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Prognostic factors and long-term survival in surgically treated brain metastases from non-small cell lung cancer

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ABSTRACT

Objective: Brain metastases (BMs) are the most common malignant brain tumors in adults. Despite multimodal treatment options such as microsurgery, radiotherapy and chemotherapy, prognosis still remains very poor. Non-small cell lung cancer (NSCLC) constitutes the most common source of brain metastases. In this study, prognostic factors in this patient population were identified through an in-depth analysis of clinical parameters of patients with BMs from NSCLC.
Patients and methods: Clinical data of 114 NSCLC cancer patients who underwent surgery for BMs at the University Hospital Heidelberg were retrospectively reviewed for age, gender, type of treatment, time course of the disease, presence of neurologic symptoms, Karnofsky Performance Status (KPS), smoking history, presence of extracranial metastases at initial diagnosis of NSCLC, number, location and size of brain metastases. Univariate and multivariate survival analyses were performed using the Log-rank test and Cox' proportional hazard model, respectively.
Results: Median survival time from surgery for BMs was 11.2 months. 18.4% (21 of 114) patients were long-term survivors (>24 months; range 26.3–75.1 months). Age, gender, size and number of intracranial metastases were not significantly associated with patient survival. Univariate analysis identified complete resection, postoperative whole brain radiotherapy (WBRT) and a preoperative KPS of >80% as positive prognostic factors. Infratentorial location and presence of extracranial metastases were shown to be negative prognostic factors. Surgery for the primary tumor was associated with a superior patient outcome both in univariate and multivariate analyses.
Conclusion: Our data strongly suggest that surgical treatment of the primary tumor and complete resection of brain metastases in NSCLC patients followed by WBRT improve survival. Moreover, long-term survivors (>2 years) were more frequent than previously reported.

1. Introduction

Brain metastases (BM) are the most common malignant central nervous system lesions in adults [1]. Clinical studies report spread to the brain in 40% of patients with malignant tumors, whereas autopsy reports suggest even higher numbers [2–4]. The rising incidence of BMs has been attributed to advancements in the control of the primary disease and increasing availability of contrast enhanced magnetic resonance imaging (MRI) [5–7]. In most cases, BMs are derived from lung cancer. Among these, non-small cell lung cancer (NSCLC) is the most common subtype and thus responsible for the majority of cases. Other common primary tumors include cancer of the breast, skin and kidney [8–10].

In addition to systemic chemotherapy for the primary tumor, specific treatment of BMs includes microsurgical resection and radiotherapy. There is evidence that complete resection of BMs in addition to whole brain radiotherapy (WBRT) improves survival time, recurrence-free survival and functional independence [11–14]. However, there is no definite consensus about the significance of microsurgery as compared to radiosurgery [8]. In small-sized lesions without mass effect both treatments seem to provide equal benefit, whereas surgery should be preferred in patients with unknown primary disease or mass effect, especially in

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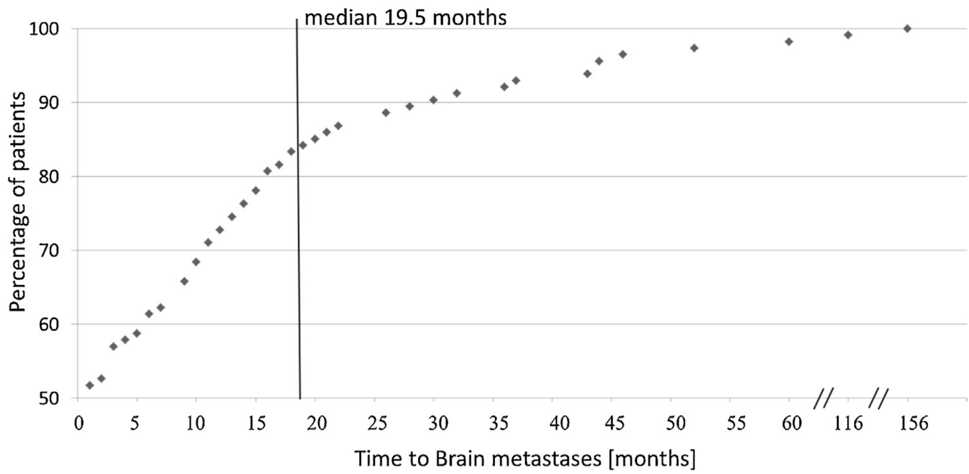

Fig. 1. Time (in months) from diagnosis of the primary tumor to brain metastases. The vertical line indicates a median of 19.5 months from diagnosis of the primary to BMs.

infratentorial lesions [15–17]. Even in the setting of multiple BMs, which account for over 50% of patients [6,7], complete microsurgical resection of all detectable BMs can be considered [18,19].

