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Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors

Leptomeningeal carcinomatosis (LMC) is defined as either diffuse or multilocular seeding of the leptomeninges by malignant cells. LMC is diagnosed in about 1–5% of cancer patients [4] with a clear prevalence for cancers originating from the breast and lung [13]. In the last few decades, an increasing incidence of LMC has been observed, mainly explained by prolonged survival due to more efficient systemic treatment even after occurrence of distant metastases and due to improved imaging tools [19].

In general, LMC occurs in the terminal course of disease and is associated with significant mortality—especially in the presence of intracranial manifestations [6]. Without treatment, median life expectancy is dramatically shortened to 4–6 weeks [2] but might be extended to over 6 months after local treatment in patients with good prognostic factors [2, 4]. Simultaneous brain metastases are diagnosed in half of the patients [16]. However, the prognosis is determined by LMC, since survival after brain metastases exceeds that of LMC by several fold [9, 14, 20]

Current treatment recommendations predominately based on retrospective series comprise chemotherapy, radiotherapy, or both modalities. Chemotherapy is given intravenously (i.v.) or intrathecaly (i.t.), particularly in cases of diffuse meningeal involvement. The invasiveness of i.t. chemotherapy and the toxicity of high dose i.v. chemotherapy in relation to the limited life expectancy lead to a more restrictive application. Furthermore, chemotherapy is less effective in bulky disease as drug permeation is limited to 2–3 mm [5].

The objective of this retrospective analysis is to evaluate overall survival (OS) and treatment response of cerebral LMC confirmed by neuropathological/neuroradiological review after WBRT alone for breast and lung cancer patients not suitable or unfit for chemotherapy with cerebral activity. Furthermore, potential prognostic factors were investigated.

Patients and methods

Patients with breast or lung cancer and intracranial manifestations of LMC who were treated with WBRT alone between 2004 and 2010 were included in this retrospective study. Concomitant i.t. or i.v. chemotherapy was not performed because patients were considered not suitable or unfit for chemotherapy with cerebral properties. The following characteristics were obtained from the patients' records: age, sex, Karnovsky Performance Status (KPS), interval from diagnosis of primary disease and LMC, time of death or last follow-up, histology, clinical presentation, extracranial tumor burden, mode of radiotherapy, neuroimaging, and cerebrospinal fluid (CSF) analysis reports.

For the diagnosis of intracranial LMC, typical signs in neuroimaging studies, i.e., leptomeningeal enhancement or nodules in the subarachnoidal space or the presence of atypical cells in the CSF in combination with characteristic findings on physical examination were mandatory. A review of all CSF samples (11/27 patients) was carried out by the Department of Neuropathology. All neuroimaging studies (27/27 patients) were reevaluated by the Department of Neuroradiology.

Conventionally fractionated WBRT was performed with 6 MV photon beams from a linear accelerator via parallel opposed fields (90° and 270°). The planned target volume (PTV) included the whole brain and the meningeal space (i.e., lamina cribrosa and basal cisterns) with adequate margin. Cumulative doses and fractionation schemes are shown in **Tab. 1**. Acute treatment related toxicities were assessed according to the Common Toxicity Criteria, National Cancer Institute, Version 2.0.

Patients were retrospectively classified as treatment responders if either an improved neurological status was documented at the end of treatment or follow-up neuro-imaging studies showed a reduced size of contrast-enhancing findings. The following potential prognostic factors were evaluated: tumor entity, age, KPS, presence of cranial nerve disorders, presence of intracerebral brain metastases, extracranial tumor burden, time between diagnosis of primary disease and LMC.

The first two authors contributed equally to the study.

Tab. 1 Patients' and treatment characteristics			
		Number	**Percent**
Total patients		27	100
Age (years)			
Median		57	
Range		26–81	
Gender			
Female		22	81
Male		5	19
Karnovsky Performance Index (%)			
Median		60	
Range		30–100	
Primary disease			
Breast cancer		20	74
Lung cancer		7	26
Initial M category			
M0		18	67
M1		9	33
Sites of systemic tumor burden besides LMC and PD			
≤2		14	52
≥3		13	48
Intracerebral metastases		11	41
Previous systemic chemotherapy		22	81
Time between diagnosis of PD and LMC (months)			
Median		35	
Range		0.4–248	
Validation of diagnosis			
Imaging study only		16	59
CSF cytology only		4	15
Imaging study and CSF cytology		7	26
Radiotherapy			
Fractionation	Cumulative dose		
5×3 Gy	30 Gy	21	78
5×2.5 Gy	35 Gy	3	11
5×2 Gy	26 Gy	1	3.7
5×2 Gy	40 Gy	1	3.7
5×2 Gy	24 Gy	1	3.7

PD primary disease, LMC leptomeningeal carcinomatosis, CSF cerebrospinal fluid.

