Whole Brain Radiotherapy-Based Combined Modality Treatment of Brain Metastases from Non-Small Cell Lung Cancer: A Retrospective Analysis of Prognostic Factors

Zhenfei Xiang, Jun Chen, Huanle Zhang, Li Shen, Qichun Wei

Introduction

Non-small lung cancer (NSCLC) is reportedly the most common primary tumor in patients with brain metastases, and brain metastases occur in up to 40% of NSCLC patients in the course of disease [1, 2]. Whole brain radiation therapy (WBRT) is currently considered to be the primary treatment modality for patient with multiple brain metastases. However, the outcome for such patients remains poor, with median survival after WBRT alone in the range of 3–6 months [3]. Longer survival times have been reported in patients who received a radiation boost delivered after WBRT [4].

A combination treatment of WBRT and stereotactic boost improved survival in patients with a single unresectable brain metastasis, and could also be considered for patients with 2 or 3 brain metastases [5, 6]. Roberge et al. [5] reported median overall survival of 17.6 months following a combination of surgery, WBRT, and stereotactic radiosurgery. Treatment delivery consisting of integrated WBRT and boost doses to multiple brain metastases has been considered to be feasible and safe, and the clinical benefit of this approach with respect to intracranial disease control is being investigated in phase II studies [7, 8]. With regard to systemic therapeutics, chemotherapy showed effectiveness in increasing the survival of patients with brain metastases from NSCLC up to 58.1 weeks [9], and previous studies have also indicated that concomitant use of WBRT and tyrosine kinase inhibitors (EGFR-TKIs) for NSCLC brain metastases was well tolerated with a median overall survival of up to 11.8 and 13 months, respectively [10, 11]. Given the above evidence, WBRT-based combined modality treatment might improve the survival of patients with brain metastases from NSCLC.

Keywords
Prognostic factor · Brain metastases · Non-small cell lung cancer · Whole brain radiotherapy · Radiation boost

Summary
Background: The prognostic factors for patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy (WBRT)-based combined modality therapy were investigated. Materials and Methods: Out of 135 patients treated with WBRT, 47 (34.8%) received a radiation boost, 84 (62.2%) underwent systemic chemotherapy, and 39 (28.9%) were given epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Results: The mean survival time was 9.3 months, and the 1-year and 2-year survival rates were 46.3 and 16.1%, respectively. In univariate analysis, improved survival was associated with age < 60 years, no extracranial metastasis, Karnofsky performance score $\geq 70$, $\geq 3$ cycles of chemotherapy after diagnosis of brain metastases, combined treatment with EGFR-TKIs, and no metastases in the cerebellum. In multivariate analysis, the above prognostic factors maintained significance with the exception of age. In an additional analysis of the 58 patients with 1–3 brain metastases, combination of WBRT with radiation boost was associated with better survival. Conclusion: We confirm previously described prognostic factors. Moreover, we found the absence of cerebellar metastases to be an independent prognostic factor for favorable outcome.

Received: September 9, 2014
Accepted: November 27, 2014
Published online: January 12, 2015

Dr. Li Shen
Department of Radiation Oncology
the Second Affiliated Hospital, Zhejiang University School of Medicine
Jifuang Road #88, Hangzhou 310009, China
lidly0506@hotmail.com

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2296-5270/15/00381-0035$39.50/0

Co-corresponding author: Dr. Qichun Wei, National Ministry of Education Key Laboratory of Cancer Prevention and Intervention, Zhejiang University School of Medicine, Hangzhou 310009, China; Qichun_Wei@zju.edu.cn
In earlier reports, the diagnosis of brain metastases was mainly based on contrast-enhanced computed tomography (CT). As CT is insensitive in the detection of small brain metastases, the number of metastases might be underestimated [12–14] and some brainstem or cerebellar metastases omitted, thus yielding a relatively worse outcome for CT-based therapeutics [14]. In recent years, contrast-enhanced magnetic resonance imaging (MRI) has become the standard screening method for brain metastases. Differences on prognosis and treatment modality might exist regarding the variations between MRI- and CT-based diagnosis [14, 15].

