Thoracic Cancer
Open Access
Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Prognostic factors and outcome of surgically treated patients with brain metastases of non-small cell lung cancer

Chunhua She[1*], Ruixia Wang[2*], Changhong Lu[3], Zengfeng Sun[1], Peng Li[1], Qiang Yin[1], Qun Liu[1], Peng Wang[1] & Wenliang Li[1]

1 Department of Neurosurgery and Neuro-Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China
2 Department of Neurology, The Second Hospital of Tianjin Medical University, Tianjin, China
3 Ultrasound Department, Binzhou People's Hospital, Binzhou, China

Keywords
Brain metastases; non-small cell lung cancer (NSCLC); prognostic factor; recursive partitioning analysis (RPA).

Correspondence
Wenliang Li, Department of Neurosurgery and Neuro-Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Huan-hu-xi Road, Hexi District, Tianjin 300060, China.
Tel: +86 22 2334 0123
Email: liwenliang2338@163.com

*These authors contributed equally to this work and should be considered co-first authors.

Received: 11 September 2018;
Accepted: 13 October 2018.

doi: 10.1111/1759-7714.12913

Thoracic Cancer **10** (2019) 137–142

Abstract

Background: Brain metastases (BM) are a common consequence of lung cancer and surgery is effective; however, the factors affecting survival after surgery are unclear. The aim of this study was to identify the outcomes and prognoses of post-metastasectomy patients with BM from non-small cell lung cancer (NSCLC) at a single institution over a 15-year period.

Methods: NSCLC patients who had undergone BM surgery were retrospectively identified. Survival was analyzed using the Kaplan–Meier curve, and univariate and multivariate factors associated with survival were identified using the Cox proportional hazards model.

Results: The median overall survival was 9.8 months, 18 (14.8%) patients survived > 24 months, and 6 (4.9%) > 36 months. The one and two-year survival rates were 41% and 18.6%, respectively. Univariate analysis revealed that recursive partitioning analysis (RPA) classification, Karnofsky Performance Scale (KPS) scores, BM number, extracranial metastasis status, different lesion locations, resection extent, postoperative treatment, and salvage therapy after recurrence significantly influenced patient survival. The different treatment modalities for primary lesions also affected postoperative survival. KPS ≥ 70, RPA class I/II, and postoperative chemotherapy were independent factors that decreased the risk of death from BM. Interestingly, the initial onset of intracranial lesions could increase the risk of death from BM.

Conclusion: A KPS score ≥ 70, RPA class I/II, and postoperative chemotherapy could benefit post-metastasectomy patients with BM from NSCLC. Conversely, the initial onset of intracranial lesions is an unfavorable factor that increases the risk of death. These findings support the use of personalized therapy for patients with BM from NSCLC.

Introduction

Lung cancer is the most common cancer and the leading cause of cancer death in China; an estimated 2 814 000 deaths and 4 292 000 new cases occurred in 2015.[1] Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers and the most common histological subtypes are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[2,3] The occurrence of brain metastases (BM) in lung cancer patients is 10% at first onset,[4] and increases as the disease progresses.[5]

Outcomes in patients with BM from NSCLC are very poor. Without treatment, patients can only survive approximately one month[6]; two-month survival can be achieved with the use of corticosteroids.[7,8] Survival could be extended from three to six months with corticosteroids and whole brain radiation therapy (WBRT),[9] and further extended from nine to 14 months with surgical

resection and postoperative WBRT.[10,11] However, > 2 year survival cannot be achieved in patients treated with combination therapy, which poses a significant challenge for the treatment of BM from NSCLC.

Surgery is effective for BM; however, factors affecting the survival of patients who have undergone a craniotomy are unclear. Therefore, the aim of this study was to analyze the outcomes and prognostic factors of these subpopulations at a single institution.

Methods

Patients

Patient data were collected from 1 January 2001 to 31 December 2014 at the Tianjin Medical University Cancer Hospital and Institute with the approval of the institution review board. All patient data was kept confidential.