Tab. 2 Leading neurological findings		
	Number	**Percent**
Cranial nerve palsy (any)	14	52
Diplopia	10	37
Facial nerve	4	15
Trigeminal nerve (sensory abnormality)	1	4
Gait disturbance/dizziness	6	22
Hemiparesis	2	7
Altered mental status	2	7
No neurological findings	3	11

Statistical analysis was performed with commercial software (SPSS 19, IBM Inc., Armonk, NY, USA). Survival time was measured from the day when either a positive CSF cytology or a neuroimaging study confirmed the diagnosis of LMC. OS was calculated using the Kaplan–Meier method. Differences between curves were evaluated by the two-tailed log-rank test. Significant results ($p \leq 0.05$) were included in a multivariate analysis (Cox regression model).

Results

Study population

Between 2004 and 2010, 27 breast and lung cancer patients with intracranial LMC were treated with WBRT alone. Median age was 57 years (range 26–81 years). The primary disease was breast cancer in 20 patients and non-small cell lung cancer in 7 patients. Median time from diagnosis of the primary disease until the detection of LMC was 35 months (range 13 days–20 years). Follow-up was performed until death. For survivors (n = 2), follow-up time was 6.1 months and 20.9 months (**Tab. 1**).

Diagnostic procedures

Seven patients had evidence of LMC in both cranial MRI scans and CSF cytology.

LMC was confirmed by contrast-enhanced neuroimaging studies in another 16 cases (13 cranial MRI, 3 cranial CT). CSF samples had not been obtained in this subgroup of patients. In four cases, CSF cytology together with the clinical presentation led to the diagnosis of intracranial LMC, while cranial imaging (2 MRI and 2 CT) did not show findings characteristic for LMC. A solitary intracerebral brain metastasis was observed in 1 of these 4 patients.

Additional MRI scans of the spine were available for 10 patients. In eight scans, deposits of leptomeningeal cells were seen. Only one of these patients required concomitant treatment (focal radiotherapy) of symptomatic spinal lesions. Intracerebral brain metastases were detected in 11 patients (40%). Median time from

the diagnosis of LMC to the initiation of WBRT was 10 days (range 0–47 days).

Clinical presentation

Median KPS on initial presentation in the Department of Radiation Oncology was 60% (range 30–100%). Besides headache, neurological signs or symptoms were observed in 24 patients (89%); 14 patients (52%) had cranial nerve dysfunctions. An overview of the initial clinical presentation is provided in **Tab. 2**. All but 1 patient received a daily dose of at least 6 mg dexamethasone prior to or during radiotherapy as an anti-edematous co-medication.

Treatment compliance and acute treatment-related toxicity

Treatment was completed by 21 patients (78%). Two patients (7.4%) died of LMC during therapy, while treatment was discontinued in 3 patients (11.1%) because of progressive neurological symptoms. One patient died of gastrointestinal perforation during treatment.

Grade 3 or 4 acute treatment-related toxicity did not occur. However, 7 patients (26%) experienced grade 1 toxicity (erythema, alopecia, nausea, headache, fatigue) and 3 patients (11.1%) grade 2 toxicity (alopecia, tinnitus, somnolence).

Treatment response

Improvement of neurological signs and symptoms was observed in 3 patients (11%): in 1 patient mental status significantly improved during therapy and 2 patients reported improved vision. Seven patients had cranial imaging studies during follow-up (three CT, four MRI scans). MRI scans were performed after a median of 7 months (range 2–22 months) after the last WBRT fraction. Three of 4 patients with follow-up MRI scans showed decreased contrast agent enhancement of previously affected leptomeninges. One patient had severe leukoencephalopathy in a follow-up MRI scan after 22 months. Unscheduled CT scans (n = 3) for the evaluation of either new or progressive symptoms took place after a median of 6 weeks

Abstract · Zusammenfassung

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Outcome after whole brain radiotherapy alone in intracranial leptomeningeal carcinomatosis from solid tumors

