Original Article

Recursive Partitioning Analysis Classification and Graded Prognostic Assessment for Non-Small Cell Lung Cancer Patients with Brain Metastasis: A Retrospective Cohort Study

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ABSTRACT

Objective: To assess prognostic factors and validate the effectiveness of recursive partitioning analysis (RPA) classes and graded prognostic assessment (GPA) in 290 non-small cell lung cancer (NSCLC) patients with brain metastasis (BM).

Methods: From Jan 2008 to Dec 2009, the clinical data of 290 NSCLC cases with BM treated with multiple modalities including brain irradiation, systemic chemotherapy and tyrosine kinase inhibitors (TKIs) in two institutes were analyzed. Survival was estimated by Kaplan-Meier method. The differences of survival rates in subgroups were assayed using log-rank test. Multivariate Cox's regression method was used to analyze the impact of prognostic factors on survival. Two prognostic indexes models (RPA and GPA) were validated respectively.

Results: All patients were followed up for 1-44 months, the median survival time after brain irradiation and its corresponding 95% confidence interval (95% CI) was 14 (12.3-15.8) months. 1-, 2- and 3-year survival rates in the whole group were 56.0%, 28.3%, and 12.0%, respectively. The survival curves of subgroups, stratified by both RPA and GPA, were significantly different (P<0.001). In the multivariate analysis as RPA and GPA entered Cox's regression model, Karnofsky performance status (KPS) ≥ 70, adenocarcinoma subtype, longer administration of TKIs remained their prognostic significance, RPA classes and GPA also appeared in the prognostic model.

Conclusion: KPS ≥70, adenocarcinoma subtype, longer treatment of molecular targeted drug, and RPA classes and GPA are the independent prognostic factors affecting the survival rates of NSCLC patients with BM.

Key words: Non-small cell lung cancer (NSCLC); Brain metastasis; Prognosis; Recursive partitioning analysis; Graded prognostic assessment

INTRODUCTION

Brain metastasis (BM) is the most common type of intracranial malignancy, occurring in 25%-50% of all cancer patients based on clinical studies and autopsy series, respectively[1, 2]. As new, more effective therapies for treating primary tumors and enhanced cerebral imaging techniques improve the detection of small and asymptomatic intracranial lesions, and their incidence is expected to increase[3]. BM is a common occurrence in patients with non-small cell lung cancer (NSCLC); about 20%-40% of patients with NSCLC develop central nervous system (CNS) metastases [4].

Treatment options of BM include surgery, whole-brain radiotherapy (WBRT), stereoradiosurgery (SRS), and some combination. WBRT is regarded as the standard therapy[5]. More aggressive approaches such as surgery or SRS are indicated in a subset of patients only, which has been clarified by randomized clinical trials (RCT) and mete-analysis[6-8]. Although the role of systemic treatment remains controversial, systemic treatment including systemic chemotherapy[9-12] and molecular targeted drug (gefitinib or erlotinib) has been introduced in treatment of NSCLC with BM[13-18].

Many pre-treatment characteristics and treatment-related variables have been studied as prognostic factors of patients with BM by the Radiation Therapy Oncology Group (RTOG). Based on data from randomized RTOG studies involving BM, the recursive partitioning analysis (RPA) classes were introduced as prognostic model for BM by Gaspar et al.[19, 20]. Because of limitations of RPA classes and new data (RTOG 9508) available, a new index, graded prognostic assessment (GPA), which was considered as prognostic as the RPA, least subjective, most quantitative and easiest to use, was developed in 2007 by Spertudo et al.[21].

However, the development of RPA classes and GPA is based on the data with preponderance of lung and breast

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cancer patients and is absent of NSCLC-specific data with systemic chemotherapy and molecular targeted drugs. It has been suggested that prognostic factors and the applicability of prognostic systems will vary by primary diagnosis[22]. To our knowledge, the RPA classes and GPA have seldom been validated to NSCLC-specific patients with BM. In this retrospective study, we assessed prognostic factors and validated the effectiveness of RPA classes and GPA in 290 NSCLC patients with one or more BM.

