-small-cell lung cancer (NSCLC) patients, have incidence rates as high as 25%–40%,[1–3] and severely impair patient survival outcome and quality of life. Current treatment options include surgical resection, whole brain radiation therapy, stereotactic radiosurgery, and combined modality approaches. Whole brain radiation therapy is the standard treatment approach for multiple brain metastases, with a response rate of 60%.[4,5] However, the median survival

time following whole brain radiation therapy alone is rather short, in the range of 2.4–4.8 months,[2,5,6] which might be due to the fact that most NSCLC patients with brain metastasis also develop extracranial metastases and thus require systemic medication in addition to local treatment of their brain tumors.

Previously published studies of whole brain radiation therapy used in combination with traditional chemotherapeutic agents, such as platinum, nitrosourea, paclitaxel, and temozolomide, have failed to show a significant improvement in overall survival compared with whole brain radiation therapy alone,[7–12] thus creating an urgent need to find more effective systemic therapies. In recent years, pemetrexed (a new multitarget antimetabolite) and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors have become regular medications for the treatment of advanced NSCLC and had good results in treating patients with brain metastases. One study showed that pemetrexed as sole medication for NSCLC brain metastases achieved a partial response in 38.4% of cases, with an overall clinical benefit obtained in 69% of patients and a median survival time of 10 months.[13]

Tyrosine kinase inhibitors used as single medication showed response rates ranging from 10% to 86%, progression-free survival of 3–10 months, and a median survival time of 8.3–18.8 months.[14–18] In order to evaluate the effectiveness of these new agents in enhancing survival rates in NSCLC patients with brain metastases, we retrospectively investigated 210 such patients for factors such as treatment modality, Karnofsky performance status, patient age, histologic type, smoking status, and number of brain metastases as well as medication regimens.

Patients and methods
Patients
We enrolled 210 NSCLC patients first diagnosed with brain metastases at Zhejiang Cancer Hospital between July 2006 and July 2010. All the patients had a Karnofsky performance status score ≥50, were aged 18–75 years, had histologically or cytologically confirmed NSCLC, and had received whole brain radiation therapy previously. All patients had complete clinical and follow-up records. The research was approved by the ethical committee of Zhejiang Cancer Hospital and informed consent was obtained from all participants.

Study design
Using patient hospital records, follow-up registration records, and follow-up phone records, we collected clinical and

survival information about the patients. The following data were collected and recorded: age when first diagnosed with brain metastasis, sex, Karnofsky performance status when first diagnosed with brain metastasis, number of brain metastases, primary tumor histologic type, whether the brain metastasis was synchronous or asynchronous, presence or absence of extracranial metastases, and systemic therapy regimens. Patients were categorized by age (<65 years, ≥65 years), sex (male, female), Karnofsky performance status (<70, ≥70), smoking status (never, former, current), number of brain metastases (one tumor, two to three tumors, more than three tumors), whether the brain metastasis was synchronous or asynchronous, presence or absence of extracranial metastases, primary tumor histology (adenocarcinoma, squamous cell carcinoma, other), and local treatment regimen (whole brain radiation therapy only; whole brain radiation therapy plus surgical resection or stereotactic radiosurgery).

Based on local treatment regimens, patients were divided into two groups, ie, whole brain radiation therapy only (n=179) and whole brain radiation therapy plus surgical resection or stereotactic radiosurgery (n=31). Patients were also divided into two groups according to whether they received systemic therapy, ie, 24 patients were treated with localized treatment only and 186 patients received both local and systemic therapy. Of the 186 patients who received systemic medication, 111 received chemotherapy and 75 were treated with EGFR tyrosine kinase inhibitors (46 patients with gefitinib and 29 with erlotinib). Of these patients, 29 were genotyped using the amplification refractory mutation system and 58.6% (17/29) had a mutated *EGFR* gene in which exon 19 contained a mutation in nine cases and exon 21 contained a mutation in eight cases, whereas 12 patients had a wild-type *EGFR* gene.[19] Within the chemotherapy group, 21 patients with adenocarcinoma were treated with pemetrexed and 90 were treated with other chemotherapeutic agents, mainly gemcitabine or docetaxel in combination with platinum (Supplementary Table 1). Two prognostic models were established separately using the recursive partitioning analysis (RPA) and revised graded prognostic assessment (GPA) models proposed by the Radiation Therapy Oncology Group.[20–22] RPA has three prognostic classes based on age at diagnosis, presence or absence of extracranial metastases, Karnofsky performance status, and primary tumor status. A higher RPA class represents a worse prognosis. GPA, on the other hand, uses four criteria (age at diagnosis, Karnofsky performance status, presence or absence of extracranial metastases, and number of brain metastases) to produce a score from 0 to 4, with a higher score corresponding to a

Table 1 Patient characteristics at baseline

	n=210 (%)
Median age, years (range)	55 (23–75)
Age, years	
<65	172 (81.9%)
≥6	38 (18.1%)
Sex	
Male	142 (67.6%)
Female	68 (32.4%)
Smoking status	
Never	85 (40.5%)
Former or current	125 (59.5%)
KPS	
≥70	145 (69.0%)
<70	65 (31.0%)
Histology	
Adenocarcinoma	137 (65.2%)
Squamous carcinoma	39 (18.6%)
Others	34 (16.2%)
Number of brain metastases	
1	63 (30.0%)
2–3	74 (35.2%)
>3	73 (34.8%)
Extracranial metastases	
No	81 (38.6%)
Vesical organ	73 (34.8%)
Others	56 (26.7%)
Interval of BM	
Synchronous	110 (52.4%)
Heterochronous	100 (47.6%)
Local treatment	
WBRT	179 (85.2%)
WBRT + surgery/SRS	31 (14.8%)
RTOG RPA class	
Class I	47 (22.4%)
Class II	98 (46.7%)
Class III	65 (30.9%)
RTOG GPA grade	
0–1	44 (20.9%)
1.5–2.5	132 (62.9%)
3	22 (10.5%)
3.5–4	12 (5.7%)

