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Original Paper

Brain Metastases in Breast Cancer: Prognostic Factors and Management

S. Lentzsch,[1] P. Reichardt,[1] F. Weber,[2] V. Budach[3] and B. Dörken[1]

[1]Department of Haematology, Oncology and Tumour Immunology, University Medical Centre Charité, Humboldt University, Campus Berlin-Buch, Robert Rössle Klinik at the Max-Delbrück-Centrum for Molecular Medicine, Lindenbergerweg 80, D-13122 Berlin-Buch; [2]Department of Neurosurgery, University of Düsseldorf, Düsseldorf; and [3]Department of Radiotherapy, University Medical Centre Charité, Humboldt University, Campus Charité, Berlin, Germany

In this retrospective study, 162 breast cancer patients were analysed in whom brain metastases had been diagnosed clinically between 1969 and 1995 at a single institution. 145 patients were treated with megavoltage irradiation (60 cobalt or 6 MV) of the whole brain using opposed fields. The most common applied schedule consisted of 30 Gy in 15 daily fractions over 3 weeks. 10 patients underwent surgery and 17 patients received symptomatic treatment only. The median age was 50 years (range 30–78 years). 81 of 162 patients (50%) were premenopausal. Women younger than 40 years of age had a shorter survival (median 12 weeks) than those of all other groups (median 29 weeks). Median survival was 82 weeks for the 10 surgical patients, 26 weeks for the 145 patients treated with radiotherapy and 5 weeks for the patients who received symptomatic (corticosteroid) therapy only. Patients with solitary metastases treated with radiation alone (45 patients) had a survival of 44 weeks versus 23 weeks in patients with multiple brain metastases. Multivariate stepwise regression analyses revealed Karnofsky Index, dose of radiation ($P < 0.001$), solitary metastases ($P < 0.04$) and primary tumour size ($P < 0.04$) as significant prognostic factors for survival.

Key words: breast cancer, brain metastases, prognostic factors, brain metastases therapy
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INTRODUCTION

BREAST CANCER is the second most common cause of brain metastases. Clinically overt brain metastases occur in approximately 10–15% of patients with breast cancer [1]. At autopsy, cerebral metastases are found in up to 30% of patients [2].

So far, no prognostic factors for the occurrence of central nervous system (CNS) metastases have been identified and optimal management remains controversial. Treatment aims at clearing symptoms like headache, nausea and vomiting, improvement of the neurological status and prolongation of survival. Therapeutic modalities apart from symptomatic therapy include surgery, radiotherapy and chemotherapy or combinations of the aforementioned methods.

Correspondence to S. Lentzsch, e-mail: lentzsch@rrk-berlin.de
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Radiation is a well-established treatment modality that results in transitory amelioration of the neurological deficits in 60–85% of patients [2]. Most patients relapse after a median of 2–3 months [3]. The role of surgery is well accepted for a selected group of patients with solitary brain metastases and no evidence of extracranial disease [4, 5]. Its value is unclear in patients with multiple brain metastases. Chemotherapy plays only a minor role as primary treatment of brain metastases and has not been studied extensively, although some investigators have reported favourable responses to systemic chemotherapy [6–8]. Rosner and colleagues treated 100 patients with CNS metastases from breast cancer with chemotherapy alone. 50 of these patients showed an objective response with a median survival for partial responders of 10.5 months, comparing favourably with non-responders who had a median survival of only 1.5 months [9].

Prognostic factors for the occurrence and the outcome of brain metastases are still unknown. This retrospective analysis was undertaken to identify high risk groups for the development of brain metastases from breast cancer, to analyse factors which influence survival and to evaluate the efficacy of different treatment modalities.

PATIENTS AND METHODS

Patients

Patients characteristics are summarised in Table 1. 162 female breast cancer patients with solitary or multiple brain metastases who were treated at the Robert-Rössle Hospital in Berlin between 1969 and December 1995 were analysed retrospectively. Follow-up was closed on 31 December, 1996. All patients had histologically confirmed carcinoma of the breast. CNS lesions were diagnosed by radionuclide brain scans ($n = 26$) and since 1981 by computed tomography (CT) scans or since 1992 by magnetic resonance imaging (MRI) ($n = 136$ patients). All patients included in this study had become symptomatic prior to further diagnostic investigations. Patients with isolated leptomeningeal carcinomatosis or second neoplastic disease were not included in this study.