In this study, 135 patients with brain metastases from NSCLC were retrospectively analyzed, and the diagnosis was made based on contrast-enhanced brain MRI. All patients underwent WBRT, and a considerable fraction received systemic chemotherapy, EGFR-TKIs, or external beam radiotherapy boost. The aim of this study was to assess the survival of patients with brain metastases from lung cancer, identify prognostic factors, and perhaps provide beneficial information for the management of brain metastases in lung cancer patients.

### Materials and Methods

The present study was approved by the Institutional Review Board. Between March, 2007 and December, 2012, a total of 135 patients underwent WBRT for brain metastases from lung cancer at Ningbo Medical Center, Lihuili Hospital, including 80 males and 55 females, ranging in age from 31 to 77 years (mean age 54 years). Patients with NSCLC were diagnosed based on histopathology or cytology. Of the 135 patients, 127 patients had contrast-enhanced MRI data available for evaluation, the other 8 cases only had written diagnostic reports of contrast-enhanced brain MRI. Among the 8 reports, 5 contained no description of the size of each brain metastasis, and 4 did not specify the number of brain metastases. Patients who had been diagnosed using CT or non-contrast-enhanced MRI only were not included. Most of the patients had 4 or more brain metastases (51.9%, 68/131), and 21.4% (28/131) had solitary metastases. 52.3% of the patients (68/130) had metastases in the cerebellum, 7.0% (9/130) had metastases (51.9%, 68/131), and 21.4% (28/131) had solitary metastases. The clinical characteristics are provided in table 1.

Of the 135 patients, 122 (90.4%) completed the prescribed WBRT dose (40 Gy/20 fractions or 30 Gy/10 fractions); the other 13 (9.6%) patients received only part of the planned WBRT dose (9–28 Gy). After WBRT, radiation boost was delivered to 47 patients; of those, 31 (23.0%) patients received an external beam X-ray radiotherapy boost (median boost dose 9 Gy, range 6–18 Gy), and 16 (11.9%) patients underwent gamma knife treatment (usually 12.8 Gy in 4 fractions). In addition, 4 patients underwent craniotomy for tumor resection surgery.

Of the 135 enrolled patients, 84 (62.2%) underwent systemic chemotherapy (1–10 cycles, median 3 cycles) after a diagnosis of brain metastases from lung cancer; chemotherapy drugs mainly included cisplatin, carboplatin, nedaplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, and pemetrexed. Most of these patients were given a platinum-based 2-drug combination treatment, while a small number of patients was treated with docetaxel single-agent chemotherapy. 39 patients were given EGFR-TKIs (gefitinib or erlotinib) until disease progression or intolerance.

Follow-up information was collected during clinic visits or by telephone, and the date of death was derived from the Ningbo City residents registration system. Survival time was calculated from the date of diagnosis of brain metastases to the date of death. Analyses were performed using SPSS software, version 21.0 (IBM Corp., Armonk, NY, USA). The Kaplan-Meier method was used to calculate survival rate, the log-rank test for gap analysis, and Cox regression for multivariate analysis (backward: likelihood ratio). p values of < 0.05 were considered to indicate statistical significance.

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### Table 1. General characteristics of 135 patients with brain metastases (BM) from non-small cell lung cancer

<table>
<thead>
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<th>Characteristics</th>
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<td>&lt; 60</td>
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<td>KPS</td>
<td></td>
</tr>
<tr>
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<td>25</td>
</tr>
<tr>
<td>≥ 70</td>
<td>108</td>
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<td>unknown</td>
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</tr>
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<td>89</td>
</tr>
<tr>
<td>no</td>
<td>46</td>
</tr>
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<td>≥ 3</td>
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</table>

KPS = Karnofsky performance score; WBRT = whole brain radiotherapy; CT = chemotherapy; EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors.
Results

Figure 1 shows the Kaplan-Meier survival curve; the mean survival time was 9.3 months. 1-year and 2-year survival rates were 46.3 and 16.1%, respectively. As shown in table 2, patients who received a combination of WBRT and radiation boost had a better outcome, and those who did not complete WBRT had a short survival time.

In univariate analysis of the entire cohort, improved survival was associated with age < 60 years (p = 0.023), no extracranial metastasis (p = 0.018), Karnofsky performance score (KPS) > 70 (p = 0.004), ≥ 3 cycles of chemotherapy after diagnosis of brain metastases (p < 0.001), combined treatment with targeted therapy (p = 0.005), and no metastases in the cerebellum (p = 0.015). The p values for adenocarcinoma and 1–3 brain metastases versus > 3 brain metastases were marginal (0.052 and 0.097, respectively). The results of the univariate analysis are summarized in table 3.