Abbreviations: BM, brain metastases; GPA, graded prognostic assessment; KPS, Karnofsky Performance Scale; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group.

better prognosis (Table 1). A major focus of the study was overall survival, defined as the duration of time from the start of therapy for brain metastases until death or the most recent follow-up.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences version 19 software (SPSS Inc, Chicago, IL, USA). Chi-square tests and nonparametric tests (Mann–Whitney) were used to compare differences in

patient characteristics. Kaplan–Meier survival curves were used to compare survival differences between subgroups (sex, age, and other factors) by using a single variant survival analysis. Log-rank tests were used to determine statistically significant differences between the survival curves for each group. Finally, the Cox proportional hazard regression model (forward Wald method) was used in multivariate analysis of groups to study the effect of prognostic factors from the Kaplan–Meier single variant test (GPA, number of metastatic sites, treatment modality, RPA classes, Karnofsky performance status, histology, smoking history, sex) and clinical factors (age, treatment, Karnofsky performance status score), and to evaluate which factors were associated with patient survival as well as to analyze differences in the survival curves for each subgroup.

Results
Patients

A total of 210 NSCLC patients diagnosed with brain metastases were enrolled in the study and 142 (67.6%) were male. The median age was 55 (range 23–73) years and 146 patients (69.5%) had a Karnofsky performance score ≥70. In 171 patients (81.4%), the tumor type was not squamous cell carcinoma. A total of 125 patients (59.5%) were smokers or had a smoking history. Synchronous brain metastasis occurred in 114 patients (54.3%), 147 patients (70.0%) developed more than one metastatic brain tumor, and 129 patients (61.4%) had extracranial metastases. In total, 179 patients (85.2%) received whole brain radiation therapy only while 14.8% underwent whole brain radiation therapy plus surgical resection or stereotactic radiosurgery. The overall median clinical follow-up duration was 12.5 (range 1–49) months. At the time of the analysis, 164 patients had died (78.1%) and 46 (21.9%) were still alive. Based on the RPA index, 46.7% of the patients were in class II, and based on the GPA index, 62.9% were in the 1.5–2.5 range (Table 1). Overall median survival time was determined to be 10 months (95% confidence interval [CI] 8.226–11.774, Figure 1).

Correlation between treatment modality and patient prognosis and survival

The group that received localized treatment had a median survival time of 3 months (95% CI 1.628–4.372), which is significantly shorter than the 11 months (95% CI 9.205–12.795) in the group receiving both localized treatment and systemic medication (P=0.000, Figure 2). Within the medication groups, treatments with EGFR tyrosine kinase inhibitors led to an overall median survival time of 12 months
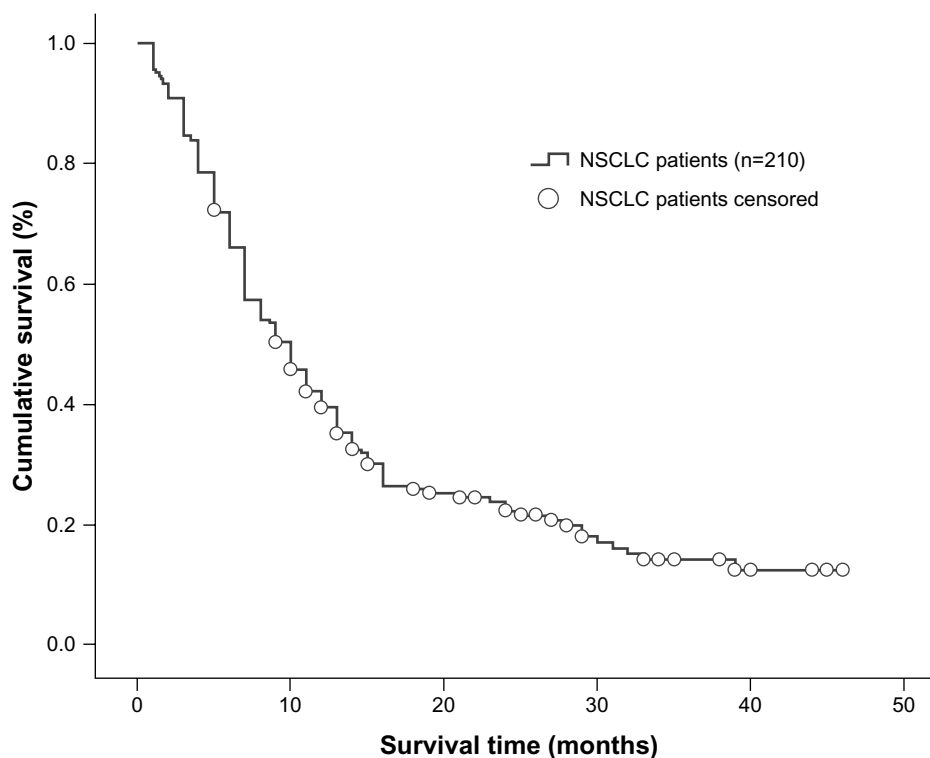
Figure 1 Kaplan–Meier curve illustrating overall survival of all NSCLC patients.
Abbreviation: NSCLC, non-small-cell lung cancer.