We evaluated 122 consecutive patients confirmed with NSCLC by pathological histology. Brain lesions were detected by enhanced magnetic resonance imaging. All patients had undergone a craniotomy and were pathologically diagnosed with BM. BM surgery was recommended to patients under the following conditions: a limited number (1–3) of newly diagnosed BM, especially in cases of lesions ≥ 3 cm in diameter (symptomatic or not); lesions with necrotic or cystic appearance and edema/mass effect; lesions located in the posterior fossa with associated hydrocephalus; lesions located in symptomatic eloquent areas; multiple lesions (> 3) with unknown primary disease, one of which caused a serious mass effect or symptoms; and recurrence after radiotherapy or radioresistant lesions. After surgery, patients received individual treatment, such as radiotherapy and/or chemotherapy or targeted therapy, but no immunotherapy.

Patients were evaluated according to the following parameters: patient demographics; BM number, location and size; histology; synchronous and metachronous BM; extracranial metastasis status; recursive partitioning analysis (RPA); preoperative Karnofsky Performance Scale (KPS) score; postoperative treatment modality; extent of tumor resection; primary lung cancer treatment; and recurrence treatment.

Overall survival (OS) was calculated from the day of craniotomy to the date of death from any cause or the last follow-up (November 2015). All patients alive at the time of the analysis were censored using the date of last follow-up.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The Kaplan–Meier method was used for survival analysis to determine the cumulative survival rate at one, two and three years. Differences between Kaplan–Meier curves were evaluated using the log-rank test. Significance was set at $P < 0.05$. Univariate and multivariate factors associated with survival were analyzed using the Cox proportional hazards model. The estimates of the models are given as hazard ratios (HRs) with 95% confidence intervals (95% CIs).

Results

Patient demographics

The median age at the time of BM surgery was 56 years (range: 31–81 years). The histopathological subtypes were: adenocarcinoma (74 patients), squamous cell carcinoma (31 patients), adeno-squamous carcinoma (6 patients), large-cell carcinoma (7 patients), and bronchioloalveolar carcinoma (4 patients). Eighty-three patients had synchronous BM from NSCLC. Synchronous presentation was defined as BM occurring within three months of NSCLC diagnosis. According to RPA classification, 45 patients were class I, 61 were class II, and 15 were class III. The general characteristics of these patients are summarized in Table 1.

Among the 122 patients, 141 lesions were resected, with complete resection achieved in 49 patients. Complete resection was confirmed by contrast-enhanced magnetic resonance imaging within 72 hours after surgery. Subtotal resection was performed in cases of multiple metastases, or in cases of specific metastasis location and intraoperative considerations, for example, infiltration into eloquent areas. Reoperation for recurrence was performed in 10 patients, two of which underwent craniotomy three times, while radiosurgery was performed in 13 patients.

Survival

Follow-up data were available for all 122 patients; 113 patients died. The median OS after the first brain metastasectomy was 9.8 months (Fig 1a), and 18 patients survived > 24 months. The one and two-year survival rates were 41% and 18.6%, respectively.

Different RPA groups showed obvious differences in survival. The median OS of RPA class I patients was 13.4 months ($P < 0.001$) (Fig 1b). RPA class III patients achieved a brief respite, followed by disease progression. Survival in patients with a preoperative KPS score < 70 was significantly shorter than patients with a KPS score ≥ 70 (1.8 vs. 10.5 months; $P < 0.001$) (Fig 1c).

Different lesion locations and extracranial metastases affected patient survival (Fig 1d,e). Surprisingly, lesions located in the posterior fossa corresponded to longer survival than lesions in the anterior fossa (16.7 vs. 11.2 months). We hypothesized that lesions in the

Table 1 Clinical characteristics and Kaplan–Meier analysis of postoperative patients with brain metastases from NSCLC

