Clinical outcome of brain metastases differs significantly among breast cancer subtypes

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Abstract. Brain metastases in patients with breast cancer are associated with a poor survival rate. A small number of studies have challenged this premise, suggesting that survival times following brain metastasis differ significantly between breast cancer subtypes. In the current study, overall survival (OS), brain metastases-free survival (BMFS) and survival following brain metastases (SFBM) were found to be associated with the intrinsic breast cancer subtype. A total of 1,147 patients with invasive breast cancer who were treated at the Hannover Medical School between January 2004 and December 2010 were included, from which 54 patients with brain metastases were identified. The Kaplan-Meier method or Cox regression analyses were performed for analysis of survival. OS was found to differ significantly between breast cancer subtypes: OS was significantly shorter in patients with triple-negative (TN) cancer compared with patients with human epidermal growth factor receptor (HER2)-enriched tumors (P<0.001). In addition, median BMFS times differed significantly between luminal (1,003 days), HER2-enriched (514 days) and TN breast cancer patients (460 days) (P=0.045). The median durations of SFBM were 386 days in luminal, 310 days in HER2-enriched and 147 days in TN breast cancer patients (P=0.029). The results suggested that patients with luminal breast cancer have a lower risk of brain metastases and the most favorable outcome with regard to BMFS, whereas patients with HER2-positive or TN breast cancer have a significantly higher risk of developing brain metastases. Compared with TN breast cancer, the duration of SFBM was doubled in HER2-enriched cancers. These findings may have important implications for treatment and follow-up strategies in patients with breast cancer.

Introduction

Breast cancer is the most frequently occurring cancer type in women and the second most common cause of brain metastases (1). The occurrence of brain metastases is typically associated with a limited survival time as well as reduced quality of life. Brain metastases usually occur late in the disease course of breast cancer, and are uncommon at the time of initial diagnosis of breast cancer (2,3). The risk factors for brain metastases include young age, tumor stage, human epidermal growth factor receptor (HER2)-positivity, triple-negativity, number of metastatic sites (n>2) and large tumor size (4-9). It has been estimated that 10-15% of patients with breast cancer will develop brain metastases (10), while postmortem studies have detected brain metastases in up to 30% of patients (11). The median time of brain metastases occurrence is 2-3 years after the initial diagnosis of breast cancer (12). Life expectancy is largely reduced following the diagnosis of brain metastases, with survival time ranging from 2 to 16 months (4). Although screening for brain metastases is not recommended as part of routine clinical care in asymptomatic patients, Miller et al (6) detected brain metastases in 15% of patients presenting with disseminated breast cancer at the initial screening. Treatment of brain metastases is challenging due to a number of factors; the number and location of brain metastases, performance status of the patient and biological subtype must be taken into consideration (13).

There is growing evidence that the risk of distant metastases differs according to the biological subtype of breast cancer (3,14). Compared with luminal subtypes, HER2-positive (15) and triple-negative (TN) breast cancer tend to spread significantly more often to the brain. However little is known about the subtype-specific outcomes with regard to brain metastases-free survival (BMFS) and survival following brain metastases (SFBM). The present study aimed to determine subtype-specific survival rates among breast cancer patients with brain metastases. The results suggest that in-depth knowledge of the natural history of brain metastases and their clinical outcome may aid in individualizing treatment strategies.

Materials and methods

Study patients. The present study retrospectively analyzed a cohort of patients with breast cancer who were treated at
the Hannover Medical School (Hannover, Germany) between January 1st, 2004 and December 31st, 2010. A total of 1,147 patients who met all inclusion criteria were identified from the Hannover Clinical Cancer Register database. The inclusion criteria were primary invasive breast cancer, no previous cancer and no simultaneous cancer of other origin. The exclusion criteria were benign diseases of the breast, ductal carcinoma in situ, microinvasive carcinoma, missing hormone receptor (HR) and/or HER2 receptor status, and rare histology (atypical carcinoid tumor, sclerosing sweat duct carcinoma, signet ring cell carcinoma, sarcoma, myoepithelioma, carcinoma-sarcoma and phyllodes tumor). All patients provided written informed consent and the study was approved by the local ethics committee.

Intrinsic breast cancer subtype. Each primary breast cancer tumor was assessed for HR and HER2 expression by immunohistochemistry (IHC). Immunohistochemical staining was part of routine diagnostics and performed according to the American Society of Clinical Oncology (ASCO)/College of American pathologists (CAP) Clinical Practice Guidelines (16,17). The results of this staining was taken from patients' records. HER2-negative by clinical assay was defined as IHC 0/1+ or 2+, confirmed by a fluorescence in situ hybridization (FISH)/chromogenic in situ hybridization amplification ratio of <2.0. Estrogen receptor (ER) and/or progesterone receptor (PR) IHC expression of ≥10% was considered positive. Hormone receptor positivity was defined as ER or PR were positive. Intrinsic subtypes were assigned as follows: Luminal subtype, HR+/HER2-; HER2-enriched subtypes, HR+/HER2+; and TN subtype, HR-/HER2-. The results were assigned according to the ASCO/CAP guidelines (16,17).

