

Disease Presentation and Treatment Outcome in Very Young Patients with Brain Metastases from Lung Cancer

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Key Words

Radiotherapy · Brain metastases: prognostic factors, age · Lung cancer

Summary

Background: While elderly patients with brain metastases from lung cancer appear to have an unfavorable prognosis, little information is available on disease presentation and treatment outcome in very young patients. **Patients and Methods:** Retrospective evaluation of radiation therapy in this particular subpopulation. The database with 149 lung cancer patients contained 9 patients aged <40 years. The majority received whole-brain radiation therapy with 30 Gy in 10 fractions plus steroids, with or without other local or systemic measures according to the institutional policy. **Results:** Five patients had small-cell histology. Median Karnofsky performance score was 70. In 6 cases, brain metastases were present already at first diagnosis. Eight patients had multiple lesions. Of 8 patients with complete follow-up, only 1 died from spread to the central nervous system (CNS), all others from extracranial disease. Maximum survival was 26 months (median 7 months). **Conclusion:** Very young patients with brain metastases did not achieve a better outcome than intermediate age groups. Radiation therapy was able to provide durable CNS control in nearly all patients, while systemic failures remained the leading cause of death. Prospective studies on treatment intensification and quality of life in these patients appear warranted.

Schlüsselwörter

Strahlentherapie · Hirnmetastasen: prognostische Faktoren, Alter · Lungenkrebs

Zusammenfassung

Hintergrund: Während ältere Patienten mit Hirnmetastasen eines Bronchialkarzinoms eine ungünstige Prognose zu haben scheinen, ist über das Krankheitsausmaß und die Behandlungsergebnisse bei sehr jungen Patienten wenig bekannt. **Patienten und Methoden:** Retrospektive Auswertung einer Gruppe strahlenbehandelter Patienten. Die Datenbank mit 149 Bronchialkarzinompatienten umfasste 9 Patienten, die unter 40 Jahre alt waren. Die Mehrzahl erhielt eine Ganzhirnbestrahlung mit 30 Gy in 10 Fraktionen plus Steroide. Weitere lokale oder systemische Behandlungen erfolgten nach den klinikinternen Konzepten. **Ergebnisse:** Fünf Patienten hatten histologisch ein kleinzelliges Karzinom. Der mediane Karnofsky-Index betrug 70. In 6 Fällen waren die Hirnmetastasen bereits bei der Tumorerstdiagnose nachweisbar. Acht Patienten hatten multiple Metastasen. Von 8 Patienten mit komplettem Follow-up starb lediglich einer an der zerebralen Metastasierung, alle anderen an einer extrakraniellen Progression. Das Überleben betrug maximal 26 Monate (median 7 Monate). **Schlussfolgerung:** Sehr junge Patienten mit Hirnmetastasen hatten keine besseren Behandlungsergebnisse als die sonstigen Patienten. Die Strahlentherapie führte bei fast allen Patienten zu einer dauerhaften Kontrolle der zerebralen Metastasierung, wohingegen systemische Rezidive die Haupttodesursache waren. Prospektive Studien zur Behandlungsentensivierung und Lebensqualität dieser Patienten erscheinen sinnvoll.

Introduction

Despite many recent advances in multimodal lung cancer treatment, development of brain metastases remains a common problem and is associated with a poor prognosis [1]. Brain metastases from lung cancer often present as multiple rather than solitary lesions and together with extracranial metastases [2–5]. Advanced age (≥ 65 years) was shown to represent an adverse prognostic factor in the large analysis that led to the development of the recursive partitioning analysis (RPA) classes in irradiated patients with brain metastases [6]. This finding has been confirmed by evaluations restricted to lung cancer patients [7]. However, little information is available on disease presentation and treatment outcome in very young patients. Therefore, we decided to evaluate our experience with radiation therapy in this particular subset. A cut-off value of 40 years was chosen for the purpose of the study.