All patients were followed until death or the end of the study period. The progression free interval was defined as the time from primary diagnosis of breast cancer to the time of first recurrence, and the intracranial metastases free interval as the time from primary diagnosis until first detection of brain metastases. The survival time with brain metastases was measured from the time of detection of brain metastases until death or the end of the study.

The performance status was determined at the diagnosis of brain metastases according to the Karnofsky classification. The cause of death was defined as related to brain metastases, to systemic metastases or other causes.

Treatment modalities

Radiotherapy consisted of megavoltage irradiation (60 cobalt or 6 MV) of the whole brain using opposed fields. The total dose varied from 20 to 50 Gy delivered in fractions of 1.5–3 Gy per day over 2–4 weeks according to the individual physicians' preference. The most common schedule used was 30 Gy in 15 daily fractions over 3 weeks. No boost doses to the metastatic lesions were used.

Neurosurgery was performed as gross total resection in patients with solitary or only few and resectable lesions. All

Table 1. *Patients' characteristics and survival data*

	n	Median survival (weeks)	Median time from diagnosis of primary tumour to brain metastases (weeks)	Median time from primary diagnosis to first recurrence (weeks)
Age (years)	$n = 162$			
< 40	15	12	126	110
40–49	66	25	138	105
50–59	50	30	156	161
60–69	26	16	156	191
≥ 70	5	12	230	44
Menopausal status	$n = 162$			
Premenopausal	81	26	184	104
Postmenopausal	81	25	196	91
Karnofsky index	$n = 155$			
< 60	41	4	156	92
60–79	106	37	135	92
80–100	8	74	268	255
Stage at diagnosis	$n = 150$			
I	18	26	126	92
II	102	26	164	109
III	18	23	72	62
IV	12	20	8	1
Tumour grading	$n = 150$			
Grade 1	0	0	0	0
Grade 2	16	14	194	112
Grade 3	115	26	151	94.5
Grade 4	19	17	104	56
Extent of brain metastases	$n = 162$			
Single	49	44	134	94
Multiple	113	19	156	92
Site of metastases	$n = 162$			
No systemic metastases	27	40	92	0
Systemic metastases	135	23	156	102
Adjuvant chemotherapy	$n = 162$			
No adjuvant therapy	56	20	160	125
Adjuvant therapy	106	26	150	92

patients received radiotherapy either immediately after surgery or in case of relapse after a second operation.

The chemotherapy regimens used were the CMF-protocol (cyclophosphamide, methotrexate, 5-fluorouracil) in the adjuvant situation or various doxorubicin-containing regimens in patients with locally advanced disease or inflammatory breast cancer. For treatment of metastatic disease, either CMF or anthracycline-based combinations were used. In our analysis, only palliative chemotherapies which were started not earlier than 6 months before the detection of brain metastases were included. Symptomatic treatment consisted of corticosteroids at various doses.

Statistical methods

Life-table analysis according to the Kaplan–Meier method was performed on survival data, which included censored events [10, 11]. For comparison of survival curves, the log rank test was used. Analyses were performed by univariate and multivariate regression models. The Cox proportional hazard regression analysis was used to test the independent contribution of multiple variables to prognosis in a forward stepwise manner [11].

We were able to obtain data on primary tumour size from a cohort of 3049 breast cancer patients without brain metastases diagnosed and treated at our institution. Furthermore, data on complete initial staging (pTNM) from our institution were available for 671 patients without brain metastases. The χ^2-test after Brandt and Suedecor ($\alpha = 5\%$) was used for the calculation of significant differences regarding primary tumour size and initial stage between our study group and these two cohorts of 3049 and 671 breast cancer patients.

RESULTS

At the end of the follow-up period on 31 December 1996, 4 of the 162 patients were alive, 191, 262, 508 and 520 weeks after the diagnosis of brain metastases (Table 2). The median overall survival for all patients was 26 weeks (range 1–520 weeks). The median interval from primary diagnosis to diagnosis of brain metastases in our series was 156 weeks, and 94 weeks from the first distant metastases to brain metastases. The cause of death was related to brain metastases in 114 patients (70%), to systemic metastases in 30 patients (19%) and reasons other than breast cancer in 18 patients (11%).