The overall survival (OS) of patients diagnosed with BMs is about 4–15 months [10,11,17,20,21]. There are different scores to estimate prognosis. Known prognostic factors include age, Karnofsky Performance Status (KPS), extracranial tumor control and the number of BMs [22–25]. Since NSCLC represents the most important and clinically relevant primary site [26], we focused our analysis exclusively on patients who received surgery for brain metastases from this entity. The homogeneity of this patient population regarding the primary tumor allows assessing survival determining parameters of extracranial disease and BMs more reliably, which is essential for investigating prognostic factors for the treatment of BMs.

2. Patients and methods

In this retrospective analysis, 141 patients undergoing first surgery for BMs from NSCLC at our department between 2002 and 2013 were identified of which 114 patients with sufficient follow-up data were included into survival analysis. Surgery for BMs was offered to patients with cerebellar lesions, unknown primary disease, large lesions causing considerable mass effect and neurologic symptoms and lesions with associated bleeding, amongst others. Data were collected by reviewing charts and contacting hospitals and registration offices. Patients were analyzed with respect to age, gender, type of treatment, time course of the disease, presence of neurologic symptoms, KPS, smoking history, presence of extracranial metastases at the initial diagnosis of NSCLC, number, location and size of BMs. Mean age at diagnosis of BMs was 62 years (range 40–82 years). The extent of resection was determined by the surgeon's estimation in the surgical report. Complete resection was defined as gross total resection of all BMs depicted on preoperative imaging. Therefore incomplete resection was either due to multiple metastases, where not all could be resected, or due to location and intraoperative considerations, e.g., infiltration of eloquent areas. Concerning treatment of the primary tumor, patients were split into two groups: surgical resection vs. conservative treatment only, e.g., radiotherapy and/or chemotherapy.

Patient survival was specified as time to death after surgery for BMs throughout the analysis. At the time of data assessment 25 patients were still alive. A positive vote from the local ethics committee was obtained and patients consented to the use of their clinical data for research purposes. The majority of patients ($n = 102$, 89.5%) received surgery within one month after diagnosis of BMs. The remainder ($n = 12$, 10.5%) underwent surgery within 2–6 months after diagnosis of BMs.

2.1. Statistical analysis

Overall survival rates (SR) were calculated using the Kaplan–Meier method. Differences between survival curves were determined using the Log-rank test and Tarone–Ware test for non-crossing and crossing Kaplan-Meier curves, respectively. Hazard ratios (HRs) with 95% confidence intervals (CI) were calculated based on a Cox' proportional hazard regression model using the following variables: (i) KPS >80%, (ii) location (infra- vs. supratentorial), (iii) extent of resection of BMs, (iv) extracranial vs. no extracranial metastases, (v) postoperative WBRT and (vi) surgical treatment of the primary tumor. Only cases with available data for all these variables ($n = 72$) were included in multivariate survival analysis. Comparison of long-term survivors (>2 years; LTS) and short-term survivors (≤2 years; STS) was performed using Fisher's exact test. Statistical analysis was conducted with XlSTAT (Microsoft) and SAS (v9.1). For all analyses, p-values <0.05 were considered as statistically significant.

3. Results

3.1. Location

Concerning location of singular and solitary BMs ($n = 75$), most patients had frontal ($n = 32$, 42.7%) or infratentorial ($n = 15$, 20%) BMs, whereas 10 (13.3%) had parietal, 9 (12%) occipital and 9 (12%) temporal metastases. For multiple BMs ($n = 38$), 21 patients (55.3%) had supratentorial spread, 1 patient (2.6%) had multiple infratentorial BMs, whereas 16 patients (42.1%) had supra- and infratentorial lesions.

3.2. Chronology of metastases

BMs were the first clinical presentation of lung cancer in 44 (38.6%) patients. Among the remainder of the patient cohort ($n = 70$, 61.4%), the time period from diagnosis of NSCLC to occurrence of BMs ranged up to 156 months (Fig. 1). Altogether, there were 59 (51.7%) patients with synchronous (<2 months) and 55 (48.3%) patients with metachronous BMs (≥2 months).