Patients and Methods

We retrospectively analyzed all patients treated with radiation therapy for brain metastases from lung cancer. They were identified from the hospital's database. All patients had histological confirmation of their primary lung cancer. Out of 149 patients with brain metastases from lung cancer in the database, 9 (6%) were < 40 years old when treatment for brain metastases was started. The outcome of this subgroup was compared to that of patients ≥ 40 years. The institutional treatment policy consisted of immediate whole-brain radiotherapy (WBRT) followed by cisplatin/etoposide systemic chemotherapy in patients with small-cell histology and symptomatic brain metastases. Asymptomatic patients were treated with the same chemotherapy regimen and deferred WBRT only if the lesions failed to respond (based on imaging criteria). Patients with non-small-cell histology

and symptomatic brain metastases started with WBRT followed by platinum-based combination chemotherapy, typically consisting of cisplatin and vinorelbine. Patients with asymptomatic lesions received WBRT between the second and third cycle. Second-line chemotherapy varied and was typically taxane- or topotecan-based. No receptor tyrosine kinase inhibitors were used. WBRT was administered via standard lateral opposed 6 MV beams from a linear accelerator with 5 fractions of 3 Gy per week and use of a thermoplastic mask fixation of the head. The dose was prescribed to the midline. Selected patients with non-small-cell histology were also treated with resection or radiosurgery for brain metastases. Dexamethasone was given in individual doses. A baseline clinical examination was performed within 1 week before the start of WBRT. Follow-up took place every 3 months and included contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Prognostic factors for survival were evaluated in all 149 patients. For this purpose, Kaplan-Meier survival curves were compared with the log-rank test. After these univariate evaluations, statistically significant variables, defined as $p < 0.05$, were entered into a Cox proportional hazards model for multivariate analysis.

Results

Table 1 contains the patient characteristics. The patients younger than 40 years were more likely to have small-cell lung cancer (SCLC), more than one brain metastasis, and a shorter interval from first lung cancer diagnosis to brain metastases diagnosis. Specifically, 5 of the 9 younger patients had primary SCLC (all with extensive disease at initial diagnosis) and none had squamous cell histology. In 6 cases, brain metastases were present already at first diagnosis, while 3 patients had metachronous presentations (3–15 months interval). In one case, a single brain lesion was resected to establish a tissue diagnosis. All other patients had multiple lesions. The median Karnofsky performance status (KPS) was 70% (range, 60–90).

Table 1. Patient characteristics

Parameter	Patients ≥ 40 years (n = 140)	Patients < 40 years (n = 9)	Significant difference ($p < 0.05$)
Small-cell primary, %	28	56	yes
Non-small-cell primary, %	72	44	yes
Median age, years	64	37	yes
Median KPS	70	70	no
Extracranial metastases in small-cell cases, %	60	78	no
Extracranial metastases in non-small-cell cases, %	50	49	no
Male patients, %	82	78	no
Solitary brain metastasis, %	44	11	yes
Metachronous brain metastases, %	61	33	yes
Incomplete WBRT, %	9	11	no
Upfront surgery or SRS, %	20	22	no
Systemic treatment after diagnosis of brain metastases, %	39	88	yes

KPS = Karnofsky performance status; WBRT = whole-brain radiotherapy; SRS = stereotactic radiosurgery.

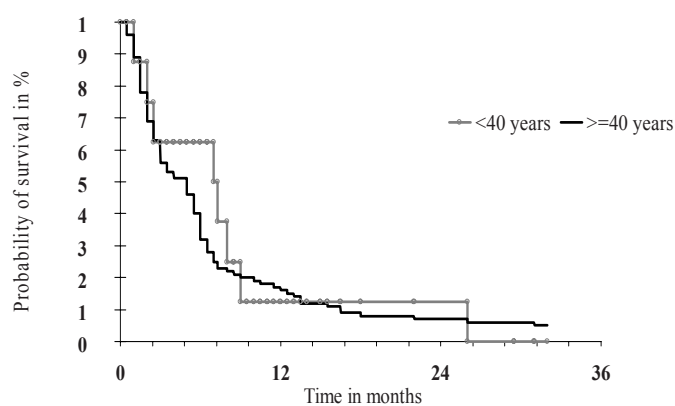


Fig. 1. Kaplan-Meier estimates of overall survival ($p > 0.1$, log-rank test).