Abstract

Background. The purpose of the present study was to investigate outcome after whole brain radiotherapy (WBRT) alone as a palliative treatment without concomitant chemotherapy for intracranial leptomeningeal carcinomatosis (LMC).
Patients and methods. Overall survival and treatment response were retrospectively analyzed in 27 consecutive patients with LMC from breast and lung cancer. All patients had evidence of intracranial manifestations of LMC. Seven potential prognostic factors were evaluated.
Results. Median overall survival (OS) for the entire group was 8.1 weeks. OS rates after 6 and 12 months were 26% and 15%, respectively. Improvement of neurological deficits was observed in 3 patients. In 3 of 4 patients with follow-up MRI studies, a decreased size of contrast-enhanced lesions was observed. Prognostic factors for improved OS on univariate analysis were absence of cranial nerve dysfunction, Karnofsky Performance Score (KPS) > 60%, and time interval > 35 months between the initial diagnosis of malignant disease and development of LMC. On multivariate analysis, absence of cranial nerve dysfunction remained the only significant prognosticator for OS (median 3.7 vs. 19.4 weeks, $p < 0.001$).
Conclusion. WBRT alone is an effective palliative treatment for patients unfit/unsuitable for chemotherapy and low performance status suffering from intracranial LMC. However, prognostic factors should be considered in order to identify patients who are likely to benefit from WBRT.

Keywords
Leptomeningeal carcinomatosis · Whole brain radiotherapy · Solid tumors · Cumulative survival rate · Prognostic factors

Behandlungsergebnisse nach alleiniger Ganzhirnbestrahlung bei intrakranieller Meningeosis carcinomatosa solider Tumoren

Zusammenfassung

Hintergrund. Die vorliegende Studie verfolgt das Ziel, den Stellenwert der alleinigen Ganzhirnbestrahlung (WBRT) ohne simultane Chemotherapie als palliative Therapiemaßnahme der intrakraniellen Leptomeningeosis carcinomatosa (LMC) zu evaluieren.
Patienten und Methodik. 27 konsekutive Patienten mit einer LMC solider Tumoren (Brustkrebs, Bronchialkarzinom), die mit alleiniger WBRT behandelt wurden, sind retrospektiv hinsichtlich Gesamtüberleben und Therapieansprechen untersucht worden. Alle Patienten wiesen einen intrakraniellen Befall der Hirnhäute auf. Darüber hinaus wurden 7 potentielle prognostische Faktoren analysiert.
Ergebnisse. Das mediane Gesamtüberleben lag bei 8,1 Wochen, das Gesamtüberleben nach 6 und 12 Monaten bei 26% bzw. 15%. Eine Besserung neurologischer Symptome ergab sich bei 3 Patienten. Bei 3 von 4 Patienten, für die eine MRT-Verlaufsbildgebung vorlag, zeigte sich eine deutliche Größenregredienz kontrastmittelaufnehmender Befunde. Prognostische Faktoren für ein verbessertes Gesamtüberleben in der univariaten Analyse waren das Fehlen von Hirnnervenausfällen, ein KPS > 60% und ein Zeitintervall > 35 Monate zwischen Primärdiagnose und Entwicklung der LMC. In der multivariaten Analyse verblieb als Prädiktor für ein besseres Gesamtüberleben das Fehlen von Hirnnervenausfällen. Das mediane Gesamtüberleben lag bei 3,7 vs. 19,4 Wochen ($p < 0{,}001$).
Schlussfolgerung. Die alleinige WBRT ist eine effektive Behandlungsoption für Patienten mit intrakranieller LMC, die nicht geeignet für eine Chemotherapie sind und einen eingeschränkten Allgemeinzustand vorweisen. Prognosefaktoren sollten in der Therapieentscheidung berücksichtigt werden, um Patienten, die wahrscheinlich von der WBRT profitieren, zu identifizieren.

Schlüsselwörter
Leptomeningeosis carcinomatosa · Ganzhirnbestrahlung · Solide Tumoren · Kumulative Überlebensrate · Prognostische Faktoren

Tab. 3 **Univariate analysis of overall survival calculated in weeks**

Parameter	Median[a]	Mean[a]	p value
Age			
≤ 57 years	8.1	36.0	
> 57 years	6.4	22.6	0.541
Karnovsky Performance Status			
≤ 60%	6.3	10.3	
> 60%	16.6	53.4	0.015
Primary disease			
Breast cancer	9.6	30.9	
Lung cancer	6.3	20.4	0.699
Systemic tumor burden			
≤2 sites (besides LMC and PD)	6.4	34.3	
≥3 sites(besides LMC and PD)	12.9	21.9	0.916
Intracerebral metastases			
Absent	8.1	35.6	
Present	7.7	24.9	0.826
Previous systemic chemotherapy			
No	7.7	17.0	
Yes	8.1	34.1	0.688
Time between diagnosis of PD and LMC			
≤ 35 months	5.9	17.3	
> 35 months	16.3	44.1	0.035
Cranial nerve affection			
Absent	19.4	56.0	
Present	3.7	6.7	< 0.001

[a]overall survival calculated in weeks **PD** primary disease, **LMC** leptomeningeal carcinomatosis.