(95% CI 6.660–17.340), which was significantly longer than the 9-month median survival time (95% CI 7.517–10.483) in the chemotherapy group (P=0.002, Figure 3).

In the group treated with EGFR tyrosine kinase inhibitors, median survival time in the 17 patients with an *EGFR* mutation was 20 months (95% CI 16.155–23.845), which was longer than that in wild-type *EGFR* patients (12 cases), whose median survival time was 8 months (95% CI 4.653–11.347, P=0.000, Figure 4). In the chemotherapy-treated patients, those receiving pemetrexed (n=21) had a median survival time of 13 months (95% CI 9.616–16.384), which was significantly longer than the 7 months (95% CI 5.012–8.988) recorded in the group treated with gemcitabine or docetaxel combined with platinum (n=90, P=0.006, Figure 5).
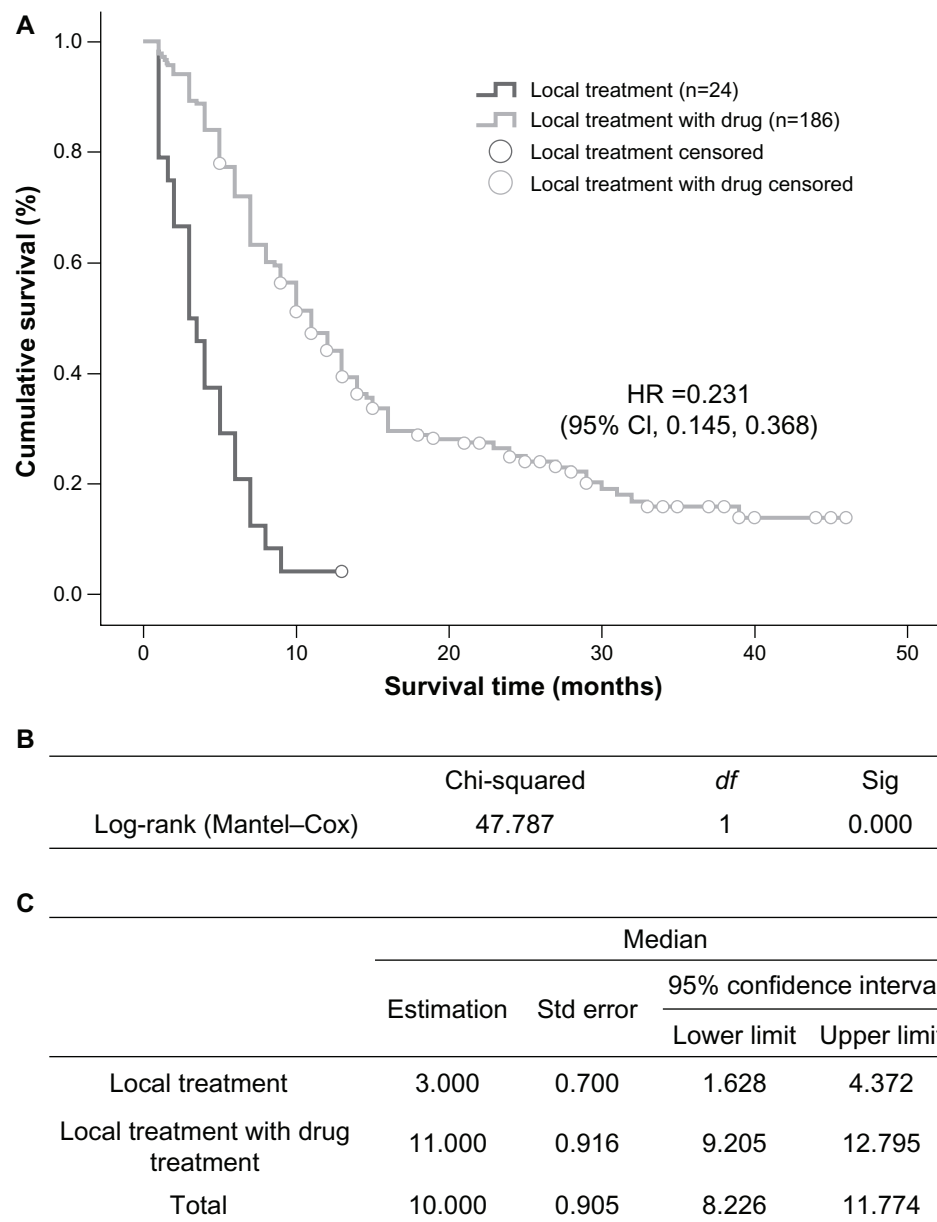
Correlation between prognostic factors and patient survival

Univariate analysis of the entire sample indicated that, of the 10 prognostic factors taken into account, only treatment modality, number of brain metastases, Karnofsky performance score, tumor histologic type, smoking status, and sex were related to overall survival, while age, presence or absence of extracranial metastases, whether the brain metastasis was synchronous or asynchronous, and local treatment

regimens did not correlate with overall survival (Table 2). On the other hand, multivariate analysis of the entire sample indicated that four factors were significantly correlated with patient outcome, ie, treatment modality (P=0.000, relative risk 0.527), Karnofsky performance status (P=0.000, relative risk 1.974), number of brain metastases (P=0.001, relative risk 1.412), and tumor histology (P=0.007, relative risk 1.220, Table 3).