Parameters	No. of patients (%)	Median survival (months) (95%CI)	*P*
Gender			
Male	73 (59.8)	9.8 (8.3–11.4)	0.61
Female	49 (40.2)	10.1 (9.2–11.0)	
Age			
< 65 years	87 (71.3)	10.5 (9.3–11.6)	0.26
≥ 65 years	35 (28.7)	9.0 (8.0–10.1)	
Smoking history			
Yes	52 (42.6)	9.7 (9.2–10.3)	0.41
No	70 (53.4)	10.1 (8.9–11.3)	
RPA classification			
I	46 (37.7)	13.4 (11.4–15.3)	< 0.001
II	61 (50)	9.1 (8.3–9.8)	
III	15 (12.3)	2.4 (1.3–3.6)	
KPS score			
≥ 70	111(91)	10.5 (8.9–12.1)	< 0.001
< 70	11 (9)	1.80 (0.1–7.5)	
No. of BM			
Solitary (= 1)	50 (41)	12.6 (11.5–13.7)	< 0.001
Multiple (≥ 2)	72 (59)	8.6 (7.6–9.5)	
Size of BM			
< 3.75	61 (50)	9.9 (8.9–10.1)	0.99
≥ 3.75	61 (51)	9.9 (8.5–11.2)	
Location			
Supratentorial	73 (59.8)	11.2 (8.9–13.5)	0.03
Infratentorial	11 (9.1)	16.7 (0–36.2)	
Supra/infratentorial	38 (31.1)	8.2 (7.3–9.0)	
Onset of BM			
Synchronous	83 (68)	10.5 (8.4–12.5)	0.49
Metachronous	39 (32)	9.3 (8.6–10.1)	
Extracranial metastases			
Yes	34 (27.9)	8.8 (8.3–9.4)	0.007
No	88 (72.1)	10.6 (8.5–12.6)	
Histology			
Adenocarcinoma	74 (60.7)	9.8 (8.8–10.9)	0.38
Squamous cell carcinoma	31 (25.4)	9.8 (8.2–11.5)	
Large cell/mix	17 (13.9)	9.8 (7.3–12.4)	
Resection			
Complete	49 (40.2)	12.6 (11.4–13.7)	< 0.001
Remaining tumor	73 (59.8)	8.7 (7.8–9.6)	
Postoperative treatment			
Yes	50 (41.0)	14.1 (11.4–16.8)	< 0.001
No	72 (59.0)	8.6 (7.1–10.0)	
Treatment of recurrence			
Yes	25 (20.5)	17.9 (4.2–31.5)	< 0.001
No	97 (79.5)	9.7 (9.1–10.3)	

CI, confidence interval; KPS, Karnofsky Performance Scale; RPA, recursive partitioning analysis.

posterior fossa revealed symptoms earlier and thus patients were hospitalized in a timely manner.

The survival differences between patients with solitary and multiple BM are shown in Figure 1f, and are consistent with the results of previous reports. A statistically significant difference in survival was found between the groups (12.6 vs. 8.6 months; $P < 0.001$). The one-year survival rates were 60% and 26.4% and two-year survival rates were 33.3% and 8% in the solitary and multiple BM groups, respectively.

Consistent with previous reports, the extent or number of lesions resected was found to be a prognostic factor (Fig 1g). A statistically significant difference was found between the two groups (12.6 [95% CI 11.4–13.7] vs. 8.7 months [95% CI, 7.8–9.6]; $P < 0.001$). The one-year survival rates were 59.2% and 27.4% and the two-year survival rates were 31.9% and 7.5% after complete and incomplete resection, respectively. However, complete resection did not alleviate the risk of death.

Patients were divided into three groups according to treatment for primary lesions: surgery, radiotherapy and/or chemotherapy, and no treatment. The mean survival duration of the different groups was statistically significant (11.2 vs. 9.9 vs. 9.5 months, respectively; $P = 0.009$). The results are summarized in Table 2, and suggest that the control of primary lesions is important. Similarly, the type of postoperative treatment modality applied for BM yielded different survival benefits (Table 3, Fig 1h). Furthermore, postoperative chemotherapy is an independent factor that reduced the risk of death, which highlights the importance of systemic therapy for advanced patients (Fig 2). Paradoxically, the initial onset of intracranial lesions did not change the OS rate, but could increase the risk of death from BM.

The median survival of patients with local or distant tumor recurrence who received salvage therapy was 17.9 months (95% CI 4.2–31.5 months) after the first surgery compared to patients who did not receive salvage therapy, with median survival of 9.7 months ($P < 0.001$). Reoperation for intracranial recurrence was performed in 10 patients, two of which underwent a third craniotomy, while radiosurgery was performed in 13 patients.