MATERIALS AND METHODS

Patients Characteristics

A total of 290 NSCLC patients treated with three brain irradiation arms for BM from Jan 2008 to Dec 2009, were included in this retrospective study. Three brain irradiation arms included SRS alone or in combination with WBRT and WBRT alone. There were 95 women and 195 men in the series with a mean age of 57.1 years (range 20–80 years), and a median age of 56.5 years. All patients met the following criteria: pathologic proof of NSCLC, stage IV disease with synchronous or metachronous BM, aged 20-80 years, Karnofsky performance status (KPS) >50, size <3 cm and eligibility for brain radiotherapy. In this series, BM was defined as synchronous, if it appeared before or within 3 months following the diagnosis of the primary tumor[23]. Primary tumor was considered as controlled, if lung cancer was managed with curative surgery and there was no clinical and/or radiological suspicion of local recurrence. For patients initially managed with conservative treatment, control of the primary was defined as a complete tumor response or a lack of local progression for at least 6 months before WBRT[23]. Diagnosis of single or multiple BM was based on the report of radiological examinations (CT or MRI).

Treatment Options

Conventional WBRT was administered with either 30 Gy in 10 fractions (2 w, 117 patients) or 40 Gy in 20 fractions (4 w, 103 patients) by 6 MV X-rays for patients with multiple (≥2) BM. As to patients with one BM, 30 Gy in 10 fractions (2 w) in whole brain in addition to 16-24 Gy in 3 fractions in tumor field was prescribed. Dose selection in SRS (Gamma knife radiosurgery) arm was made on the basis of tumors with diameter up to 2.0 cm, which were covered completely with a mean marginal dose of 18.0 Gy; tumors with diameter 2.0–3.0 cm with 16.0 Gy. WBRT was administered in Zhejiang Cancer Hospital, and SRS alone or in combination with WBRT arms was performed in Zhejiang People's Hospital. Platinum/gemcitabine, platinum/vinorelbine, and platinum/taxotere as the first-line chemotherapy drugs were administered for 2-6 cycles in 164 patients, and tyrosine kinase inhibitors (TKIs) (i.e., gefitinib or erlotinib) was administered for 1-22 month in 105 patients with informed consent after first–line chemotherapy (64 patients) or savage therapy (41 patients).

Study Endpoints

Ten pretreatment factors and five treatment-related factors were reviewed and analyzed, of which primary tumor status, KPS, extracranial systemic metastases, and age, were used to stratify patients according to the 3 classes of RPA developed by the RTOG[19, 20] (Table 1). Primary tumor status, KPS, extracranial systemic metastases, age and the number of BM were used to stratify patients according to the 4 classes of GPA developed by RTOG[21] (Table 2). We applied both RPA and GPA systems based on clinical information in the medical records. Major study endpoint was overall survival (OS). OS was defined as the time from the starting date of cranial treatment to the date of death or the last follow-up.

Table 1. RPA classes

Classes	Variables
Classes I	Age <65 y, KPS ≥70, controlled primary tumor, no extracranial metastases
Classes II	All patients not in Class I or III
Classes III	KPS <70

KPS: Karnofsky performance status. The Table 1 was cited from reference 21.

Table 2. GPA score

	Score		
	0	0.5	1.0
Age	>60	50–59	<50
KPS	<70	70–80	90–100
No. of CNS metastases	>3	2–3	1
Extracranial metastases	Present	–	None

KPS: Karnofsky performance status; CNS: central nervous system. The Table 2 was cited from reference 20.

Statistical Analysis

Overall survival was calculated according to the Kaplan-Meier method from the first date of cranial treatment to the date of death. If a patient was not dead, then survival was censored at the time of the last visit. Two multivariate Cox's proportional hazards models were developed by using stepwise regression with the predictive variables. Version 11.0 of the SPSS statistical program was used for analysis. A P value of less than 0.05 (P<0.05) was considered to be statistically significant.

RESULTS

All patients had data of 10 pretreatment factors and 5 treatment-related factors (Table 1). The median follow-up was 15 months (range, 1-44 months). At the time of the analysis, 217 patients were dead. Intracranial progression in 70 (32%), extracranial progression in 84 (39%), both extracranial and intracranial progression in 60 (28%) led to the death. Three patients (1%) died from cancer and treatment-unrelated causes. The 1-, 2- and 3-year survival rates of the whole group were 56.0%, 28.3%, and 12.0%, respectively (Figure 1). The median1 survival time (MST) after brain irradiation was 14 months (95% CI: 12.3-15.8) (Figure 1).