Correlation between prognostic model and survival

Univariate analysis showed that the RPA and GPA prognostic index models were both correlated with overall survival (P=0.001 and P=0.000, respectively). According to the RPA prognostic index model, median survival time in patients categorized into classes I, II, and III was 11, 11, and 6 months, respectively, and a statistically significant difference was observed between class III patients and class I/II patients (Figure 6). Using the GPA prognostic index model, 66.5% of patients with a GPA score of 3.5–4.0 were alive at the end of the study; for patients with a GPA score of 3.0, median survival time was 13 months, while it was 10 months for patients with GPA scores of 1.5–2.5 and 5 months for patients with a GPA score of 0–1. Using the GPA index, statistically

A

B

	Chi-squared	*df*	Sig
Log-rank (Mantel–Cox)	47.787	1	0.000

C

	Median			
			95% confidence interval	
	Estimation	Std error	Lower limit	Upper limit
Local treatment	3.000	0.700	1.628	4.372
Local treatment with drug treatment	11.000	0.916	9.205	12.795
Total	10.000	0.905	8.226	11.774

Figure 2 Comparison of median survival time in patients who received only localized treatment or localized treatment plus systemic medication. (**A**) Kaplan–Meier survival curve, (**B**) Mantel–Cox test, and (**C**) median values with 95% CI.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; HR, hazards ratio; Sig, significance; Std, standard.
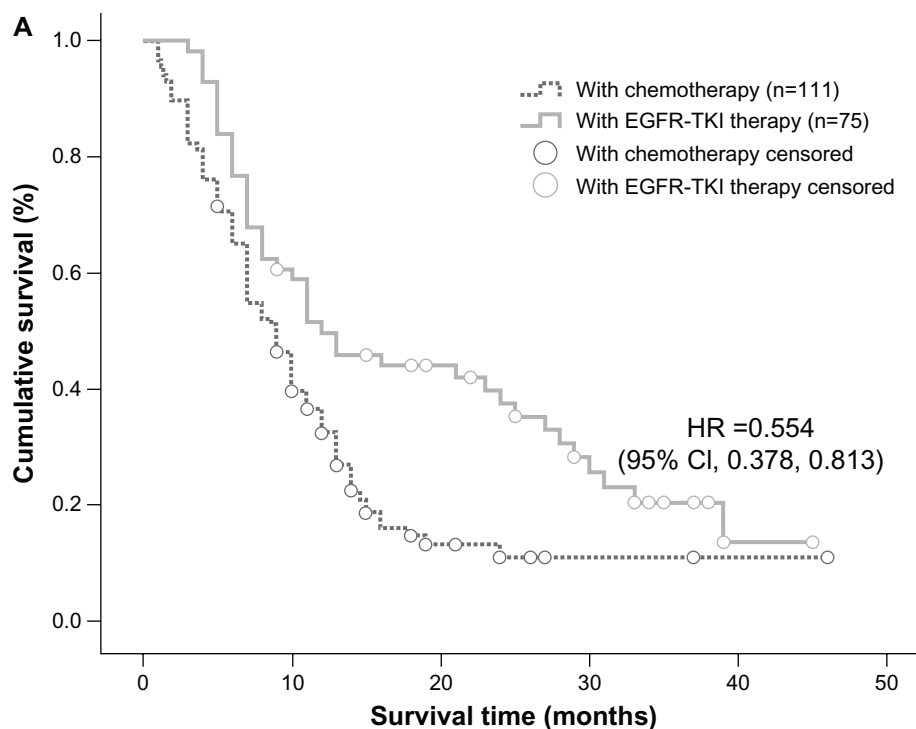
significant differences in median survival time could be detected between all subgroups ($P=0.000$), with clear separations of the survival curves (Figure 7). However, when the RPA and GPA models were included in multivariate analysis, only treatment modality ($P=0.000$, relative risk 0.529) and GPA index ($P=0.000$, relative risk 0.474) continued to show a correlation with treatment outcomes (Table 4).

These results suggest that when treating NSCLC brain metastases, a combined modality of localized therapy plus systemic medication should be the first choice. Within the medication options, EGFR tyrosine kinase inhibitors should

be given preference, and within the chemotherapeutic agents, pemetrexed showed better efficacy than the others. Treatment modality, Karnofsky performance status, number of brain metastases, and tumor histology are four factors that were significantly correlated with patient outcome. The GPA index model showed superior correlations for prognostic evaluation.