(range 4–12 weeks), revealing no change in terms of LMC in all cases. An overall treatment response rate cannot be provided due to the short life expectancy accompanied by too short follow-up time to perform a response evaluation in each patient. Likewise, follow-up CSF or imaging studies of the spine were not available. However, the response rate for survivors of at least 6 months (n = 7) was 57%.

Overall survival and prognostic factors

Median OS for the entire group was 8.1 weeks (range 8 days–34.7 months). At the time of analysis, 2 patients were alive with survival times of 6.1 months and 20.9 months, respectively. Survival after 6 months and 1 year was 26% and 15%, respectively. All patients surviving for at least 6 months (n = 7) received systemic treatment after completion of WBRT. The applied therapeutics were carboplatin, capecitabine, gemcitabine, docetaxel, doxorubicine, pemetrexed, and erlotinib.

On univariate analysis, KPS > 60% (p = 0.015), interval > 35 months between the initial diagnosis of malignant disease and LMC (p = 0.035), and the presence of cranial nerve dysfunction (p = 0.001) were associated with significantly longer OS (**Tab. 3**). In a multivariate Cox regression analysis only the presence of cranial nerve affection maintained significant influence on OS (HR 4.11; 95% confidence interval (CI) 1.43–11.77, p = 0.009). Median OS for patients with cranial nerve dysfunction was 3.7 weeks compared to 19.4 weeks for patients without (**Fig. 1**).

Discussion

The present single institution study analyzed treatment response, OS, and prognostic factors of 27 consecutive breast and lung cancer patients diagnosed with intracranial LMC and treated with WBRT alone. Concomitant chemotherapy was not performed. In most cases, a poor KPS, bulky lesions, age, medical contraindications, or refusal of chemotherapy were reasons for restriction to WBRT alone. The decision to omit systemic treatment was made interdisciplinarily. For instance, WBRT was preferred to chemotherapy in the only patient with a KPS of 100% because of skull metastases. However, due to the retrospective nature of this series, each individual reason for omitting chemotherapy could not be assessed.

Various definitions with different emphasis on clinical, cytological, and imaging response have been applied to indicate "treatment response" in LMC [8, 10, 13, 16, 17]. Therefore, a comparison of response rates after WBRT or other treatment modalities is very limited. Treatment response, defined as either improvement of neurological function (n = 3) or decreased size of contrast-enhancing leptomeningeal lesions (n = 3), was observed in a total of 6 patients (22%). However, this rate might underestimate the real response in patients re-evaluated by computed tomography since CT scans have limited sensitivity for the evaluation of LMC [24]. In a retrospective study, 155 LMC patients were treated with chemotherapy (i.t. or i.v.), radiotherapy (focal, WBRT, or craniospinal), or a combination of both resulting in a size reduction of contrast-enhancing areas in 50% of imaging studies during follow-up [16]. In this series, 43% (n = 3/7) of patients with follow-up imaging showed radiologic response. However, tumor regression was no predictor of clinical response as reported by others [18, 22].

Delayed treatment was discussed as a possible explanation for this finding since longer duration of local alterations could result in irreversible neurologic damage. Regarding our patient group, the median time from the diagnosis of LMC by imaging or/and CSF to the first radiotherapy fraction was 10 days (range 0–47 days). The patient who received WBRT 47 days after the diagnosis of LMC belonged to the neurologically asymptomatic group of patients. A detailed analysis of duration of symptoms and treatment response