Perioperative mortality

The surgical mortality rate was 7.4%; nine patients died within 30 days of surgery. All of these patients were RPA class III, and four were aged > 70 years. The causes of death were: postoperative hemorrhage in the resection cavity (1 patient), rapid extracranial tumor progress (1 patient), acute hydrocephalus (2 patients), acute cardiac infarction (2 patients), and postoperative pulmonary infection (3 patients).

Discussion

Brain metastases are an increasingly common malignant cancer complication. Approximately half of the patients with NSCLC develop BM during the course of their disease.[12] Advances in diagnostic and therapeutic approaches have largely improved craniotomy for BM. Nevertheless,

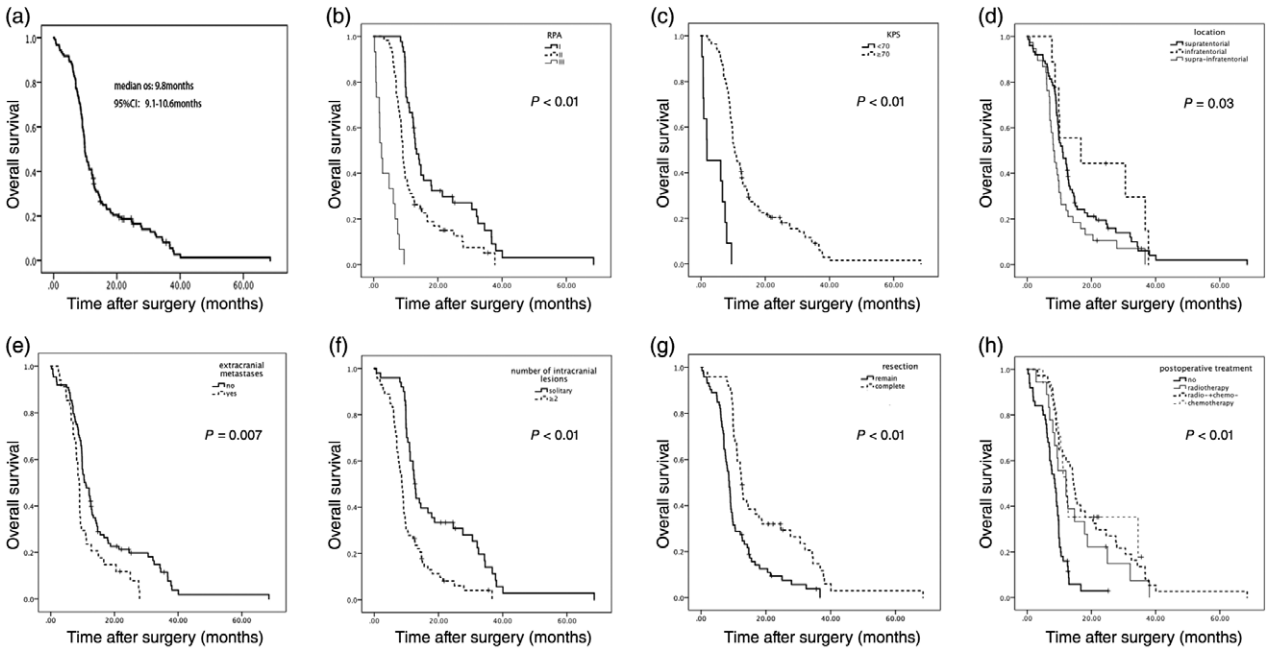

Figure 1 Kaplan–Meier analysis of parameters significantly associated with overall survival (OS, calculated from the first craniotomy for brain metastases). (**a**) Patients in different recursive partitioning analysis (RPA) classes; (**b**) Karnofsky Performance Scale (KPS) score; (**c**) number of intracranial lesions; (**d**) extracranial metastases; (**e**) location of lesions; (**f**) treatment modality after surgery; (**g**) extent of resection; and (**h**) postoperative treatment. CI, confidence interval.