Discussion

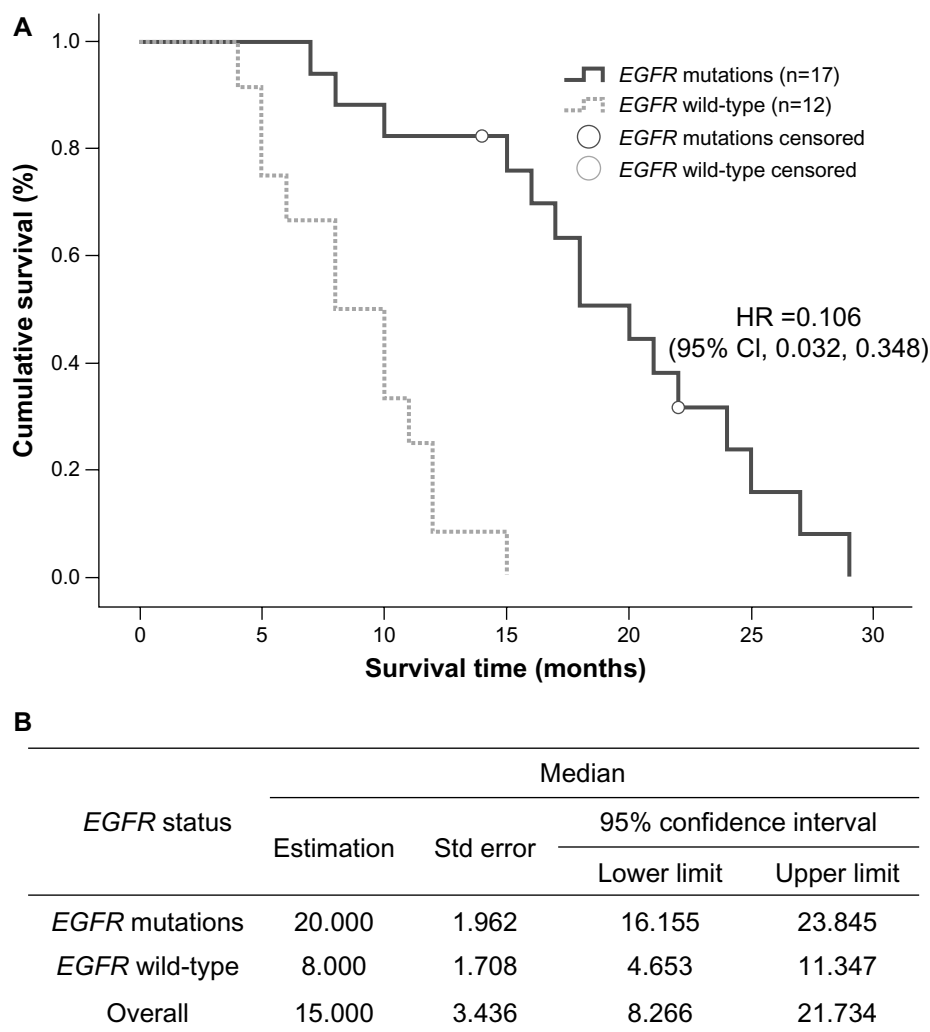Patients with brain metastases from NSCLC usually have a poor prognosis, with a median survival time of about one

Figure 3 Comparison of median survival time in patients who received EGFR tyrosine kinase inhibitors or chemotherapy (*pemetrexed included). (**A**) Kaplan–Meier survival curve, (**B**) Mantel–Cox test, and (**C**) median values with 95% CI.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; HR, hazards ratio; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; Sig, significance; Std, standard.

month without treatment,[23] 2 months with glucocorticoid therapy, and 2.4–4.8 months with whole brain radiation therapy.[2,5,6,24] The majority also develop extracranial and multiple brain metastases. Even though there are localized treatment methods available for managing intracranial lesions, their effectiveness is limited and additional medication is required for these patients. There is currently a lack of randomized, controlled studies with large sample sizes that address this issue; further, several smaller Phase II/III clinical studies and some retrospective analyses disagree

about the efficacy of traditional chemotherapeutic agents for the treatment of brain metastases.[7–12,25,26] Some of the studies showed that whole brain radiation therapy combined with traditional chemotherapy failed to enhance patient survival,[7–12] which is thought to be largely due to the inability of drugs to cross the blood–brain barrier or because they possess low activity in NSCLC. However, other studies have shown that chemotherapy enhances survival time to a certain extent,[25,26] especially since the introduction of EGFR tyrosine kinase inhibitors and pemetrexed.

A

B

EGFR status	Median			
	Estimation	Std error	95% confidence interval	
			Lower limit	Upper limit
EGFR mutations	20.000	1.962	16.155	23.845
EGFR wild-type	8.000	1.708	4.653	11.347
Overall	15.000	3.436	8.266	21.734

Figure 4 (**A**) Kaplan–Meier curve illustrating overall survival based on EGFR status (EGFR mutation and EGFR wild-type) and (**B**) median values with 95% CI.
Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazards ratio; Std, standard.

The results of our study indicate that localized treatment combined with medication increases the overall survival rate more than localized treatment alone. Further, median survival time in our EGFR tyrosine kinase inhibitor group was significantly longer than in our chemotherapy group. Within the chemotherapies, median survival time was significantly longer in patients on pemetrexed than in those receiving other medications. In a study by Bearz et al,[13] of 39 patients with NSCLC brain metastases treated with pemetrexed alone, 38.4% showed a partial response, 69% showed an overall clinical benefit, 82% showed radiologic cerebral benefit, and overall median survival was 10 months. Barlesi et al[27] reported that when pemetrexed was used in combination with platinum as the primary treatment for NSCLC patients with asymptomatic and inoperable brain metastases, the cerebral response rate was 41.9% and the extracerebral response rate was 34.9%, with a median

survival time of 7.4 months and a time to progression of 4.0 months. Studies have shown that the EGFR mutation rate in patients with brain metastases is about 50% in Western populations and as high as 63% in Asian populations.[28,29] Because EGFR mutation status significantly affects the efficacy of EGFR tyrosine kinase inhibitors,[30] the fact that patients treated with these agents in this study showed an enhanced survival rate may be related to the fact that NSCLC patients with brain metastases have a higher than normal EGFR mutation rate. In our study, mutations were detected in 58.6% of the 29 patients analyzed for EGFR mutation, and median survival time was longer in these patients than in those with wild-type EGFR.