In multivariate analysis, KPS (risk ratio (RR) 0.382; 95% confidence interval (CI) 0.224–0.651; p = 0.001), extracranial metastasis (RR 1.964; 95% CI 1.212–3.184; p = 0.006), combined treatment with targeted therapy (RR 0.408; 95% CI 0.250–0.666; p < 0.001), number of cycles of chemotherapy after diagnosis of brain metastases (RR 0.498; 95% CI 0.303–0.820; p = 0.006), and cerebellar metastases (RR 1.911; 95% CI 1.238–2.950; p = 0.003) maintained significance.

In an additional analysis of the 58 patients with 1–3 brain metastases, ≥ 3 cycles of chemotherapy after diagnosis of brain metastases (p = 0.001), combined treatment with targeted therapy (p = 0.023), and combination of WBRT with radiation boost (p = 0.009) were associated with survival in univariate analysis. In multivariate analysis, ≥ 3 cycles of chemotherapy after diagnosis of brain metastases (RR 0.028; 95% CI 0.125–0.236; p = 0.002) and combination of WBRT with radiation boost (RR 0.362; 95% CI 0.171–0.765; p < 0.008) maintained significance.

In an additional analysis of the 57 patients with > 3 brain metastases, extracranial metastasis (RR 3.202; 95% CI 1.442–7.114; p = 0.004), ≥ 3 cycles of chemotherapy after diagnosis of brain metastases (RR 0.384; 95% CI 0.185–0.794; p = 0.010), combined treatment with targeted therapy (RR 0.367; 95% CI 0.177–0.763; p = 0.007), and cerebellar metastases (RR 2.475; 95% CI 1.107–5.535; p = 0.027) were correlated with survival in multivariate analysis. Radiation boost had no impact on patient survival. The results were similar to those of the analysis of the entire cohort.

Discussion

In the present study of brain metastases from NSCLC treated with WBRT-based combined modality therapy, the significant positive prognostic factors for overall survival after a diagnosis of brain metastases included good performance status, no extracranial metastasis, no cerebellar metastases, ≥ 3 cycles of chemotherapy after diagnosis of brain metastases, and combination treatment with EGFR-TKIs. Furthermore, in patients with 1–3 brain metastases, significant positive prognostic factors included ≥ 3 cycles of chemotherapy after a diagnosis of brain metastases and a combination of WBRT with radiation boost. In previous reports, several prognostic factors were identified for patients with brain metastasis from NSCLC, including age, performance status, number of brain metastases, and extracranial metastases [16, 17]. In a retrospective study by Gerdan et al. [18], the number of involved extracranial organs was found to be an additional prognostic factor in patients with brain metastasis from NSCLC; patients with involvement of only 1 extracranial organ had better survival than those with involvement of 2 or more extracranial organs.

According to our study, active systemic chemotherapy after a diagnosis of brain metastases should be considered a prognostic factor in patients with brain metastasis from NSCLC. Patients who received 3 or more cycles of systemic chemotherapy had a significantly better survival than patients with less chemotherapy cycles. The result is consistent with previous reports [9]. The brain requires a stable internal environment, which is established by an intact blood-brain barrier. The efficacy of chemotherapy for brain malignancies is often hampered by the presence of the blood-brain barrier.

Table 2. Survival of patients treated with whole brain radiotherapy (WBRT) alone or WBRT plus boost

<table>
<thead>
<tr>
<th>Survival</th>
<th>WBRT alone</th>
<th>WBRT + boost</th>
<th>Non-completed WBRT</th>
</tr>
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<tr>
<td>MST, months</td>
<td>7.3</td>
<td>16.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Survival at 6 months, %</td>
<td>57.1</td>
<td>76.1</td>
<td>23.1</td>
</tr>
<tr>
<td>Survival at 12 months, %</td>
<td>41.8</td>
<td>62.5</td>
<td>0.0</td>
</tr>
</tbody>
</table>

MST = Mean survival time.