Table 2. Long term survivors

Patient no.	No. of brain metastases	Systemic disease	Treatment for brain metastases	Symptoms at last follow-up	Survival (weeks)
1	Single	Bone	RT	Worse	508
2	Single	None	Surgery/RT	Asymptomatic	520*
3	Multiple	None	RT	Asymptomatic	508*
4	Multiple	Bone	RT	Worse	264
5	Multiple	None	RT	Asymptomatic	262*

RT, radiotherapy. *Alive at the end of follow-up.

Age and menopausal status

The median age of the patients at the diagnosis of brain metastases was 50 years (range 30–78 years). 81 patients (50%) were premenopausal (15 patients under 40 years of age) and 81 patients (50%) were postmenopausal. Premenopausal patients demonstrated a slightly but not significantly shorter interval from primary diagnosis to brain metastases compared with postmenopausal patients (184 versus 196 weeks, Tables 1, 3), but the median interval from primary diagnosis of breast cancer to the development of systemic metastases (104 versus 91 weeks) and the median time of detection of brain metastases until death (26 versus 25 weeks) were similar. Median survival for premenopausal and postmenopausal patients was 26 and 25 weeks, respectively. Women younger than 40 years of age had a shorter survival (median 12 weeks) than those of all other groups (median 29 weeks), but this was not significant (Table 3).

Karnofsky index

Multivariate stepwise regression analyses revealed that the performance status at the time of diagnosis of brain metastases was a prognostic factor for survival ($P < 0.001$, Table 3). Patients with a Karnofsky index higher than 80 had a median survival time of 74 weeks (range 1–520 weeks) after diagnosis of brain metastases compared with 4 weeks (range 1–167 weeks) in patients with a Karnofsky index lower than 60 (Table 1).

Primary stage, grading, histology

At primary diagnosis, 18 patients (12%) had stage I disease, 102 (68%) had stage II disease, 18 (12%) had stage III disease, 12 (8%) had stage IV disease and in 12 patients the initial stage of disease could not be determined. With regard to the primary stage at the time of diagnosis, we found a significantly higher proportion of advanced stages in our group compared with a control group of 671 breast cancer patients without brain metastases diagnosed at our institution. Interestingly, the size of the primary tumour was shown to be an independent predictor for survival with brain metastases in the multivariate analysis ($P < 0.04$; Table 3). We observed a

Table 3. Univariate and multivariate analyses of patient survival and treatment-related factors of 162 breast cancer patients with brain metastases

Variable (categories)	Univariate analyses *P* value	Multivariate analyses *P* value
Age (< 40 years versus ≥ 40 years)	0.54	0.77
Number of brain metastases (1 versus > 1)	< 0.025	< 0.04
Size (T) of primary tumour (I/II versus III/IV)	0.33	< 0.04
Grading of primary tumour (1/2 versus 3/4)	< 0.001	0.07
Dose of radiation (< 30 Gy versus ≥ 30 Gy)	< 0.001	< 0.001
Adjuvant chemotherapy (yes versus no)	0.2	0.15
Palliative chemotherapy (yes versus no)	0.7	0.6
Menopausal status (pre versus post)	0.8	0.8
Systemic metastases (yes versus no)	0.24	0.07
Karnofsky Index (< 60 versus > 60)	< 0.001	< 0.001

significantly higher proportion of large primary tumors in our group compared with a cohort of 3051 breast cancer patients without cerebral metastases. The proportion of T3 tumours was 21.3 versus 7.6% in the control group.

None of the primary tumours showed grade 1 anaplasia. Grade 2 and 3 anaplasia was observed in 16 (11%) and 115 (77%) patients, respectively. 19 (13%) patients had an inflammatory breast carcinoma.

Median survival since diagnosis of brain metastases was 26 weeks in patients with grade 3 tumours and 17 weeks in patients with inflammatory breast cancer (Table 1). In the univariate analysis, dedifferentiation and especially inflammatory cancer could be identified as a risk factor for shorter survival with brain metastases ($P < 0.001$).

Sites of metastases, disease status and extent of brain metastases

Median survival with brain metastases in patients with no systemic disease ($n = 27$) was 40 weeks (range 1–520 weeks) versus 23 weeks in patients with systemic metastases (range 1–508 weeks). The most common sites of extracranial disease were bone, lung and liver. In 13 of the 135 with systemic disease patients, the brain was the first site of distant metastases. 49 patients (30%) suffered from a solitary brain lesion and 113 patients (70%) had multiple brain metastases. The median survival was 44 weeks in patients with solitary lesions and 19 weeks in patients with multiple brain lesions. The presence of a solitary lesion was an independent prognostic factor in the multivariate analysis ($P < 0.04$, Table 3). 5 patients with solitary or up to two brain lesions, no evidence of visceral metastases and low grade breast carcinoma, who were treated with surgery and/or radiation, survived a median of 508 weeks (range 262–520 weeks) showing a potential for long-term remission in selected patients (Table 2).

