Long-term follow-up of patients with metastatic breast cancer: results of a retrospective, single-center analysis from 2000 to 2005

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Recent epidemiological studies suggest that chemotherapy for metastatic breast cancer (MBC) has not contributed to a marked improvement in the patient outcome during the last decades. Randomized trials that investigated the efficacy of a first-line schedule for MBC, observed a median survival of 18–24 months. This study aimed to analyze patients with MBC who have been treated in a single university outpatient clinic for survival. Patients with MBC who had received their complete anticancer treatment in our outpatient clinic between 2000 and 2005 were analyzed for treatment schedules and survival. A total of 232 patients [median age, 53 years; range, 27–87 years; estrogen receptor and/or progesterone-positive hormone receptor, *n*=174 (75%); human epidermal growth factor receptor 2 overexpression (human epidermal growth factor receptor 2 positive), *n*=79 (34%)] were included in this analysis, of which 43.7% of hormone receptor-positive patients received 1–2, 28.3% received 3–4, and 1.7% received more than four hormonal regimens. In addition, 53.4% of all patients received up to three chemotherapeutic agents in palliative intent, whereas four to six regimens were applied in 22.1, and 12.9% received more than six subsequent regimens. An increased number of regimens were associated with an improvement in survival. The median overall survival was 44 months (95% confidence interval: 39–49). HR positivity, bone only, or single-site metastases were associated with an improved survival. An improved survival was also shown in patients who underwent locoregional procedures for oligometastatic disease (*n*=31; median overall survival >50 months), whereas triple-negative breast cancer was related to worse outcome (16 months; 95% confidence interval: 7–25). These data collected from a selective patient population of a single center support the hypothesis that the sequential use of all treatment modalities for MBC to its full potential may result in an increased survival. Whether innovative medicine, a step-by-step escalation of all treatment modalities according to standard guidelines and individualized clinical requirements, and a multidisciplinary treatment approach contribute to these good outcomes is debatable.

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Introduction

Metastatic breast cancer (MBC) has a dismal prognosis with a median survival that ranges between 18 and 24 months [1,2]. During the last decade, a series of new drugs have been developed and approved for daily practice in this setting. These new drugs include chemotherapeutics, antihormonal agents, and monoclonal antibodies such as trastuzumab [3–5]. The trials that have led to the approval of these drugs showed a tumor response rate that ranges from 20 to 70%. Although an increased progression-free survival has been documented in most of these trials, an increased overall survival (OS) has been observed only in some of these trials, which included innovative drugs. Although the magnitude of the effect on survival remains unclear, there is a consensus that these modern approaches exhibit anti-tumor activity for MBC [6].

In addition to new antineoplastic drugs, similar advances have been made in supportive care, such as the introduction of the bisphosphonates or the improvements in the management of severe neutropenia and infections [7,8]. Moreover, considerable technical advances have been made in surgical and minimal-invasive interventional procedures such as radio-frequency ablation (RFA) [9–15].

Although clinical trials suggest some advances in the management of MBC, it still remains unclear whether survival of these patients has improved in the context of daily practice. In this study, we retrospectively analyzed

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patients with MBC who had received anticancer treatment for survival in a period between 2000 and 2005 in a single-institutional outpatient clinic.

Patients and methods

Patient recruitment

Patient recruitment was based on an institutional data bank search for the diagnosis 'C50.9', 'breast cancer', and 'metastatic'. Among 669 patients with MBC, 232 patients were identified who had received complete anticancer treatment in our outpatient clinic between 2000 and 2005. These patients were analyzed for baseline characteristics, treatment modalities, and survival.

Statistical analysis

All data were collected retrospectively. Patient characteristics were analyzed with descriptive statistical methods. OS was calculated from first diagnosis of metastatic disease until death from any cause (intent to treat). Probability of survival was estimated by the Kaplan–Meier analysis and compared using the log-rank test [16]. Differences were considered statistically significant with a P value of less than 0.05.