Table 2 Survival analysis of different treatment modalities for primary lesions

Treatment of primary	No. of patients	Median survival (months)	One-year survival	Two-year survival	Three-year survival
Surgery	39	11.2	48.70%	26%	8.80%
Chemotherapy/radiotherapy	22	9.9	40.90%	24.50%	6.10%
No treatment	61	9.5	32.80%	8.20%	0

Table 3 Survival analysis of different treatment modalities after surgery

Treatment	No. of patients (*n*, %)	Median survival (months)	*P*
WBRT	18(14.8%)	12.1 (6.957–17.163)	0.0096
Chemo	17(13.9%)	12.3 (10.465–14.175)	0.0005
WBRT+ chemo	37(30.3%)	14.5 (12.571–16.409)	< 0.0001
Non-treatment	50(41.0%)	8.6 (7.105–10.035)	—

Chemo, chemotherapy; WBRT, whole brain radiotherapy.

the outcome for patients after surgery for BM from NSCLC remains poor. This study evaluated the prognostic factors and survival in patients after craniotomy for BM from NSCLC over the past decade, in which 59% patients showed multiple metastases.

The median OS, and one and two-year survival rates in our study were 9.8 months, 41%, and 18.6%, respectively, consistent with the results of previous reports (approximately 8–9 months, 20–40%, and 5–12%, respectively).[13–15] Our results showed that RPA class I/II, KPS score > 70, solitary metastasis, no extracranial metastases, infratentorial lesions, complete resection, postoperative treatment, and recurrence treatment were associated with improved survival, whereas gender, age, smoking history, histological classification of metastases, the diameter of metastases, metastases onset, and preoperative prophylactic cranial irradiation were not associated with improved survival.

Prolonged survival and improved quality of life are aspects commonly achieved in recent times. Irradiation of primary lesions and BM improves patient survival. In this study, primary lesion treatment was associated with improved survival, particularly two and three-year survival, consistent with results of Patchell *et al.* and Magilligan *et al.*[10,16] However, primary lesion treatment was not an independent risk related factor.

The Radiation Therapy Oncology Group (RTOG) developed an RPA classification system in which patients are statistically classified by KPS score, age, and status of extracranial disease.[17] In this study, patients were also classified into three classes according to the RPA classification: the

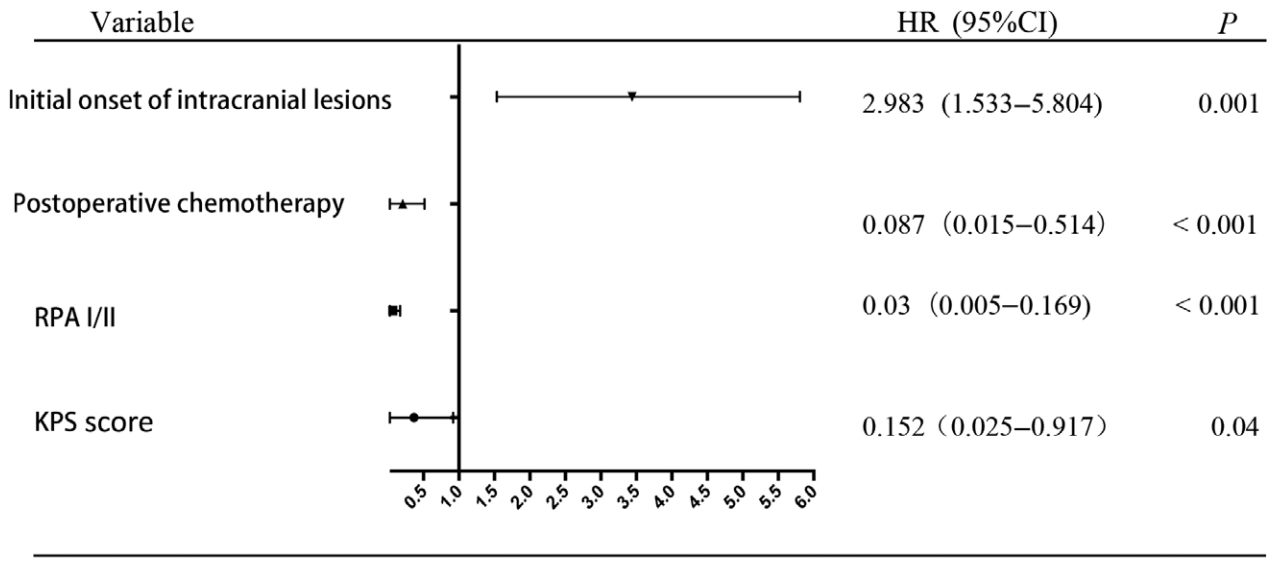

Figure 2 Multivariate analysis of prognostic factors associated with overall survival. CI, confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Scale; RPA, recursive partitioning analysis.