Surgery

10 patients were operated upon (4 with solitary and 6 with up to two lesions) and 8 of these received postoperative whole brain radiotherapy. Both patients who did not receive postoperative radiotherapy developed an intracranial relapse. After re-operation, radiotherapy was performed and 1 patient was still alive without recurrence 191 weeks after first diagnosis of brain metastases. Of the 49 patients with solitary brain metastases, only 4 were surgically resected. The remaining 45 patients were not resected due to a poor performance status, progressive systemic metastases and other unspecified reasons. Median survival of these 10 patients was 82 weeks (range 20–520 weeks) and exceeded 10 years in 1 patient at the end of the follow-up period. Outcome according to palliative treatment strategy is presented in Table 4. The Karnofsky index for all 10 patients was ≥ 70, the median age was 52.5 year (range 44–59 years). 5 of 10 had no systemic metastases, 2 patients had one metastatic site and 3 patients had more than one metastatic site.

Table 4. Outcome of patients according to clinical management of brain metastasis (BM)

Treatment modality	Number of patients	Median survival (weeks)	Range (weeks)
Surgery of BM	10	82	20–520
Radiotherapy of BM	145	26	1–508
Radiotherapy of single BM	45	44	1–508
Radiotherapy of multiple BM	100	23	1–444
Palliative chemotherapy	112	26	1–520
No palliative chemotherapy	50	25	1–508
Symptomatic therapy	17	5	1–144

Radiotherapy

Whole-brain irradiation was most frequently applied in patients suffering from brain metastases. The median overall survival time of the radiotherapy group (145 patients) was 26 weeks (range 1–508 weeks). The dose of radiation played an important role and was shown to be an independent predictor for survival after diagnosis of brain metastases in the multivariate analysis ($P < 0.001$, Table 3). Patients with solitary metastases treated with radiation alone (45 patients) had a survival of 44 weeks versus 23 weeks in patients with multiple metastases ($n = 100$) (Table 4).

Chemotherapy

56 patients received adjuvant chemotherapy depending on the stage of the primary breast lesion. The median survival with brain metastases was 20 weeks (range 1–520 weeks) in patients with adjuvant chemotherapy versus 26 weeks (range 1–508 weeks) in patients who had not received adjuvant chemotherapy (Table 1).

The intracranial metastases free interval was not significantly prolonged by adjuvant chemotherapy (160 versus 150 weeks). The progression-free interval of extracranial metastases was longer in patients who received adjuvant chemotherapy (125 versus 92 weeks), as expected.

9 of 13 patients who showed brain metastases as the first site of systemic relapse, had received adjuvant chemotherapy.

112 patients were treated with palliative chemotherapy, some of whom also received hormonal therapy for systemic disease prior or concomitant to therapy for brain metastases. In total, 85 patients received hormonal therapy. All had extracranial systemic disease. The median survival was identical in patients who received or did not receive systemic chemotherapy (26 versus 25 weeks).

Symptomatic therapy

17 patients received corticosteroids only due to their poor general condition. Their median survival was 5 weeks.

DISCUSSION

Our analysis was undertaken to identify prognostic factors for the development of brain metastases in female breast cancer and to evaluate the impact of different treatment modalities.

The median age of our patients at the time of first diagnosis of brain metastases was 50 years. This is more than 5 years younger than the median age at which systemic metastases normally occur in breast cancer patients [12], a finding that has been previously reported by other investigators [13]. De La Monte and colleagues reported that with increasing age, the frequency of CNS metastases was significantly lower [14]. Also, the survival time with brain metastases was lower in patients under the age of 40 years.

The median interval from primary diagnosis to diagnosis of brain metastases in our series was 156 weeks, and 94 weeks from the first distant metastases to brain metastases. Di Stefano and associates [1] reported similar results with a median interval between primary diagnosis and CNS metastases of 34 months, and 12 months between the first metastases and CNS metastases in 101 patients.