One patient with SCLC was not able to complete WBRT due to rapid systemic progression and died after 4 weeks. Of 8 patients with complete follow-up, only 1 died from spread to the central nervous system (CNS), all others from extracranial disease. However, in 2 patients with short survival time, imaging follow-up of the brain was not available. All others had at least stable disease in the brain. Maximum survival was 113 weeks (median 30.5 weeks or 7 months). In the 140 patients ≥ 40 years of age, median survival was 5 months (fig. 1), and there was no significant difference between those with small-cell and non-small-cell histology. Statistically significant prognostic factors for survival after multivariate analysis were higher KPS, absence of extracranial metastases, and solitary brain metastasis. Neither median age nor age < 40 years influenced survival significantly.

Discussion

The present retrospective analysis is to our knowledge the first one that focuses on very young patients with lung cancer metastatic to the brain. The interpretation of the results needs to take into account the limited number of patients. It appears, however, that these patients tend to harbor multiple cerebral lesions, which already are found at initial cancer diagnosis. These features possibly might suggest the presence of an aggressive malignancy, although they might also result from a delay in diagnosis in a patient group where lung cancer is rather uncommon and initial symptoms might be misinterpreted. Gaspar et al. suggested that younger patients (≤ 50 years) have a higher risk for development of brain metastases from stage III non-small-cell lung cancer (NSCLC) [8]. Median survival was 10 months for patients with brain metastases only and 4.5 months for those with additional sites of disease. Other authors have also suggested that this age group is at higher risk of distant failure and brain failure [9]. Our data show that the 3 patients that would belong to RPA class I, if one assumes that systemic treatment controls their primary tumor (no. 2, 5, 8), survived for 30, 39, and 113 weeks, respectively. Therefore, a

combination of KPS ≥ 70 , controlled primary tumor, and absence of extracranial metastases might identify patients with better prognosis. Median survival both in RPA class I and the total patient population was shorter in the WBRT study by Kepka et al. [7], which also included patients with all histological types of lung cancer ($n = 322$), than in our group of very young patients (5.2 months and 4 months, vs. 9 and 7 months, respectively). In the SCLC series by Videtic et al. ($n = 154$), none of the patients was younger than 40 years [10]. Median survival in RPA class I was 8.6 months (4.9 months for the total patient group). In the NSCLC series by Antoniou et al. ($n = 155$), median survival was 5 months for the total patient group [5]. Comparable survival was observed in patients ≥ 40 years of age in our institution. We were, however, not able to demonstrate a significant impact of age on survival. Taking the limitations of retrospective analyses of small patient groups into account, the prognosis of very young patients is not tremendously different from that of patients ≥ 40 years of age.

Ultimately, only 1 patient died from CNS spread, suggesting that current treatment algorithms, which include resection or radiosurgery for selected patients, result in adequate brain control for the remaining life time. However, overall survival is clearly unsatisfactory despite the effects of chemotherapy, which was shown to improve survival [11]. Simultaneous administration of chemotherapy and WBRT or immediate chemotherapy with postponed WBRT in patients whose neurologic symptoms respond to steroids might contribute to increased systemic control [12, 13]. A randomized study in patients with brain metastases from NSCLC compared these strategies: arm A ($n = 86$) received cisplatin plus vinorelbine repeated every 4 weeks [3]. After 2 cycles, responders continued with up to 4 additional cycles. Nonresponders received WBRT with 10 fractions of 3 Gy. In arm B ($n = 85$), simultaneous WBRT with 30 Gy started on day 1 of the first chemotherapy cycle. There was no significant difference between simultaneous and deferred WBRT in terms of response of brain metastases (27 vs. 33%) and median overall survival (24 vs. 21 weeks). Ongoing investigations examine the role of prophylactic cranial irradiation in subgroups of patients with NSCLC [2], but this will not impact on patients with manifest brain disease at initial diagnosis.

Conclusions

Very young patients with brain metastases did not achieve a better outcome than intermediate age groups. Such patients might predominantly harbor aggressive types of lung cancer. As in other populations, KPS and extracranial disease extent might guide the choice of brain treatment. Radiation therapy was able to provide durable CNS control in nearly all patients, while systemic failures remained the leading cause of death. Prospective studies on treatment intensification [14–16] and quality of life in this patient subgroup appear warranted.

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