median survival rates were 13.4 (class I), 9.1 (class II), and 2.4 (class III) months ($P < 0.001$), similar to the results of previous reports.[18,19] BM patients could also benefit from better KPS scores. The Cox hazard model suggested that RPA classification and KPS score were both independent factors that reduced the risk of death.

The relationship between the number of lesions and survival is unclear. Bindal *et al.* reported that patients with multiple BM achieved the same survival as patients with a single metastasis if all of the metastases were surgically resected.[20] Hazuka *et al* and Nakagawa *et al.* showed that patients with multiple metastases suffered more acute symptoms and poorer survival than patients with a single metastasis.[21,22] Our clinical data suggests a statistically significant difference between solitary and multiple metastases ($P < 0.001$). However, Pojskic *et al.* concluded that the mean survival of patients with multiple BM was not statistically different from that of patients with a single metastasis.[18] Similarly, Hong *et al.* showed that outcomes in patients with multiple symptomatic BM who underwent metastasectomy leaving asymptomatic lesions unresected were equivalent to outcomes in patients who underwent complete cerebral metastasectomy.[23] It is possible that postoperative patients received different drugs, the metastases had different molecular characteristics, or the patients had other diseases, which led to a faster death. The number of cranial lesions may not have been a crucial factor.

Postoperative treatment includes WBRT, chemotherapy, and a combination of WBRT and chemotherapy. Adjuvant WBRT improves local tumor control and survival.[13,24–26] Our results showed that WBRT prolonged survival by 3.5 months (12.1 vs. 8.6 months). Interestingly, chemotherapy increased the mean survival duration from 8.6 to 12.3 months, while chemotherapy combined with WBRT could prolong survival to 14.5 months. Multivariate analysis showed that chemotherapy was an independent factor for prolonged survival in postoperative patients. This suggests that systematic therapy is superior to local treatment for BM, and systematic therapy combined with local treatment is a superior treatment choice. However, in patients with a poor postoperative KPS score, supportive care without active treatment is a reasonable alternative.[27]

Salvage therapy after recurrence, such as surgery or radiosurgery, achieved a significant survival advantage in the treated groups. The mean survival after salvage therapy was 17.9 months, with 14.8% of patients living > 24 months and 4.9% living > 36 months; 50% of these patients received salvage therapy. These patients most likely represent a sample with relatively better prognosis because they were eligible for additional salvage therapy.

This study has some limitations. First, as the study was conducted in a single, academic medical center, some referral bias may be present. Second, information on the type of chemotherapy administered to these patients was not available, and some patients received chemotherapy and a subsequent targeted therapy. Third, 60.7% of patients were affected by adenocarcinoma, but there was no integrated information available on *EGFR* mutations or *ALK* rearrangement status, which are both associated with improved outcomes in tyrosine kinase inhibitor treatment. To obtain a complete picture of this group, prospective studies specifically designed to measure the value of these indicators should be performed.

In conclusion, a KPS score ≥ 70, RPA class I/II, and postoperative chemotherapy were independent predictors of better survival for post-craniotomy patients with BM

from NSCLC, while initial onset of intracranial lesions is unfavorable to survival. These findings support the use of personalized therapy for patients with BM from NSCLC. In this era of targeted therapy, prospective randomized trials are required to assess the advantage of different treatment modalities in patients with BM from NSCLC.

Disclosure

No authors report any conflict of interest.