Results of Univariate Analysis

Results of the univariate analysis for the entire group are shown in Table 3. Of 15 prognostic variables, adeno-

carcinoma subtype of lung cancer (χ^2=20.668, P=0.000), KPS >70 (χ^2=19.763, P=0.000), surgery of lung cancer (χ^2=4.893, P=0.028), single BM (χ^2=8.535, P=0.014), surgery of BM χ^2=4.953, P=0.026), better RPA class (χ^2=63.484, P=0.000) and higher GPA (χ^2=32.728, P=0.000), and longer administration of TKIs (χ^2=20.277, P=0.000), were associated with improved survival. Age, gender, surgery of lung cancer, interval from diagnosis of the primary to the diagnosis of BM, surgery of BM, extracranial metastases status and control of the primary tumor had no prognostic value. Our MST (months) by RPA classes were: 23 (RPA I), 16 (RPA II), and 5 (RPA III) respectively. Our MST (months) by GPA score were 30 (GPA 3.5-4.0), 24 (GPA 3.0), 13 (GPA 1.5-2.5), and 9 (GPA 0-1.0), respectively. The survival curves of subgroups, stratified by both RPA and GPA, were significantly different (P<0.001) (Figure 2, 3).

Table 3. Characteristic and results of univariate analysis of 290 NSCLC patients with BM

Variables (cases)	1-year survival	2-year survival	3-year survival	MST	Log-rank χ^2	P
Gender					1.040	0.308
Male (195)	53.9	28.0	12.2	13 (10.92-15.08)		
Female (95)	60.4	28.6	11.2	16 (13.37-18.63)		
Age					0.667	0.454
≤65 y (227)	56.7	29.5	11.0	15 (12.77-17.23)		
>65 y (63)	53.5	23.8	17.0	13 (10.75-15.25)		
Histology subtype					20.668	0.000
Adenocarcinoma (224)	58.8	31.5	13.7	16 (13.71-18.29)		
No-adenocarcinoma (66)	45.6	16.7	6.0	10 (5.50-13.44)		
KPS					19.763	0.000
<70 (160)	47.3	20.2	4.2	12 (10.85-13.15)		
≥70 (130)	66.7	38.2	21.0	21 (17.70-25.30)		
Surgery of lung cancer					4.839	0.028
Yes (60)	61.7	38.2	24.0	19 (12.27-25.73)		
No (230)	54.5	25.6	8.8	14 (12.28-15.72)		
Extracranial status					0.974	0.615
Bone only (77)	53.4	23.7	13.8	16 (11.21-20.78)		
Verscial organ (40)	54.0	29.9	5.1	13 (13.95-18.05)		
No (173)	57.6	30.6	12.8	14 (12.10-15.89)		
Lung lesion status					2.481	0.117
Controlled (62)	64.5	37.3	15.0	17 (8.17-25.81)		
Uncontrolled (228)	53.7	25.7	11.3	14 (12.57-15.83)		
Number of BM					8.535	0.014
1 (121)	63.9	36.4	23.1	17 (13.76-20.24)		
2-3 (34)	48.0	20.9	7.0	12 (6.69-17.31)		
>3 (135)	51.0	22.9	6.3	13 (11.23-14.76)		
Previous surgery of BM					4.953	0.026
Yes (12)	91.7	51.3	12.8	28 (14.13-41.86)		
No (278)	54.5	27.2	12.5	14 (12.38-15.62)		
Interval of BM					3.672	0.055
Synchronous (192)	54.4	22.2	9.2	13 (11.17-14.83)		
Metachronous (98)	59.2	38.0	16.4	16 (10.52-21.48)		
Systemic chemotherapy					1.219	0.270
0-1 cycle (126)	52.4	26.2	13.4	13 (11.06-14.94)		
≥2 cycles (164)	58.8	29.8	10.2	16 (13.41-18.59)		
Molecular targeted therapy					20.277	0.000
0 (185)	46.7	26.8	11.2	12 (9.95-14.05)		
1-3 months (35)	48.1	11.8	0	12 (9.23-14.78)		
>3 months (70)	84.3	40.9	20.5	21 (16.78-25.22)		
Brain irradiation arms					2.645	0.450
SRS alone (70)	51.4	26.5	7.7	13 (10.32-15.68)		
WBRT alone (200)	57.6	29.0	12.8	15 (12.89-17.12)		
SRS+WBRT (20)	45.0	25.0	12.5	12 (9.82-14.18)		
RPA class					63.484	0.000
RPA I (32)	78.1	43.5	19.3	23 (13.81-32.19)		
RPA II (211)	59.8	31.1	13.8	16 (13.95-18.05)		
RPA III (47)	23.3	4.7	0	5 (2.83-7.17)		
GPA					32.728	0.000
0-1 (56)	37.9	8.5	0	9 (5.50-12.49)		
1.5-2.5 (169)	54.7	26.3	12.6	13 (10.97-15.03)		
3 (43)	72.1	47.7	12.1	24 (12.89-35.10)		
3.5-4 (22)	81.1	56.1	46.7	30 (16.44-43.56)		