Fig. 1. Overall survival in 135 patients with brain metastases from non-small cell lung cancer treated with whole brain radiotherapy-based combined modality therapy.
However, the integrity of the barrier may become compromised during tumor growth, as a result of more permeable tumor vessels. Brain radiation with a dose of 20–30 Gy in 2-Gy fractions may also increase the permeability of the blood-brain barrier, permitting increased drug entry [19]. Thus, systemic chemotherapy could be effective in the management of brain metastases. Moreover, 65.9% of the analyzed cases in this study had extracranial metastases; active chemotherapy might also be helpful in controlling disseminated lesions beyond the brain.

The results of the present study indicated that targeted therapy with EGFR-TKIs was associated with survival benefit. In agreement with our findings, Welsh et al. [10] in their phase II trial of erlotinib plus concurrent WBRT for patients with brain metastases from NSCLC found a median survival time of 11.8 months. In another study by Ma et al. [11], the concomitant use of WBRT and gefitinib for NSCLC brain metastases was well tolerated, with a median overall survival of 13 months. In addition, EGFR-TKIs have exhibited favorable effects on brain metastases in several studies [20–22], and improvement in the treatment response to EGFR-TKIs following radiotherapy has also been reported [23, 24]. Cersoli et al. [24] conducted a prospective study with the aim to evaluate the efficacy of gefitinib in pretreated patients with brain metastases from NSCLC. 41 consecutive NSCLC patients with measurable brain metastases were treated with gefitinib, 18 of them

<table>
<thead>
<tr>
<th></th>
<th>MST, months</th>
<th>Survival at 6 months, %</th>
<th>Survival at 12 months, %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>6.3</td>
<td>51.9</td>
<td>35.5</td>
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<tr>
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<td>13.6</td>
<td>67.7</td>
<td>53.3</td>
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<td></td>
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</tr>
<tr>
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<td>7.5</td>
<td>58.8</td>
<td>43.5</td>
<td></td>
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<tr>
<td>Female</td>
<td>12.9</td>
<td>63.6</td>
<td>50.3</td>
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<td>51.5</td>
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<td>13.8</td>
<td>70.6</td>
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MST = Median survival time; KPS = Karnofsky performance score; CT = chemotherapy; EGFR-TKIs = epidermal growth factor receptor tyrosine kinase inhibitors.
having previously been treated with WBRT. The disease control rate was higher in patients pre-treated with WBRT compared to those who did not receive WBRT (56 vs. 9%). The authors hypothesized that WBRT may disrupt the blood-brain barrier, resulting in an increase in TKI entrance, or that WBRT may induce the development of radiation-resistant clones that may be more sensitive to an alternative treatment modality such as EGFR-TKIs.

In the present retrospective study, EGFR-TKIs were administered as a second-line treatment after the diagnosis of brain metastases; EGFR mutations were not routinely analyzed. According to the literature, in Asian patients [25, 26], high frequencies (e.g., 52.9%, 63%) of EGFR mutations have been detected in brain metastases from NSCLC, and a high concordance rate of EGFR mutation status was found between brain metastases and the corresponding primary lung lesions [25]. It could be speculated that NSCLC patients with brain metastases have a higher than usual probability of EGFR mutations, which may partially explain the effectiveness of EGFR-TKIs in the treatment of brain metastases. According to the report by Casanova et al. [27], the pattern of disease progression for brain metastases from NSCLC was mainly extracranial, and more than 70% of patients with disease progression died from systemic disease. Extracranial lesions might also benefit from oral administration of EGFR-TKIs.

In this study, patients with metastases in the cerebellum had a worse outcome. According to the report by Ghia et al. [28], the most common location for metastatic disease are the cerebral hemispheres, and cerebellar metastases account for approximately 20% of brain metastases. In the present series, more than half of the cases had metastatic lesions in the cerebellum. Patients with cerebellar metastases usually have a worse performance status, which may be one of the reasons for the worse outcome. Due to the retrospective nature of our data, whether or not cerebellar metastases from NSCLC could serve as a prognostic indicator, needs to be verified.