A univariate analysis was made to investigate the relation between prognostic factors and OS. A P value of global test was calculated for categorical variables. According to Hosmer and Lemeshow [17], significant variables at the 20–25% level ($P < 0.2$) in the bivariate analysis were selected for the multivariate analysis.

Results

Patient characteristics ($n = 232$)

Among 669 patients with MBC of the data bank, 232 have received their complete anticancer treatment in our outpatient clinic. Patients were diagnosed with primary breast cancer at a median age of 49 (range, 25–84 years) and 53 years (range, 27–87 years) with metastatic disease. The median time of follow-up of the live study participants was 35.5 months.

Approximately a quarter of patients had nodal negative tumor ($n = 64$, 27.6%). Of the 232 women who were analyzed for this research, 32 had synchronous metastasis at the time of diagnosis. The median time between primary lesion and metastatic disease was 35.5 months (range, 0–18 years). Hormone receptor (HR)-positive tumors were found in 174 patients (75%). They were subdivided as follows: 70% of the women ($n = 163$) had an estrogen receptor-positive tumor and 65% ($n = 151$) had progesterone receptor-positive tumor. An overexpression of the human epidermal growth factor receptor 2 (HER2, by immunohistochemistry or fluorescent in-situ hybridization) was detected in one-third of patients ($n = 79$, 34%). A triple negative tumor was diagnosed in 15 patients (6.5%).

Regarding metastatic disease, visceral involvement was diagnosed at initial presentation of metastasis in 118 patients (50.9%). The site of first metastases was (in descending order) bone (27.2%), soft tissue including lymph nodes and skin (24.8%), liver (22.3%), lung (18.6%), others (4.0%), and brain (3.1%). Considering the course of disease, almost one-third of patients (28.9%) developed more than three different sites of metastasis, whereas 70% developed two different sites or less. Patient characteristics are given in detail in Table 1.

Treatment modalities for metastatic breast cancer

Patients with HR-positive tumors had received antihormonal regimens as follows: 43.7% received up to two regimens, 28.3% received up to three to four regimens, and 1.7% received more than four endocrine regimens. For three women, the endocrine treatment could not be analyzed. Almost half of all endocrine agents given (46%)

Table 1 Patient characteristics

	n (%)
Patients (*n*)	232 (100)
Median age at diagnosis of primary lesion (range; years)	49 (25–84)
Median age at diagnosis of metastases (range; years)	53 (27–87)
Tumor size	
Tis	2 (0.8)
T1	90 (38.8)
T2	85 (36.6)
T3	18 (7.8)
T4	15 (6.5)
Unknown[a]	22 (9.5)
Nodal status	
N0	64 (27.6)
N+	142 (61.2)
Unknown[a]	26 (11.2)
Metastases	
M0	198 (85.3)
M1	34 (14.7)
Grading	
G1	7 (3)
G2	99 (42.7)
G3	113 (48.7)
Unknown	13 (5.6)
Steroid receptor status	
HR positive	174 (75)
HR negative	49 (21.1)
Unknown	9 (3.9)
HER2 status	
HER2 positive	79 (34.1)
HER2 negative	119 (51.3)
Unknown	34 (14.6)
Triple negative	15 (6.5)
Site of first metastasis	
Liver	72 (22.3)
Lung	60 (18.6)
Bone	88 (27.2)
Brain	10 (3.1)
Soft tissue (including lymph nodes and skin)	80 (24.8)
Other	13 (4)
Nonvisceral metastases	114 (49.1)
Visceral metastases	118 (50.9)
Number of metastatic sites in the course of treatment	
1	83 (35.8)
2	82 (35.3)
≥ 3	67 (28.9)

HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
[a]High rate of 'unknown' due to primary metastatic disease (synchronous metastases).

were aromatase inhibitors. Sixty-one of 79 women, whose tumors overexpressed HER2, received trastuzumab (77.2%). The majority of those patients who received trastuzumab were beyond progression.