WBRT: whole-brain radiotherapy; KPS: Karnofsky performance status; RPA: recursive partitional analysis; GPA: graded prognostic assessment; SRS: stereoradiosurgery; OS: overall survival; MST: Median survival time.

Table 4. Multivariate analysis of factors affecting OS in NSCLC patients with BM (as RPA and GPA did not enter) Cox's regression model

Variables	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Histology subtype	0.333	0.118	7.901	0.005	1.395	1.106-1.759
No. of BM	0.369	0.153	5.803	0.016	1.447	1.071-1.953
TKIs	-0.315	0.084	13.932	0.000	0.730	0.618-0.861
KPS	-0.623	0.418	17.785	0.000	0.536	0.401-0.715

KPS: Karnofsky performance status; BM: brain metastases; TKIs: tyrosine kinase inhibitors

Table 5. Multivariate analysis of factors affecting OS in NSCLC patients (as RPA and GPA entered) Cox's regression model

Variables	B	SE	Wald	Sig	Exp (B)	95% CI for Exp (B)
Histology	0.317	0.120	7.000	0.008	1.373	1.086-1.737
TKIs	-0.372	0.089	17.594	0.000	0.701	0.580-0.820
KPS	-0.430	0.155	7.725	0.005	0.651	0.481-0.881
GPA	-0.866	0.160	29.331	0.000	0.421	0.307-0.575
RPA	0.370	0.168	4.846	0.028	1.448	1.041-2,014

KPS: Karnofsky performance status; RPA: recursive partitional analysis; GPA: graded prognostic assessment; OS: overall survival; TKIs: tyrosine kinase inhibitors

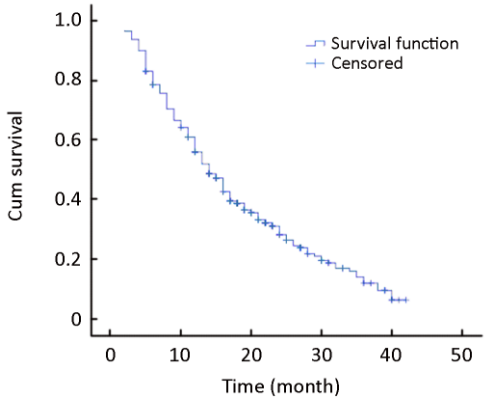

Figure 1. Kaplan-Meier survival curves for 290 NCLC patients with BM.

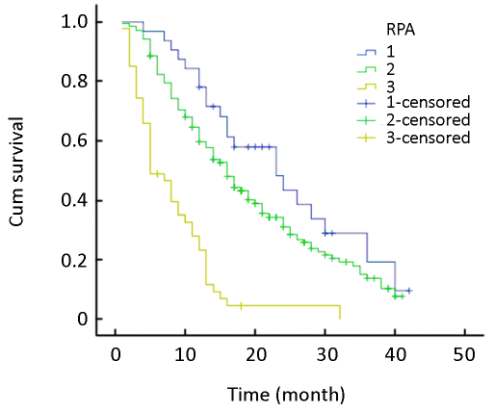

Figure 2. Kaplan-Meier survival curves for patients with BM stratified by RPA.