As an interesting finding in our study, independent from the nodal status, we found a significantly larger primary tumour size in our group compared with a control group without brain metastases. If this could be confirmed by larger studies, implications on adjuvant strategies and follow-up could result.

One of the most striking findings was the, not unexpected, strong and significant correlation of poor histological grading, especially the diagnosis of inflammatory breast cancer, with the development of brain metastases and short survival time. Seventy-seven per cent of our patients showed undifferentiated primary tumours with grade 3 anaplasia. Thirteen per cent of patients had inflammatory primaries, which is in contrast to the normally reported incidence of 1–4% [15]. This is in accordance with Cho and colleagues who described that brain metastases are derived from tumours with great proliferative potential [16].

Whereas brain metastases are usually associated with systemic disease, they can still develop whilst extracranial metastases are in remission [17] or even as the first metastatic site. In our series, 27 patients (17%) had no evidence of extracranial disease, whereas the lungs were the most common site of systemic disease in the other patients, as reported by other investigators [13]. The absence of extracranial metastases was a prognostic factor for survival in a multivariate analysis, with a median survival from diagnosis of CNS involvement of 40 versus 23 weeks in those without and with these metastases. These findings suggest that the diagnosis of brain metastases does not necessarily represent the limiting factor in the course of the disease. Thirty per cent of our patients died of causes other than brain metastases.

In 30% of the patients, solitary lesions were found, although many diagnoses were made before the availability of modern imaging techniques, especially magnetic resonance imaging (MRI). Solitary brain metastases were associated with a significantly better outcome, regardless of the therapeutic procedures (44 weeks versus 19 weeks for patients with multiple brain metastases). Independently, the Karnofsky index was the most important prognostic factor for survival. The longest median survival rate of 82 weeks was found in patients who underwent surgical resection of their brain lesion. This finding should be interpreted with care due to the small and highly selected group of patients with a good performance status and without systemic disease. However, cerebral metastasectomy represents an excellent tool for fast relief of symptoms and may result in prolonged survival, especially when combined with postoperative radiotherapy [18].

The effectiveness of radiation therapy on brain metastases is well established. Numerous retrospective studies have demonstrated a prolongation of the median survival by 3–6 months [3]. In our series, patients with a solitary brain lesion receiving radiotherapy had a median survival of 44 weeks compared with 23 weeks in patients with multiple lesions. Higher doses of radiation were associated with a significantly better control of brain metastases ($P < 0.001$). Patients with a good performance status received a second course of radiotherapy of up to 50 Gy for the whole brain in case of relapse after surgery and/or radiotherapy. Among these patients, there were long-term survivors. Due to the poor performance status of some patients, radiotherapy was discontinued. These were the patients with the worst outcome. In contrast to other investigators, we found no late sequelae after radiotherapy in the long-term survivors. Since randomised data are missing, a comparison of the effectiveness between radiotherapy and surgery is difficult to assess, due to a high selection bias. Most of the long-term survivors in our study were treated with radiotherapy alone (Table 2), so that no definitive conclusion can be drawn.

As expected, in our analysis the progression free interval of extracranial metastases was longer in patients who received adjuvant chemotherapy (125 versus 92 weeks), but the intracranial metastases free interval was not significantly prolonged by adjuvant chemotherapy. One reason for this might be that adjuvant chemotherapy does not affect micrometastatic breast cancer cells within the brain due to the blood–brain barrier. Thus the development of systemic metastases can be delayed, but not the onset of brain metastases. Even with all the limitations of a non-randomised trial, this finding seems to be important and should be evaluated in larger prospective trials. In the case of confirmation, prophylactic radiation of the CNS could be considered for patients at a high risk of brain metastases. Whereas some recent prospective non-randomised studies have shown responses of brain metastases from breast cancer [9, 19], the role of chemotherapy remains controversial.

In conclusion, brain metastases seem to develop more frequently in younger patients with larger or aggressive tumours, especially inflammatory breast cancer, regardless of whether or not they receive adjuvant chemotherapy.

The prognosis is still very poor, but in a highly selected group of patients with isolated CNS metastases and without visceral disease and well-differentiated tumours, some long-term remissions were seen, even in patients with multiple brain lesions, a finding rarely reported before [20]. All patients suitable for surgical resection of their metastases should probably be operated upon and receive postoperative radiotherapy at sufficient doses. The role of chemotherapy in the management of brain metastases in female breast cancer remains to be evaluated in randomised trials.

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