Patients evaluated for this study received up to three chemotherapy regimens in palliative intent in 53.4%, whereas four to six regimens were applied in 22.1%, and 12.9% received more than six subsequent regimens during the course of their metastatic disease.

Locoregional treatment modalities including surgery and RFA to liver metastases were applied in 31 patients. RFA was offered to 17 patients, whereas surgery (partial liver or lung resection) was performed in 14 patients. RFA or surgery was offered only to those with oligometastatic disease. Moreover, none of the patients within this subgroup were diagnosed with primary MBC.

Probability of survival

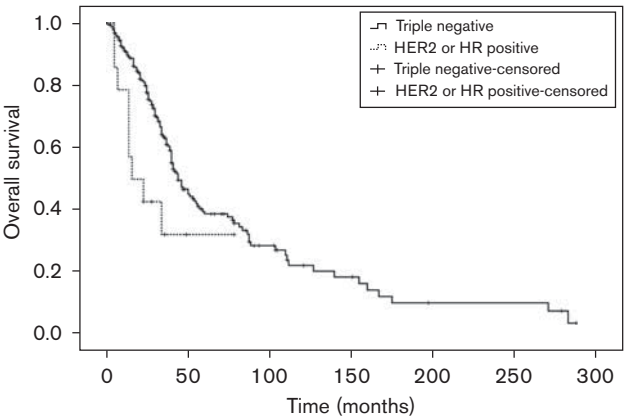
For the whole study population, the median OS was 44 months [95% confidence interval (CI): 39–49; Fig. 1]. When only patients with HR-positive tumors were considered, median survival was 46 months (95% CI: 38–54), whereas the survival of those with HR-negative tumors was inferior with 34 months (95% CI: 18–50; $P = 0.16$).

Patients who received trastuzumab for HER2-overexpressing tumors survived for a median of 44 months (95% CI: 36–52). The most inferior results were observed in patients with triple-negative breast cancer. Triple negativity was clearly related to a poor outcome with a median survival of 16 months (95% CI: 7–25; $P = 0.02$; Fig. 2).

Visceral involvement at initial presentation of metastasis was associated with a shorter median survival compared with nonvisceral disease (34, 95% CI: 17–48 vs. 57, 95% CI: 41–68 months; $P = 0.001$; Fig. 3). Moreover, the number of metastatic sites was significantly related to median survival (Fig. 4). Patients with a single-organ involvement survived a median of 60 months (95% CI: 42–73), whereas those with more than or equal to three involved sites survived a median of 36 months (95% CI: 18–45; $P = 0.007$). An improved median survival was also observed in patients with bone metastases only ($n = 40$; 46 months; 95% CI: 28–62).

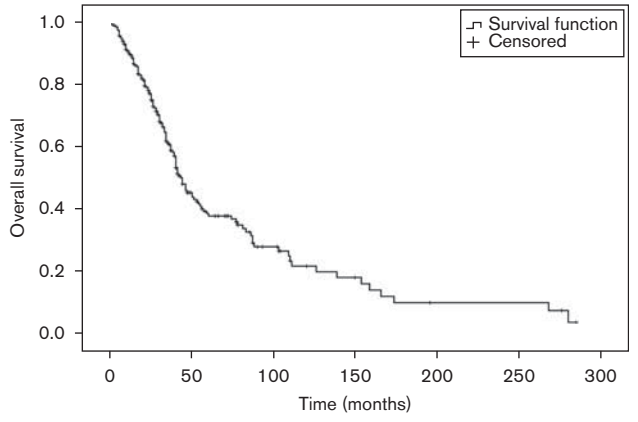
An improved survival was shown in patients with oligometastatic disease who underwent locoregional procedures (all $n = 31$; metastasectomy $n = 14$, RFA $n = 17$). Patients with resected lung metastases survived a median of 56 months (95% CI: 23–89) and those who had been treated by RFA to the liver survived a median of 50 months (95% CI: 31–69).

