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Prevalence and risk factors of brain metastases in patients with newly diagnosed advanced non-small-cell lung cancer

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ABSTRACT

Micro-abstract: Brain metastases are a frequent finding in patients with advanced non-small cell lung cancer (NSCLC). The characteristics of 118 patients with synchronous brain metastases (BM) out of a cohort of 678 individuals with advanced NSCLC (17%) are reported, with synchronous BM having a negative impact on survival. Prognostic factors for survival of the patients with and without BM are presented.

Background: Brain metastases occur frequently in patients with newly diagnosed non-small cell lung cancer. We aim to describe the characteristics, treatment and course of disease in patients with synchronous BM in an advanced NSCLC cohort, and to comparatively analyze prognostic factors for patients with and without BM.

Patients and methods: Of 678 consecutive unselected patients with stage IV NSCLC, 118 presented with synchronous BM (17%; 95% confidence interval [CI]: 15–20%). The patient characteristics, prognostic factors, therapeutic approach and use of specific therapeutic measures including systemic treatment were analyzed.

Results: BM were found more frequently in younger patients, females, non-smokers and those with a lower thoracic stage. 29% of patients with BM exhibited neurologic symptoms. Patients with BM showed worse overall survival (median survival 8.0 vs 9.7 months; HR 1.24 [1.05–1.54]; $p=0.045$). In multivariable analysis poor performance status at diagnosis showed the strongest negative association with survival.

Conclusion: Synchronous BM are frequent among patients with NSCLC even in early thoracic stages and negatively impact survival. Based on the findings presented in this paper, a therapy algorithm for treating BM is proposed, with systemic therapy being one valuable option.

1. Introduction

Lung cancer is one of the most common types of cancer and the leading cause of cancer death worldwide (www.who.int). Non-small cell lung cancer (NSCLC) accounts for 80–85% of the cases and most patients are diagnosed in advanced stages of the disease [1] or will progress after surgery. Between 15% and 22% of patients with stage IV NSCLC exhibit synchronous brain metastases (BM) at time of diagnosis [2–5], and up to 40% will eventually develop brain metastases during the course of their disease. Little is known about the course of patients with synchronous BM and their response to systemic therapies since most clinical studies exclude their participation.

The acute treatment of patients with symptomatic BM usually involves systemic steroids, but there is no generally accepted standard approach to specific therapy. Surgery or radiotherapy are often used early in the course of disease, whereas the value of systemic treatments is still under discussion [6]. The assumption that chemotherapy is ineffective in this setting because of poor penetration of the blood-brain barrier has been called into question by data showing increased permeability in patients with BM

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[7].

We present data on a cohort of unselected patients with metastatic NSCLC treated at our centre and show the characteristics of patients with and without synchronous BM. Furthermore, we explore prognostic factors for survival of patients with BM and the use of local and systemic treatments. On the basis of our findings, the literature, and our experience, we propose a practical treatment algorithm for patients with stage IV NSCLC and synchronous BM.

2. Patients and methods

An access data base was first launched in 2003 and since then prospective data of all patients seen with any malignant diseases on our oncological ward at the Asklepios Lung Hospital have been entered. The data base has been described in detail before [5]. In brief, all information on patient demographics, histology, the exact tumour stage including metastases location and all therapeutic measures, time and type of tumour progression were documented. Out of this data pool all patients with histologically or cytologically confirmed primary advanced NSCLC (stage IV according to 6th ed. of TNM classification) were included in this prospective observational study. In the majority of the cases histological diagnosis was confirmed by immunohistochemistry. Molecular analyses were not routinely performed during the study period. From January 2003 to December 2010, 678 unselected consecutive patients were included for further analyses.

Routine imaging using enhanced CT scan of the chest, brain, upper abdomen, and bone scan was performed in all patients at baseline. In case of doubt, or when single brain lesions were suspected at baseline, additional MRT scans of the CNS were performed. Most patients underwent systemic treatment at our centre or were referred to cooperating centres for radiotherapy. In those patients who were subsequently treated at our centre sequential CT scans were performed every second cycle (every 6 weeks) during chemotherapy and/or after radiotherapy, and every 12 weeks during treatment free intervals in clinically stable patients. For patients lost to follow up information on mortality status was obtained from the regional tumour registry.