Several Phase II clinical trials and retrospective studies in unselected NSCLC patients with brain metastases have shown that treatment with tyrosine kinase inhibitors alone achieved response rates of 10%–60%, with

A

B
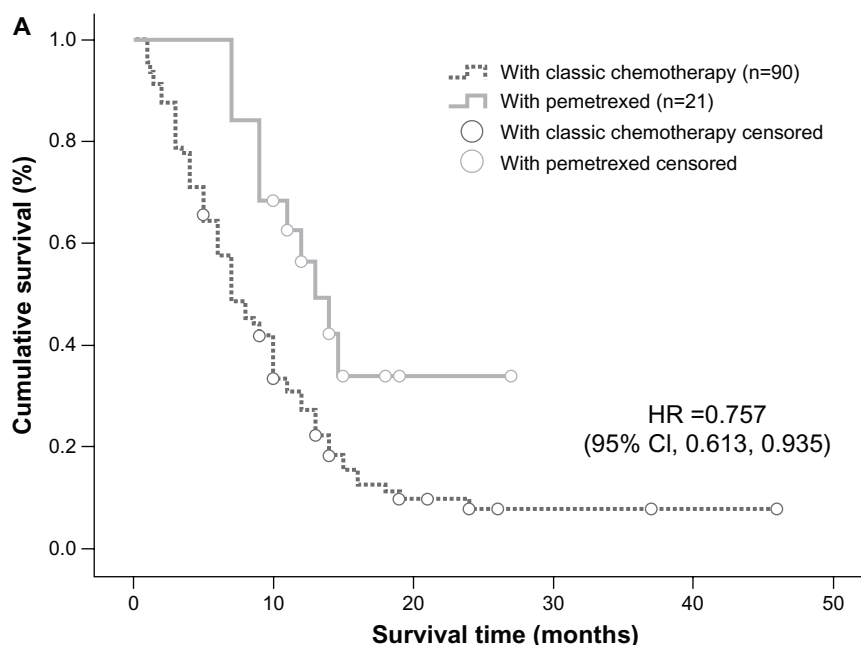
	Chi-squared	*df*	Sig
Log-rank (Mantel–Cox)	7.666	1	0.006

C

Combined therapy	Median			
	Estimation	Std error	95% confidence interval	
			Lower limit	Upper limit
Chemotherapy	7.000	1.014	5.012	8.988
Pemetrexed	13.000	1.727	9.616	16.384
Total	9.000	0.757	7.517	10.483

Figure 5 Comparison of median survival time in patients who received pemetrexed or other chemotherapies. (**A**) Kaplan–Meier survival curve, (**B**) Mantel–Cox test, and (**C**) median values with 95% CI.
Abbreviations: CI, confidence interval; *df*, degrees of freedom; HR, hazards ratio; Sig, significance; Std, standard.

Table 2 Univariate analysis of factors affecting overall survival

	Chi-square	P-value
GPA	33.642	0.000
Metastatic sites (n)	16.35	0.000
Treatment modality	78.322	0.000
RPA classes	13.439	0.001
KPS	11.847	0.001
Histology	11.71	0.008
Smoking history	4.335	0.037
Sex	3.914	0.048
Local treatment	1.535	0.223
Metastatic sites	2.701	0.259
Age	0.579	0.447
Initial or retreated	0.464	0.496

Abbreviations: GPA, graded prognostic assessment; KPS, Karnofsky performance status; RPA, recursive partitioning analysis.

progression-free survival of 3–9 months and overall survival of 8.3–15 months.[14,16,17] The survival benefit using tyrosine kinase inhibitors in patients with adenocarcinoma or *EGFR* mutations was even greater, with objective response rates reaching 56.0%–82.0%, progression-free survival times of 6.6–10.1 months, and overall survival times of 12.9–19.8 months.[15,18,31,32] Studies have shown that concomitant treatment using tyrosine kinase inhibitors and whole brain radiation therapy in NSCLC patients with brain metastases produced response rates as high as 81%–86%, with overall survival times of 11.8–13 months.[28,33] Dai et al believe that the effectiveness of pemetrexed and tyrosine kinase inhibitors in the treatment of brain metastases is

Table 3 Multivariate analysis of factors affecting overall survival in patients without RPA and GPA in the Cox regression model

|	B	SE	Wald	df	Significance	HR (95% CI)
Histology	0.199	0.074	7.170	1	0.007	1.220 (1.055–1.411)
Number of metastatic sites	0.345	0.108	10.159	1	0.001	1.412 (1.142–1.746)
Treatment modality	−0.640	0.094	46.137	1	0.000	0.527 (0.438–0.634)
KPS	0.680	0.171	15.735	1	0.000	1.974 (1.411–2.763)

Abbreviations: CI, confidence interval; df, degrees of freedom; HR, hazards ratio; KPS, Karnofsky performance status; SE, standard error; RPA, recursive partitioning analysis; GPA, graded prognostic assessment; B, regression coefficient; Wald, wald test.

related to their ability to penetrate the blood–brain barrier to a certain extent. The small molecule tyrosine kinase inhibitors reach cerebrospinal fluid concentrations that are 1.5%–7% of their plasma concentration,[34,35] and pemetrexed has a greater ability to penetrate the blood–brain barrier than methotrexate, another antimetabolite.[36]

The results of our retrospective analysis also indicate that NSCLC patients with brain metastases could benefit from combinations of localized treatment with chemotherapy and/ or tyrosine kinase inhibitors. However, one shortcoming of this study was the lack of *EGFR* mutation data for the majority of patients; because of this, the overall effect of *EGFR* mutation rates could not be determined with certainty. We also analyzed prognostic factors for patients with brain metastases. In both univariate and multivariate analyses, we found that Karnofsky performance score, number of brain metastases, and histologic type were all significant predictors

of patient prognosis. However, if the RPA and GPA prognostic index models were included in multivariate analysis, only treatment modality and the GPA model remained correlated with prognosis.