Results of Multivariate Analysis

In the multivariate analysis as RPA and GPA didn't enter Cox's regression model, histology subtype (P=0.005; RR=1.395; 95% CI: 1.106-1.759), KPS (P=0.000; RR=0.536; 95% CI: 0.401-0.716), single BM (P=0.016; RR=1.447; 95% CI: 1.0471–1.953), and longer administration of TKIs (P=0.000; RR=0.730; 95% CI: 0.618-0.861), maintained their prognostic significance for survival (Table 4). Age, gender, surgery of lung cancer, surgery of BM extracranial metastases status and control of the primary tumor had no prognostic value (P<0.05). In the multivariate analysis as RPA and GPA entered Cox's regression model (Table 5), histology subtype (P=0.0085; RR=1.373; 95% CI: 1.086-1.737), KPS (P=0.005; RR=0.651; 95% CI: 0.481-0.881), and longer administration of TKIs (P=0.000; RR=0.701; 95% CI: 0.580-0.820) remained their prognostic significance, and RPA classes (P=0.028; RR=1.448; 95% CI: 1.041-2.014) and GPA (P=0.000; RR=0.421; 95% CI: 0.307-575) also appeared in the new prognostic model. However, single BM lost its prognostic significance.

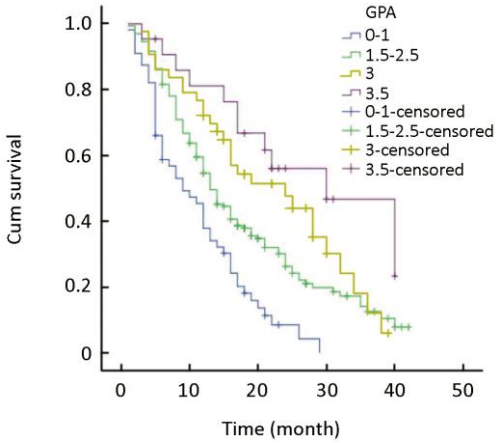

Figure 3. Kaplan-Meier survival curves for patients with BM, stratified by GPA.

DISCUSSION

Multiple Modalities and Overall Survival

Systemic chemotherapy is largely unsuccessful because

drugs cannot effectively penetrate the blood–brain barrier and NSCLC is normally poorly to moderately sensitive to this treatment[24]. The present study shows that systemic chemotherapy had no prognostic value. The role of systemic chemotherapy in NSCLC with BM remains controversial. Some scholars suggested that WBRT in combination with systemic chemotherapy was a standard treatment for NSCLC patients with BM and 0 to 2 performance status (PS) score[9, 10]. Kim and his coworkers[11] suggested that a potential role of systemic chemotherapy alone or upfront SRS followed by chemotherapy instead of WBRT as an initial treatment of NSCLC patients with synchronous and asymptomatic BM. However, in a systematic review regarding the role of chemotherapy in the management of newly diagnosed BM, there is level-1 evidence demonstrating that routine use of chemotherapy following WBRT for BM has not been shown to increase survival and is not recommended[12].

Somatic mutations in epidermal growth factor receptor (EGFR) have been detected in patients with NSCLC and are associated with sensitivity to treatment with gefitinib or erlotinib, which are adenosine triphosphate-competitive inhibitors of the receptor's tyrosine kinase. These mutations are more common in non-smokers, women, Asians, and patients with adenocarcinoma, possibly explaining the association of these characteristics with response to treatment. Several studies[13-18] have documented the effectiveness of gefitinib in the treatment of CNS metastasis of NSCLC. There have been few reported cases of responses to brain metastases in NSCLC in patients receiving erlotinib by 2008[15-17]. A recent retrospective study[25] claimed that erlotinib is active in BM from NSCLC and the clinical benefit is related to the presence of activating mutations in Exon 19 or 20 of EGFR gene. In this study, *EGFR* status was not assessed in most of patients, 105 patients received 1-33 months TKIs after systemic chemotherapy or brain irradiation, 35 patients received only 1-3 months administration of TKIs because of ineffectiveness, and 70 patients received more than 3 months TKIs with 21 months of MST. Therefore, the application of TKIs for NSCLC patients with BM is warranted in the future.

Three radiotherapy arms, namely, SRS alone or in combination with WBRT and WBRT alone, were used as local measures in the retrospective study. There are no significant survival differences found in univariate analysis of entire group. In 1996, to assess the effectiveness of SRS alone or in combination with WBRT compared to surgery and/or WBRT in prolonging survival of patients with BM, a systematic review and a meta-analysis review were conducted. The results demonstrated that adding SRS to WBRT improved survival in patients with one BM, combining SRS and WBRT improved local tumor control and functional independence in all patients[6]. In 2010, another systematic review was conducted regarding the role of SRS in the management of patients with newly diagnosed BM. Regarding SRS plus WBRT vs. WBRT alone, there is class I evidence demonstrating that single-dose SRS along with WBRT leads to significantly longer patient survival compared with WBRT alone for patients with single metastatic brain tumors who have a KPS ≥70. Regarding SRS plus WBRT vs. SRS alone, there is level-2 evidence demonstrating that single-dose SRS alone may provide an equivalent survival advantage for patients with BM compared with WBRT. Regarding single-dose SRS alone vs. WBRT alone, there is level-3 evidence showing that single-dose SRS alone appears to be superior to WBRT alone for patients with up to three metastatic brain tumors in terms of patient survival advantage control[7].