3. Statistical analyses

Survival probabilities were estimated by using the Kaplan Meier method. The log-rank test was used to compare survival curves between independent sub groups. Survival time was specified as the interval (in days) between the date of diagnosis until date of death or loss to follow-up.

Age, gender and Karnofsky performance score (KIN) were considered to be potential confounding variables and generally included in the multivariable analyses. To identify other potentially relevant variables univariable testing was carried out prior to establishing multivariable models.

Uni- and multivariable analyses were performed by Cox proportional hazard models.

All statistical tests were conducted two-sided at a local type I error level of 5%. No multiplicity correction of *p*-values was applied. 95% confidence intervals were reported for estimated proportions and hazard ratios.

All analysis were carried out using the statistical software package R (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.).

4. Results

Between January 2003 and December 2010a total of 678 patients were diagnosed with stage IV NSCLC. At the time of analysis, 582 patients had died (85.8%); median time of observation was 262 days (37.4 weeks; min/max 1–447 weeks), and one EGFR mutated patient with initial pleural carcinosis was still alive after 8 years. The median survival of the total cohort was 288 days (9.6 months), with survival rates ($\pm$ standard error) of 69% ($\pm$ 18), 41% ($\pm$ 19), and 15% ($\pm$ 15) at 6, 12, and 24 months. The patient characteristics of the whole patient group with advanced NSCLC which served as the source population are shown in table 1.

One hundred and eighteen of the 678 patients (17%; 95% confidence interval [CI]: 15–20%) were found to have synchronous

Table 1
Patient characteristics of total patient group and subgroup with and without synchronous brain metastases.

NSCLC, stage IV	**All patients (% of total)**	**With SBM (% of group)**	**Without SBM (% of group)**	**χ^2 test SBM=1 vs SBM=0**
Total cohort	678 (100)	118 (100)	560 (100)	*p*-value
Age-median [range]	66 years [27; 91]	62 years [32; 83]	66 years [27; 91]	**0.001**
< 65 years	303 (44.7)	69 (58.5)	234 (41.8)	
≥ 65 years	375 (55.3)	49 (41.5)	326 (58.2)	
Sex				**0.004**
Male	429 (63.3)	62 (52.5)	367 (65.5)	
Female	249 (36.7)	56 (47.5)	193 (34.5)	
ECOG (KIN %)				**0.627**
0 (90–100)	329 (48.5)	62 (52.5)	267 (47.6)	
1 (80–70)	276 (40.7)	44 (37.3)	232 (41.4)	
≥ 2 (≤ 60)	73 (10.8)	12 (10.2)	61 (11.0)	
Histology				**0.193**
Adenocarcinoma	424 (62.5)	77 (65.3)	347 (61.9)	
Squamous cell carcinoma	172 (25.4)	23 (19.5)	149 (26.7)	
Undifferentiated/not specified	82 (12.1)	18 (15.3)	64 (11.4)	
Thoracic stage (excluding M1b)				< **0.001**
I/II	29 (4.3)	10 (8.5)	19 (3.4)	
III	277 (40.9)	69 (58.5)	208 (37.1)	
IV	372 (45.9)	39 (33.1)	333 (59.5)	
Extracranial metastases				**0.003**
Pulmonary	322 (47.5)	38 (32.2)	284 (50.6)	
Hepatic	93 (13.7)	13 (11.0)	80 (14.2)	
Adrenal gland	102 (15.0)	26 (22.0)	76 (13.4)	
Bone	209 (30.8)	42 (35.6)	167 (29.8)	
Smoking status				**0.017**
Never	143 (21.1)	35 (29.7)	108 (19.2)	
Current/ever	535 (78.9)	83 (70.3)	452 (80.8)	
Therapy of thoracic primary				**0.138**
Systemic	664 (97.9)	108 (91.5)	556 (99.2)	
Radiotherapy/ radiochemotherapy	62 (9.1)	16 (13.6)	46 (8.2)	
Surgery	18 (2.6)	4 (3.4)	14 (2.5)	

Characteristics of total group and subgroups with and without synchronous BM; differences in the distribution of brain metastases in the various subgroups are shown; *p*-value for difference in distribution by χ^2 test.