Fig. 2



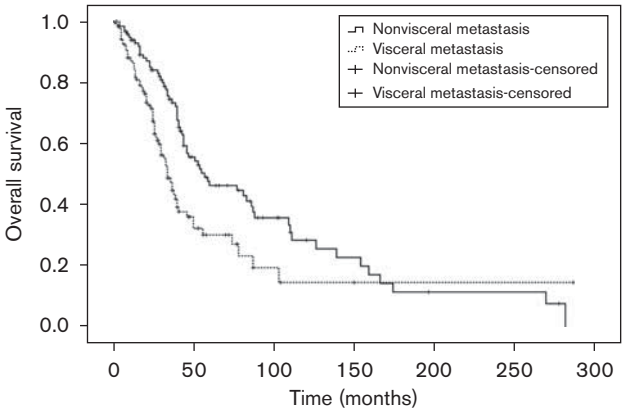
Median survival triple-negative breast cancer (TNBC) vs. hormone receptor (HR) and/or human epidermal growth factor (HER2)-positive patients: TNBC vs. HR+ and/or HER2+ 16 months [95% confidence interval (CI): 39–49] vs. 44 months (95% CI: 36–52); $P = 0.02$.

Fig. 1



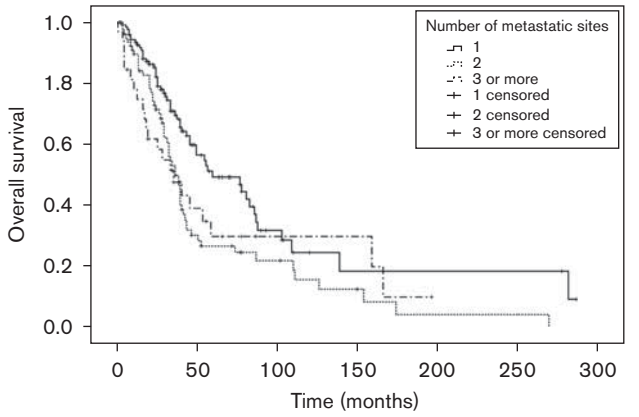
Median overall survival ($n = 232$), 44 months [95% confidence interval (CI)].

Fig. 3



Median survival visceral vs. nonvisceral involvement. Visceral vs. nonvisceral, 34 vs. 57 months; $P = 0.001$.

Fig. 4



Median survival number of metastatic sites developed during the course of disease: ≥ 3 vs. 1 metastatic site; 36 vs. 60 months; $P=0.007$.

Patients who had received three or fewer chemotherapy regimens ($n = 53.4\%$) survived 40 months compared with those with four to six regimens (22.1%) or 54 months in patients (12.9%) with more than six subsequent regimens during the course of their disease (≥ 6 vs. ≤ 3 regimens; $P = 0.66$).

Univariate and multivariate analyses

A univariate analysis was made to investigate the relation between prognostic factors and OS (Table 2). A P value of global test was calculated for categorical variables. Significant variables at the 20–25% level ($P < 0.2$) in the bivariate analysis were selected for the multivariate analysis.

For this study, the covariates tumor stage, node stage, estrogen receptor, progesterone receptor, HR, triple-negative disease, number of metastatic sites, visceral metastases, and distant metastases were therefore part of the multivariate logistic regression model. To avoid the problem of multicolinearity, this study took triple-negative disease (most significant associated with OS, $P = 0.02$) as a factor for the multivariate analyses and left estrogen receptor, progesterone receptor, and HR out of the analysis. The final model included 199 patients. The proportional hazards assumption of the Cox regression model was reasonably fulfilled ($P = 0.16$).

In the multivariable model tumor stage (P value of global test: < 0.01), triple-negative disease ($P = 0.02$), number of metastatic sites ($P = 0.02$), and visceral metastasis ($P < 0.01$) were statistically significant associated with worse OS after adjusting for all factors in the table (Table 3).