Prognostic Factors and Prognostic Systems

Prognostic factors can help identify patients who may benefit from more aggressive treatment. Gaspar et al. suggested in the RTOG RPA report that a younger age, better performance status, lack of extracranial metastases, lower RPA class and a longer interval from tumor diagnosis to treatment of BM were the most relevant prognostic factors for patient survival[19, 20]. Sperduto et al. developed GPA, in which, age, KPS, extracranial metastases, and number of metastases were the most relevant prognostic factors for patient survival[21]. In Pan's multivariate analysis, a younger age, higher KPS, no pre-existing neurological deficits, multiple GKS sessions and a prior craniotomy were important factors for improved survival[26]. The present study showed that KPS ≥70, and single BM are independent prognostic factors impacting the survival of NSCLC with BM.

The study used prognostic classes of RPA, and the results showed that the survival curves of subgroups were significantly different (P<0.001).This study also used a statistical prognostic model of GPA, and the results showed that the survival curves of subgroups, stratified by GPA, was significantly different (P<0.001), and consistent with RPA model. The RPA classes and GPA have been validated in the multivariate analysis**.** It was believed that the utilization of these classes would allow new treatment techniques to be tested and reported in homogeneous patient groups. A number of studies have been published validating the robustness of this model in evaluating patient outcomes[20, 27–29]. Therefore, more aggressive treatment should be taken for RPA I group or GPA 0-1 group patients.

However, it did not use the primary site as a parameter in both the RPA classes and GPA. Because BM patients are a heterogeneous population, it has been suggested that prognostic factors and the applicability of prognostic systems will vary by primary diagnosis and site-specific prognostic systems should be developed. Diagnosis-Specific GPA (DS-GPA) was also created based on a retrospective database of 5,067 patients treated for BM[30]. The authors concluded that the prognostic factors for BM patients varied by diagnosis. The original GPA was confirmed for NSCLC and SCLC. Despite of retrospective nature of our study, GPA was proved in NSCLC-specific population with BM.

The present study also showed that histology subtype was a prognostic factor. Some authors[31, 32] suggested that adenocarcinomas had a higher median survival than other histologies of NSCLC with BM. Therefore, the use of histology as a prognostic factor for BM from NSCLC warrants further investigation. The time of appearance of BM was closed to statistically significant in our study (P=0.055). However, there are some studies demonstrating

that a long disease-free interval from the diagnosis of the primary until craniotomy is associated with a favorable prognosis[17, 28, 33]. The finding that a longer interval from tumor diagnosis to WBRT is associated with improved survival can be explained by the slower growth of less aggressive tumors[34].

In summary, KPS ≥70, adenocarcinoma subtype, single BM, and longer treatment of molecular targeted drug are the independent prognostic factors impacting the survival rate of NSCLC with BM in our study. Both RPA and GPA model prognostic indexes could better reflect the prognosis. For some subgroups of patients with good prognosis, aggressive treatment including TKIs can further improve survival.