The correlation between Karnofsky performance status and prognosis in univariate analysis has been supported in the majority of studies. Sanghavi et al[37] retrospectively analyzed 502 patients with brain metastases, who had received stereotactic radiosurgery ± whole brain radiation therapy, and their results showed that patients with a higher Karnofsky performance score, a controlled primary tumor, no extracranial metastases, and a lower RPA class had a better prognosis. Frazier et al[38] retrospectively analyzed 273 patients with brain metastases who had undergone stereotactic radiosurgery ± whole brain radiation therapy, and showed that patients under 65 years of age with a Karnofsky performance score >70 had a longer median survival time.
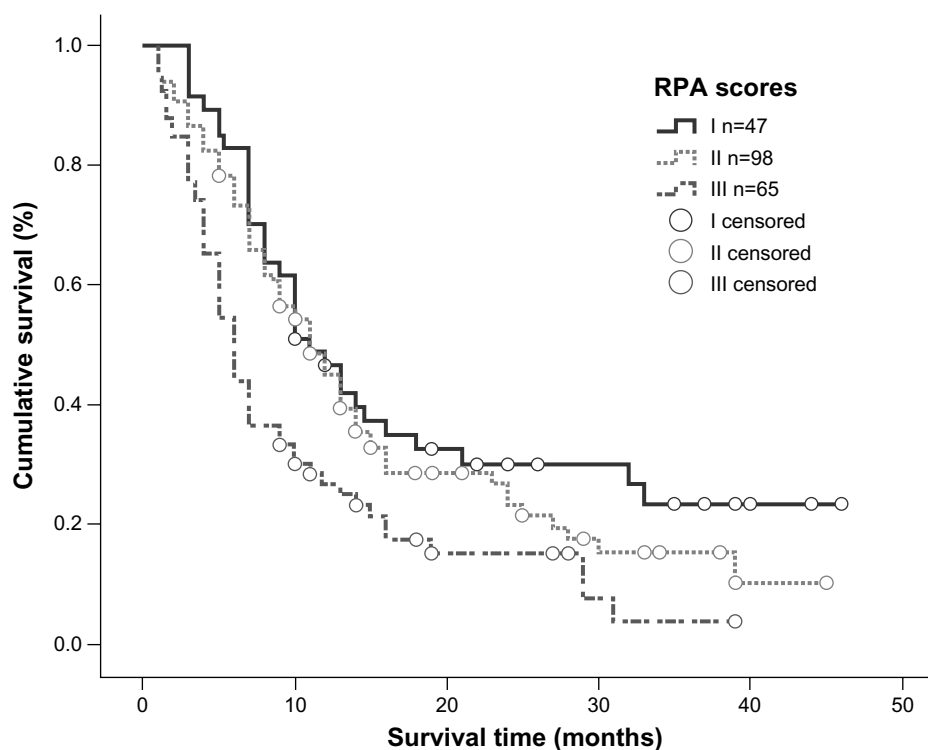
Figure 6 Kaplan–Meier curve illustrating overall survival based on RPA.
Abbreviation: RPA, recursive partitioning analysis.
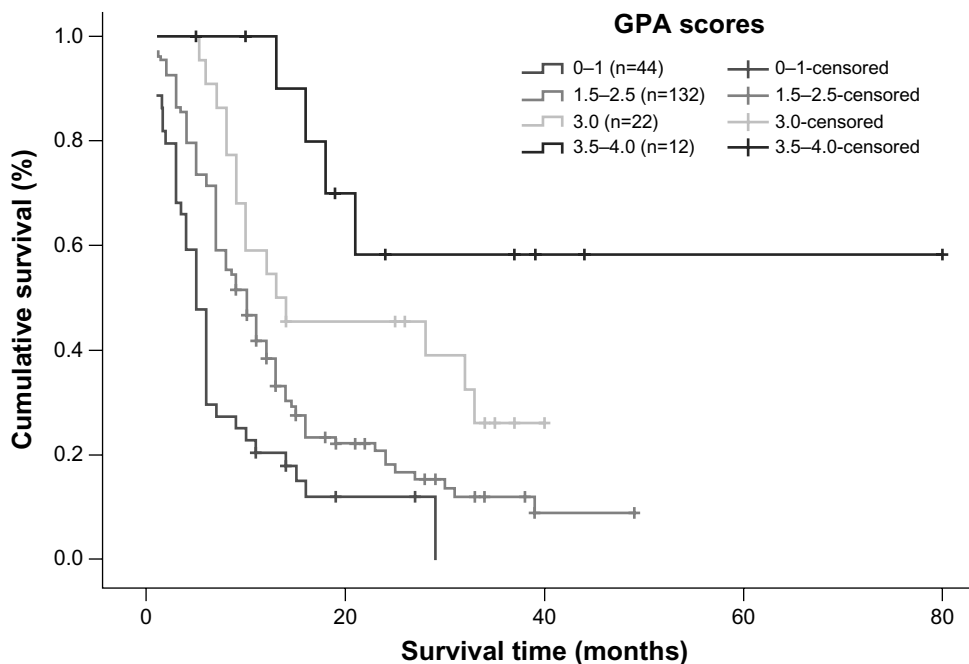
Figure 7 Kaplan–Meier survival curve illustrating overall survival based on GPA.
Abbreviation: GPA, graded prognostic assessment.