Discussion

Advances in the treatment of MBC have not only been made in supportive care as expressed by the wide use of the bisphosphonates or in the management of severe myelotoxicity but also in the introduction of innovative antihormonal therapies such as aromatase inhibitors and anticancer drugs such as taxanes [7,8,18,19]. Targeted strategies, such as the introduction of trastuzumab, improved survival of the HER2 overexpressing subgroup of patients with MBC [4,5]. Moreover, favorable advances have been made in the fields of surgery, radiotherapy, and minimal-invasive procedures such as thermodestructive techniques directed toward the liver [9,10,12,14,15,20]. Although there is a consensus that some active treatment modalities have emerged over the last decade in MBC, the impact of these advances in daily practice remains to be determined.

Generally, the median survival of patients with MBC ranges between 18 and 24 months [1,2]. Whether the introduction of innovative treatment approaches finally results in a prolonged survival still remains debatable [3,21].

Our retrospective analysis was based on the impression that the survival of patients with MBC in daily clinical practice differs considerably from the commonly published median survival of 18–24 months.

Above all, it is notable that our retrospective analysis represents approximately solely 1.6% of all patients with breast cancer in the catchment area of the tumor center of Munich. Moreover, it is critical to discuss that the interval between primary tumor and metastatic relapse, which is one of the most important prognostic factors in MBC, amounts to 35.5 months. This relatively long disease-free interval probably induced a bias due to selection of patients with a better prognosis. Finally, these data of these analyses have been collected retrospectively and represent solely the data of a single institution. One can argue that a university outpatient clinic preferentially selects those patients with a better prognosis or at least those who qualify for locoregional approaches such as RFA. As these techniques are not available all over the country, it is clear that patients with oligometastatic disease are over-represented in a specialized center.

The median OS of the entire study population in this analysis was 44 months, which is in clear contrast to the commonly reported range of 18–24 months, and also to the median OS of 29 months, which was reported by Andre *et al.* [3]. Apart from the mentioned probable bias, another possible explanation could be the period evaluated. Andre *et al.* [3] analyzed a period between 1994 and 2000 and they finally stated that most of their patients had never received trastuzumab or capecitabine. Particularly, the widely use of trastuzumab in the management of HER2-overexpressing MBC has markedly improved the prognosis of this subset of patients when compared with the prognosis of these patients in the pretrastuzumab era [4,22]. The median survival of 44 months in patients with HER2-overexpressing MBC

Table 2 Univariate analysis of prognostic factors for overall survival

	Overall survival			
Characteristics	Hazard ratio	95% CI	*P*	*P* value of global test for categorical variables
Age at metastatic disease	1.00	0.98–1.01	0.60	
Tumor stage				0.16
T1	5.16	1.10–23.58	0.04	
T2	0.86	0.44–1.66	0.65	
T3	0.71	0.37–1.37	0.31	
T4	1.54	0.68–3.46	0.30	
Node stage				0.18
N1	1.28	0.18–9.37	0.81	
N2	1.98	0.27–14.23	0.50	
N3	1.97	0.25–15.56	0.52	
Metastasis stage	0.98	0.60–1.62	0.94	
Grading				6.11
G1	0.00	0.00–8.55	0.95	
G2	0.84	0.59–1.19	0.32	
G3	–	–	–	
Estrogen receptor	0.72	0.49–1.06	0.09	
Progesterone receptor	0.70	0.49–1.06	0.09	
Hormone receptor	0.73	0.49–1.09	0.12	
HER2 receptor	1.25	0.85–1.83	0.26	
Triple-negative disease	2.22	1.12–4.40	0.02	
Number of metastatic sites				0.01
1	0.61	0.37–1.01	0.06	
2	1.09	0.66–1.78	0.75	
≥ 3	–			
Visceral metastases	1.76	1.24–2.50	<0.01	
Distant metastases	3.68	1.50–9.02	<0.01	

CI, confidence interval; HER2, human epidermal growth factor receptor 2.