References

1 Chen W, Zheng R, Baade PD *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; **66**: 115–32.
2 Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: New biological insights and recent therapeutic advances. *CA Cancer J Clin* 2011; **61**: 91–112.
3 Travis WD, Brambilla E, Noguchi M *et al*. American Thoracic Society, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: International multidisciplinary classification of lung adenocarcinoma: Executive summary. *Proc Am Thorac Soc* 2011; **8** (5): 381.
4 Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. Factors associated with the development of brain metastases: Analysis of 975 patients with early stage nonsmall cell lung cancer. *Cancer* 2010; **116**: 5038–46.
5 Hsiao SH, Chung CL, Chou YT, Lee HL, Lin SE, Liu HE. Identification of subgroup patients with stage IIIB/IV non-small cell lung cancer at higher risk for brain metastases. *Lung Cancer* 2013; **82**: 319–23.
6 Andrade F, Aguiar PH, Fontes RBV *et al*. Clinical presentation, treatment and outcome of patients with cerebral metastases: The University of Sao Paulo series. *Arq Neuropsiquiatr* 2004; **62**: 808–14.
7 Ruderman NB, Hall TC. Use of glucocorticoids in the palliative treatment of metastatic brain tumors. *Cancer* 1965; **18**: 298–306.
8 Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol Radium Ther Nucl Med* 1971; **111**: 334–6.
9 Trifiletti DM, Brown PD. The role of whole-brain radiation therapy in patients with cerebral metastases. *Cancer* 2018; **124**: 2072–4.
10 Patchell RA, Tibbs PA, Walsh JW *et al*. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; **322**: 494–500.
11 Wronski M, Lederman G. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1997; **80**: 1002–4.
12 Sorensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol* 1988; **6**: 1474–80.
13 Putora PM, Ess S, Panje C *et al*. Prognostic significance of histology after resection of brain metastases and whole brain radiotherapy in non-small cell lung cancer (NSCLC). *Clin Exp Metastasis* 2015; **32**: 143–9.
14 Abrahams JM, Torchia M, Putt M, Kaiser LR, Judy KD. Risk factors affecting survival after brain metastases from non-small cell lung carcinoma: A follow-up study of 70 patients. *J Neurosurg* 2001; **95**: 595–600.
15 Claus EB. Neurosurgical management of metastases in the central nervous system. *Nat Rev Clin Oncol* 2011; **9**: 79–86.
16 Magilligan DJ Jr, Duvernoy C, Malik G, Lewis JW Jr, Knighton R, Ausman JI. Surgical approach to lung cancer with solitary cerebral metastasis: Twenty-five years' experience. *Ann Thorac Surg* 1986; **42** (4): 360.
17 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.
18 Pojskic M, Bopp MHA, Schymalla M, Nimsky C, Carl B. Retrospective study of 229 surgically treated patients with brain metastases: Prognostic factors, outcome and comparison of recursive partitioning analysis and diagnosis-specific graded prognostic assessment. *Surg Neurol Int* 2017; **8**: 259.
19 Nieder C, Nestle U, Motaref B, Walter K, Niewald M, Schnabel K. Prognostic factors in brain metastases: Should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes? *Int J Radiat Oncol Biol Phys* 2000; **46**: 297–302.
20 Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. *J Neurosurg* 1993; **79**: 210–6.
21 Hazuka MB, Burleson WD, Stroud DN, Leonard CE, Lillehei KO, Kinzie JJ. Multiple brain metastases are associated with poor survival in patients treated with surgery and radiotherapy. *J Clin Oncol* 1993; **11**: 369–73.
22 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.
23 Hong N, Yoo H, Gwak HS, Shin SH, Lee SH. Outcome of surgical resection of symptomatic cerebral lesions in non-small cell lung cancer patients with multiple brain metastases. *Brain Tumor Res Treat* 2013; **1**: 64–70.
24 Slottje DF, Kim JH, Wang L *et al*. Adjuvant whole brain radiation following resection of brain metastases. *J Clin Neurosci* 2013; **20**: 771–5.
25 Mekhail T, Sombeck M, Sollaccio R. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: Results of the EORTC 22952-26001 study. *Curr Oncol Rep* 2011; **13**: 255–8.
26 Lam TC, Sahgal A, Lo SS, Chang EL. An update on radiation therapy for brain metastases. *Chin Clin Oncol* 2017; **6**: 35.
27 Nieder C, Norum J, Dalhaug A, Aandahl G, Pawinski A. Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. *Clin Exp Metastasis* 2013; **30**: 723–9.