The negative correlation between number of brain metastases and patient outcome is in agreement with several other studies,[39,40] indicating that number of brain metastases significantly affects patient outcome. A correlation analysis between histologic tumor type and prognosis indicated that patients with adenocarcinoma had a better prognosis. This is possibly due to the fact that 96 patients in the study (45.7%) received tyrosine kinase inhibitors or pemetrexed, and these two drugs are both more effective against adenocarcinoma. Our study found no correlation between presence or absence of extracranial metastases and patient prognosis; whether or not this is related to the fact that 88.6% of the patients received systemic treatment is a question that warrants further research.

NSCLC patients with brain metastases are a very heterogenous group, with a wide variation in terms of prognosis. Any prediction of outcome must be done based on an overall evaluation of factors affecting survival. In this study, when patients were divided into three classes according to the RPA prognostic model, only median survival time in class III was significantly different from that in the other two classes, while

the survival curves of classes I and II showed no significant differences. In comparison, the GPA model provided a more valuable prognostic classification; it was significantly correlated with patient prognosis in both univariate and multivariate analyses and all GPA subgroups had significantly different survival curves. A recent study by Sperduto et al provides further evidence of the prognostic value of the GPA model in NSCLC patients with brain metastases.[40] Thus, it is likely that the GPA prognostic model will be more widely utilized in predicting survival for NSCLC patients.

In summary, treatment modality, Karnofsky performance score, number of brain metastases, and histologic type were significantly correlated with patient prognosis. Our results suggest that patients who receive chemotherapy, especially pemetrexed and/or tyrosine kinase inhibitors concomitantly with localized treatments, are likely to have a greater survival benefit, and further clinical studies focusing on tumor histology and molecular characteristics may be warranted. We also found that the GPA index is a robust model for prognostic evaluation.

Table 4 Multivariate analysis of factors affecting overall survival in patients with RPA and GPA included in the Cox regression model

	B	SE	Wald	df	Significance	HR (95% CI)
Treatment modality	−0.637	0.092	47.897	1	0.000	0.529 (0.441–0.633)
GPA	−0.746	0.120	38.871	1	0.000	0.474 (0.375–0.600)

Abbreviations: CI, confidence interval; df, degrees of freedom; GPA, graded prognostic assessment; HR, hazards ratio; RPA, recursive partitioning analysis; SE, standard error; B, regression coefficient; Wald, wald test.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary table

Table S1 The clinical characteristics of patients in different treatment groups

	Localized treatment	Localized treatment + systemic medication	P-value	Localized treatment + TKIs	Localized treatment + chemotherapy	P-value	Localized treatment + pemetrexed	Localized treatment + other chemotherapy	P-value
Total	n=24	n=186		n=75	n=111		n=21	n=90	
Median age	57.5	56		57	57		60	56	
Age, years			0.514			0.720			0.279
<65	18	154		63	91		15	76	
≥65	6	32		12	20		6	14	
Sex			0.411			0.026			0.469
Male	18	124		43	81		14	67	
Female	6	62		32	30		7	23	
Smoking status			0.230			0.003			0.123
Never	7	78		41	37		10	27	
Former or current	17	108		34	74		11	63	
KPS			0.227			0.298			0.538
≥70	14	131		56	75		13	62	
<70	10	55		19	36		8	28	
Histology			0.035			0.113			0.029
Adenocarcinoma	12	125		55	70		20	50	
Squamous carcinoma	7	32		8	24		0	24	
Others	5	29		12	17		1	16	
Number of brain metastases			0.791			0.637			0.656
1	10	53		16	37		6	31	
2–3	4	70		36	34		7	27	
>3	10	63		23	40		8	32	
Extracranial metastases			0.153			0.407			0.438
No	12	69		26	43		7	36	
Vesical organ	8	65		25	40		7	33	
Others	4	52		24	28		7	21	
Brain metastases distribution			0.047			0.065			0.068
Synchronous	8	102		35	67		9	58	
Heterochronous	16	84		40	44		12	32	
Local treatments			0.779			0.006			0.929
WBRT	20	159		71	88		17	71	
WBRT + surgery/SRS	4	27		4	23		4	19	
RTOG RPA class			0.085			0.983			0.962
Class I	6	41		14	27		4	23	
Class II	9	89		42	48		9	39	
Class III	9	56		19	36		8	28	

(Continued)

Table S1 (*Continued*)

	Localized treatment	Localized treatment + systemic medication	P-value	Localized treatment + TKIs	Localized treatment + chemotherapy	P-value	Localized treatment + pemetrexed	Localized treatment + other chemotherapy	P-value
RTOG GPA grade			0.494			0.249			0.443
0~1	8	36		11	25		4	21	
1.5–2.5	11	121		54	67		14	53	
3	3	19		7	12		2	10	
3.5–4	2	10		3	7		1	6	

Abbreviations: GPA, graded prognostic assessment; KPS, Karnofsky Performance Scale; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; RPA, recursive partitioning analysis; RTOG, Radiation Therapy Oncology Group; TKIs, tyrosine kinase inhibitors.