Original Article

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

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

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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; 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.\textsuperscript{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 institutional 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
Brain metastases are an increasingly common malignant cancer complication. Approximately half of the patients with NSCLC develop BM during the course of their disease.\textsuperscript{12} Advances in diagnostic and therapeutic approaches have largely improved craniotomy for BM. Nevertheless,
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). 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. 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. In this study, patients were also classified into three classes according to the RPA classification: the

Table 2 Survival analysis of different treatment modalities for primary lesions

| Treatment of primary | No. of patients (n, %) | Median survival (months) | One-year survival | Two-year survival | Three-year survival |
|---------------------|------------------------|--------------------------|-------------------|------------------|-------------------|
| Surgery             | 39 (14.8%)             | 11.2                     | 48.70%            | 26%              | 8.80%             |
| Chemotherapy/radiotherapy | 22 (13.9%)        | 9.9                      | 40.90%            | 24.50%           | 6.10%             |
| Non-treatment       | 61 (41.0%)             | 9.5                      | 32.80%            | 8.20%            | 0                 |

Chemo, chemotherapy; WBRT, whole brain radiotherapy.

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.

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.
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 \textit{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 \textit{et al.} and Nakagawa \textit{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 \textit{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 \textit{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 \((12.1 \,\text{vs.} \,8.6 \,\text{months})\). 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 \textit{EGFR} mutations or \textit{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 \(\geq \,70\), RPA class I/II, and postoperative chemotherapy were independent predictors of better survival for post-craniotomy patients with BM.

### Table 1: Multivariate Analysis of Prognostic Factors Associated with Overall Survival

| Variable | HR (95% CI) | \(P\) |
|----------|-------------|------|
| Initial onset of intracranial lesions | 2.983 (1.533–5.804) | 0.001 |
| Postoperative chemotherapy | 0.087 (0.015–0.514) | < 0.001 |
| RPA I/II | 0.03 (0.005–0.169) | < 0.001 |
| KPS score | 0.152 (0.025–0.917) | 0.04 |

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.
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.

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