Table 3 Multivariate analysis for overall survival

	Overall survival			
Characteristics	Hazard ratio	95% CI	*P*	*P* value of global test for categorical variables
Tumor stage				<0.01
T1	6.96	1.35–35.91	0.02	
T2	1.10	0.52–2.31	0.82	
T3	0.70	0.33–1.49	0.35	
T4	2.16	0.86–5.42	0.10	
Node stage				0.19
N1	2.83	0.37–21.37	0.31	
N2	3.81	0.51–28.34	0.19	
N3	5.31	0.65–43.61	0.12	
Triple-negative disease	2.53	1.18–5.41	0.02	
Visceral metastasis	2.10	1.34–3.18	<0.01	
Number of metastatic sites				0.02
1	0.95	0.53–1.71	0.86	
2	1.07	0.95–3.07	0.08	
≥ 3	–	–		
Distant metastasis	2.12	0.73–6.18	0.17	

CI, confidence interval.

underscores the advances that have been made in this subset of patients.

Analyzing the subgroup of patients with HR-positive tumors, we observed a median survival of 46 months, which is in accordance to the reported median survival (45 months) of this subset of patients in the study by Andre *et al.* [3].

A major concern is related to the selection of patients. One can argue that a single-institutional outpatient clinic selects much better patients. However, in our analyzed patient population 6% were negative for all three markers (triple-negative breast cancer) and 51% presented with visceral involvement. These percentages are comparable with previous studies of Gennari *et al.* [23] and Andre *et al.* [3] who reported a rate of visceral metastases in 57 and 54%, respectively. More than three metastatic sites during the clinical course have been observed in almost one-third of the analyzed patients, which is relatively high when compared with the 10-year follow-up study by Falkson *et al.* [24,25]. They reported a rate of 8–24% having more than three metastatic sites.

Some breast cancer subgroups have become a chronic disease. However, despite all advances in the management of MBC, there are still remaining problems as expressed by the dismal prognosis of those patients with triple-negative tumors (16 months, $P = 0.018$). The lack of any improvement of survival in this subgroup underscores the advances that have been undertaken in patients who are candidates for targeted immunotherapeutic strategies or antihormonal treatments. The introduction of poly (ADP ribose) polymerase inhibitors is probably a step toward an improved survival in this subset of patients with MBC [26,27].

The introduction of innovative approaches and drugs and the continuous and sequential treatment of patients seem beneficial for patients with MBC. This is supported by the observation that patients who have received three or fewer chemotherapy regimens survived for a shorter time period when compared with those who have received more than six subsequent regimens during the course of their disease (≥ 6 vs. ≤ 3 regimens, 54 vs. 40 months, $P=0.66$).

Although oligometastatic disease is a rare clinical presentation of MBC (< 5%), some efforts have been made in minimal-invasive locoregional procedures and/or surgical approaches [10,12,28–45]. Such an improved survival was observed in our small number of patients with oligometastatic disease who underwent locoregional procedures. A locoregional approach was offered to 31 of 232 patients (surgical metastasectomy $n = 14$, RFA $n = 17$). The survival of these preferentially selected patients was favorable with 56 months (95% CI: 23–89) in patients with resected lung metastases and with 50 months (95% CI: 31–69) in those who had been treated by RFA of liver metastases. In conclusion, these approaches seem to be valuable in the management of oligometastatic breast cancer and should therefore be offered to selected patients.

Although results from such a small and retrospective single-center analysis should be interpreted with caution, these data support the hypothesis that continuous and sequential treatment of patients with MBC may result in

a clinically relevant prolongation of survival. Considerable advances have been made in minimal-invasive procedures and supportive care. The use of all available treatment regimens and modalities for MBC to their full potential may result in a benefit of survival. Although these data seem to be in contrast to some epidemiological analyses, further prospective studies with clearly defined treatment sequences and full use of all available treatment modalities are necessary. These data show a selective patient population in a single-center setting, which report improved survival rates. Whether innovative medicine, a step-by-step escalation of all treatment modalities according to standard guidelines and individualized clinical requirements, and a multidisciplinary treatment approach contribute to these good outcomes is debatable.

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Conflicts of interest

There are no conflicts of interest.

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