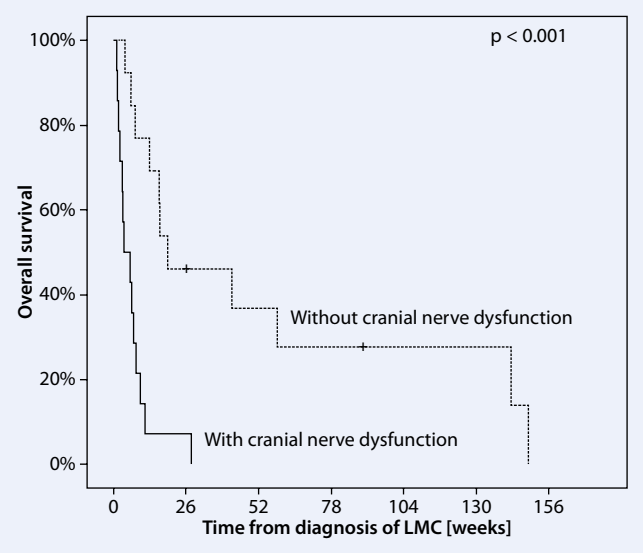

Fig. 1 ◀ Overall survival after whole brain radiotherapy for intracranial leptomeningeal carcinomatosis (n = 27). Median overall survival was significantly shorter in cases of cranial nerve dysfunction (3.7 vs. 19.4 weeks)

was not performed due to limited information on the course of disease in this retrospective series.

Like chemotherapy, radiotherapy of the neuroaxis allows treatment of the entire CSF. However, in patients pretreated with chemotherapy, craniospinal irradiation is frequently associated with considerable grade 3 and 4 hematological toxicities. In contrast, WBRT alone has advantages regarding toxicity and feasibility even in patients with very low KPS. These considerations are substantiated by outcome parameters: WBRT alone for a very poor risk group in this series reached comparable OS rates like a more intensified radiotherapy regimen consisting of craniospinal irradiation for LMC [15].

Median survival times of 10–24 weeks have been reported for LMC treated with chemotherapy [6, 10, 13, 16, 21, 23]. However, three crucial differences in patient characteristics must be considered. First, most studies did not differentiate between intracranial and spinal involvement of the leptomeninges [10, 12, 21, 23]. The importance of this distinction was shown in a series investigating breast cancer patients with LMC treated with i.t. methotrexate or radiotherapy alone (WBRT, focal, or craniospinal axis) or a combination of both. Median survival time was 3 weeks for patients with signs of cranial manifestations of LMC and 21 weeks for patients with spinal manifestations only [6]. In our analysis, intracranial LMC was either diagnosed by imaging studies or patients suffered from symptoms related to cranial nerves with positive CSFs. Therefore, our patients had a very unfavorable prognosis due to the intracranial location of LMC. Second, prospective studies frequently only include patients with KPS of at least 60% and age ≤ 75 years who are considered fit enough to tolerate chemotherapy [3, 10, 12]. In contrast, our series included patients with a KPS of 30% and age of 81 years.

Third, i.t. chemotherapy without concomitant WBRT has been recommended by guidelines and expert panels for "non-adherent type" LMC, which is associated with a better prognosis than LMC with cell deposits visible on imaging studies [7, 25]. One prospective study compared i.t. cytarabine to i.t. methotrexate for LMC from solid tumors. Median survival was 14 weeks for the cytarabine arm and 10 weeks for the methotrexate arm. However, only approximately 20% of patients had features of LMC in imaging studies and, thus, "adherent type" LMC [11]. In the present study, this was the case for 85% of the patients, which again indicates the very poor prognostic subgroup treated in this series. In the absence of an untreated control group with a similarly poor prognostic profile, survival benefits generated by WBRT in the present study cannot be quantified. Of the 27 patients in our study, 4 patients survived for at least 1 year. All long-term survivors received i.v. chemotherapy for extracranial tumor manifestations. The substances applied do not reach sufficient CSF levels [1]. Thus, an important role of WBRT on survival in these patients can be assumed.

The absence of cranial nerve dysfunction was identified as the only significant positive prognostic factor for OS on a multivariate analysis. A KPS > 60% and interval > 35 months between the first diagnosis of malignant disease and LMC were significant prognosticators for improved overall survival on univariate analysis only. These factors should be re-evaluated in a larger study.

In view of the limited life expectancy associated with LMC, the decision between WBRT and "best supportive care" for patients who are unfit or unsuitable for chemotherapy is challenging. In this situation, prognostic factors as mentioned above can help to identify patients who are likely to benefit from WBRT.

Conclusion

WBRT alone is an effective and feasible palliative treatment option for patients unfit/unsuitable for chemotherapy and low performance status suffering from intracranial LMC. However, prognostic factors such as cranial nerve dysfunction should be considered in order to identify patients who are likely to benefit from treatment.

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Conflict of interest. The corresponding author states that there are no conflicts of interest.

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