REFERENCES

1. Posner JB. Management of brain metastases. Rev Neurol 1992; 148: 477-87.
2. Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. Neurology 1985; 35: 219-26.
3. Davey P. Brain metastases: treatment options to improve outcomes. CNS Drugs 2002; 16:325-38.
4. Shahidi H, Kvale PA. Long-term survival following surgical treatment of solitary brain metastasis in non-small cell lung cancer. Chest 1996; 109: 271-6.
5. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:17-32.
6. Stafinski T, Jhangri GS, Yan E, et al. Effectiveness of stereotactic radiosurgery alone or in combination with whole brain radiotherapy compared to conventional surgery and/or whole brain radiotherapy for the treatment of one or more brain metastases: a systematic review and meta-analysis. Cancer Treat Rev 2006; 32:203-13.
7. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:45-68.
8. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:33-43.
9. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993; 342:19-21.
10. Kim DY, Lee KW, Yun T, et al. Efficacy of platinum based chemotherapy after cranial radiation in patients with brain metastases from non-small cell lung cancer. Oncol Rep 2005; 14:207-11.
11. Kim KH, Lee J, Lee JL, et al. Can upfront systemic chemotherapy replace stereotactic radiosurgery or whole brain radiotherapy in the treatment of non-small cell lung cancer patients with asymptomatic brain metastases? Lung Cancer 2010; 68:258-63.
12. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010; 96:71-83.
13. Ceresoli GL, Cappuzzo F, Gregorc V, et al. Gefitinib in patients with brain metastases from non-small-cell lung cancer: a prospective trial. Ann Oncol 2004; 15:1042-7.
14. Rosell R, Taron M, Sanchez JJ, et al. Setting the benchmark or tailoring treatment with EGFR tyrosine kinase inhibitors. Future Oncol 2007; 3:277-83.
15. Fekrazad MH, Ravindranathan M, Jones DV Jr. Response of intracranial metastases to erlotinib therapy. J Clin Oncol 2007; 25:5024-6.
16. von Pawel J, Wagner H, Duell T, et al. Erlotinib in patients with previously irradiated, recurrent brain metastases from non-small cell lung cancer: two case reports. Onkologie 2008; 31:123-6.
17. Gounant V, Wislez M, Poulot V, et al. Subsequent brain metastasis responses to epidermal growth factor receptor tyrosine kinase inhibitors in a patient with non-small-cell lung cancer. Lung Cancer 2007; 58:425-8.
18. Nishi N, Kawai S, Yonezawa T, et al. Effect of gefitinib on brain metastases from non-small cell lung cancer. Neurol Med Chir (Tokyo) 2006; 46:504-7.
19. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 1997; 37: 745-51.
20. Gaspar LE, Scott C, Murray K, et al. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 2000; 47:1001-6.
21. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys 2008; 70:510-4.
22. Golden DW, Lamborn KR, McDermott MW, et al. Prognostic factors and grading systems for overall survival in patients with radiosurgery for brain metastases: variation by primary site. J Neurosurg 2008; 109(Suppl):77-86.
23. Kepka L, Cieslak E, Bujko K, et al. Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: the RTOG RPA intra-classes analysis. Acta Oncol 2005; 44:389-98.
24. Schuette W. Treatment of brain metastases from lung cancer: chemotherapy. Lung Cancer 2004; 45(Suppl 2):S253-7.
25. Porta R, Sanchez-Torres JM, Paz-Ares L, et al. Brian metastases from lung cancer responding to erlotinib : the importance of EGFR mutation. Eur Respir J 2011; 37:624-31.
26. Pan HC, Sheehan J, Stroila M, et al. Gamma knife surgery for brain metastases from lung cancer. J Neurosurg 2005; 102(Suppl):128-33.
27. Agboola O, Benoit B, Cross P, et al. Prognostic factors derived from recursive partition analysis (RPA) of Radiation Therapy Oncology Group (RTOG) brain metastases trials applied to surgically resected and irradiated brain metastatic cases. Int J Radiat Oncol Biol Phys 1998; 42:155-9.
28. Sanghavi SN, Miranpuri SS, Chappell R, et al. Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. Int J Radiat Oncol Biol Phys 2001; 51:426-34.
29. Cannady SB, Cavanaugh KA, Lee SY, et al. Results of whole brain radiotherapy and recursive partitioning analysis in patients with brain metastases from renal cell carcinoma: a retrospective study. Int J Radiat Oncol Biol Phys 2004; 58:253-8.
30. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys 2010; 77:655-61.
31. Nakagawa H, Miyawaki Y, Fujita T, et al. Surgical treatment of brain metastases of lung cancer: retrospective analysis of 89 cases. J Neurol Neurosurg Psychiatry 1994; 57:950-6.
32. Saitoh Y, Fujisawa T, Shiba M, et al. Prognostic factors in surgical treatment of solitary brain metastasis after resection of non-small-cell lung cancer. Lung Cancer 1999; 24:99-106.
33. Galicich JH, Sundaresan N, Arbit E, et al. Surgical treatment of single brain metastasis: factors associated with survival. Cancer 1980; 45: 381-6.
34. White KT, Fleming TR, Laws ER Jr. Single metastasis to the brain. Surgical treatment in 122 consecutive patients. Mayo Clin Proc 1981; 56: 424-8.