The effect of radiation boost following WBRT on survival in patients with 1–3 brain metastases was the main finding of this analysis. The addition of a radiation boost to WBRT appeared to substantially increase the median overall survival to approximately 17.8 months. Since the literature on external beam radiation boost following WBRT for the management of brain metastases is sparse, it was difficult to compare our results to outcome after stereotactic radiosurgery boost following WBRT. According to a report of the DEGRO (Deutsche Gesellschaft für Radioonkologie) on stereotactic radiotherapy [29] and the literature referred to in the report [6, 30], adding stereotactic radiosurgery as boost to WBRT was recommended for several subgroups of patients with brain metastases. In the RTOG 9508 study [6], patients with a single brain metastasis treated with adjuvant stereotactic radiosurgery boost following WBRT had significantly better survival than those without boost treatment. The data also support the use of stereotactic surgery boost after WBRT to improve performance in patients with up to 3 brain metastases. In a trial conducted by Kondziolka et al. [30], patients with 2–4 brain metastases were randomized to WBRT alone or WBRT plus stereotactic radiosurgery; better local control was seen in the group with stereotactic radiosurgery boost. Moreover, when stereotactic radiosurgery alone was employed in the treatment of brain metastases, higher doses (18 and 20 Gy) resulted in better local control than lower doses (13–16 Gy) [31]. However, in the RTOG 9508 study, metastases of up to 2 cm in broadest diameter were given a stereotactic radiosurgery dose of 24 Gy as a boost after WBRT; corresponding doses were 18 and 15 Gy for metastases of no more than 3 and 4 cm, respectively [6].

Several retrospective studies have been carried out concerning radiation boost following WBRT for patients after brain metastasectomy. In a Swiss retrospective study by Casanova et al. [27], a total of 53 patients with brain metastases from lung cancer were treated with WBRT followed by an external beam radiotherapy boost (median boost dose 9 Gy, range 7.5–18 Gy); brain metastasectomy was performed in 38 (72%) patients. The authors concluded that a subgroup of younger patients with good performance status and no extracranial disease might benefit from a dose escalation after WBRT to the metastatic site. Likewise, after surgical resection of 1–2 brain metastases, a boost of 10–15 Gy in addition to WBRT was found to improve outcome [32]. Our results are in line with the above retrospective analyses of patients with 1–2 or 1–3 brain metastases.

In our study, the diagnosis of brain metastases was made based on contrast-enhanced brain MRI, and in 37.7% of the patients the brain metastases were asymptomatic. Contrast-enhanced MRI has been demonstrated to be very sensitive in the detection of small lesions. Post-contrast MRI was capable of detecting asymptomatic metastatic brain lesions that were missed on contrast-enhanced CT in lung cancer patients, and can be regarded as superior to contrast-enhanced CT in diagnosing occult brain metastases [12–14]. Yokoi et al. [33] reported median survival times of 10 months for CT-detected brain metastases and 17 months for MRI-detected brain metastases. Patients who presented with symptomatic brain metastases had worse clinical outcomes as compared to those without symptoms. A high percentage of patients had occult brain metastases diagnosed by contrast-enhanced MRI, which might partially account for the relatively good outcome of the studied cohort.

WBRT has become the standard of care for patients with brain metastases since its beginning in the 1970s. It improves patient survival as well as quality of life. The survival time of patients with brain metastases from lung cancer treated with WBRT alone ranged from 3 to 6 months [3]. It has also been reported that a radiation boost delivered after WBRT increased median overall survival to 11.2 months [4]. In the present study, the mean survival time of the entire cohort was 9.3 months, the 1-year survival rate was 45.4%, and the 2-year survival rate was 14.5%. Possible explanations for the better outcome compared to previously reported data for this patient group include i) good performance status in the majority of patients, and ii) active systemic therapeutics in addition to WBRT, as more than 60% of the patients received chemotherapy and around 30% received EGFR-TKIs. Additionally, a high proportion of those with 1–3 brain metastases received a radiation boost following WBRT. However, given the retrospective nature of this study, the better overall survival may also have been attributable to less advanced disease or favorable biological behavior.
References

8. Rodrigues G, Yartsev S, Yaremko B, Perera F, Dar AR, Ma S, Xu Y, Deng Q, Yu X: Treatment of brain metastases was found to be an independent prognostic factor for favorable outcome, and patients with 1–3 brain metastases might benefit from a radiation boost following WBRT.

Acknowledgment

The authors thank all colleagues at the Department of Radiation Oncology. This work was supported by the National Natural Science Foundation of China (No. 81071823 and 81201811) and Zhejiang University Research Foundation.

Disclosure Statement

All of the authors declare that there are no conflicts of interest in connection with this paper.

Xiang/Chen/Zhang/Shen/Wei