Outcomes. Overall survival (OS) was defined as the time from the initial breast cancer diagnosis to the final follow-up or mortality. BMFS was defined as the time from breast cancer diagnosis to the diagnosis of brain metastases. SFBM was defined as the time from diagnosis of brain metastases to the date of mortality or last follow-up.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM SPSS, Armonk, NY, USA) and GraphPad Prism 5 (GraphPad Inc., La Jolla, CA, USA) to create figures. Categorical data were compared with χ² test or Fisher's exact test, as appropriate. Group differences were calculated using Kruskal-Wallis test for nonparametric data. Survival was estimated by the Kaplan-Meier method and compared with the log-rank (Mantel-Cox) test between breast cancer subtypes. Cox regression analysis was performed to evaluate the hazard ratio and corresponding 95% confidence interval (95% CI). P≤0.05 was considered to indicate a statistically significant difference. All survival times were calculated in days for the purpose of precise results.

Results

Patient and tumor characteristics. Patient and tumor characteristics are specified in Table I. Among the 1,147 total patients, 770 patients (67.13%) had luminal-type, 202 (17.61%) had HER2-enriched and 175 (15.26%) had TN breast cancer. Among the group of HER2-enriched tumors, 113 (9.85%) were HR-positive and 89 (7.76%) were HR-negative.

Distant metastases were found in 77 of the 1,147 patients (6.71%) at the time of diagnosis of breast cancer; in total, 217 patients (18.92%) developed distant metastases during the course of the disease. There were 54 patients (4.71%) who developed brain metastases, including 9 (11.69%) who already had brain metastases at the time of initial breast cancer diagnosis. Among those with brain metastases, 12 patients (1.56%) had luminal, 20 (9.90%) had HER2-enriched and 22 (12.57%) had TN primary breast cancer (P<0.001). The number and the treatment of brain metastases among these patients are shown in Table II. Between the various intrinsic subtypes of breast cancer, there were no significant differences in the number of brain metastases or the type of treatment, with the exception of anti-hormone therapy.

Overall survival in the entire study population. The OS time in the entire study cohort [n=1,147; median, 1,376 days (46 months)] differed significantly according to breast cancer subtype (P<0.001; Fig. 1A). Patients with TN breast cancer had a significantly shorter OS than patients with luminal breast cancer (hazard ratio, 2.20; 95% CI, 1.59-3.04; P<0.001) and patients with HER2-enriched tumors (hazard ratio, 1.66; 95% CI, 1.11-2.50; P=0.015). There was no significant difference between the luminal and HER2-positive breast cancer subtypes (hazard ratio, 1.32; 95% CI, 0.93-1.89; P=0.123). Of the 202 patients with HER2-positive breast cancer, 153 (75.74%) received anti-HER2 therapy whereas 33 patients (16.34%) did not; in the remaining 16 cases (7.92%), this information was not available.

It is well-recognized that HER2-positive tumors are of a heterogeneous nature (18). Therefore, a comparison was also performed after dividing the patients into four distinct subgroups: Luminal, HR+/HER2+, HR-/HER2+ and TN subtypes. From this analysis, significant differences in OS were detected (P<0.001; Fig. 1B): Patients with HR-/HER2+ cancer had a significantly reduced OS compared with those with luminal breast cancer (P=0.049; hazard ratio, 1.58; 95% CI, 1.00-2.49); and patients with TN cancer had a significantly poorer OS compared with those with luminal (P<0.001; hazard ratio, 2.20; 95% CI, 1.59-3.04) and those with HR+/HER2+ cancer (P=0.011; hazard ratio, 1.97; 95% CI, 1.17-3.33).

Survival outcomes in patients with brain metastases. Among the 54 patients who developed brain metastases, the median BMFS was 600 days (20 months) (95% CI, 379.15-820.85 days) and differed significantly by breast cancer subtype. The median BMFS was 1,003 days (33 months) (95% CI, 840.05-1,165.95 days) in luminal, 514 days (17 months) (95% CI, 283.91-744.09 days) in HER2-enriched and 460 days (15 months) (95% CI, 154.33-765.67 days) in TN breast cancer patients (P=0.045; Fig. 2). In addition, slight differences in BMFS were observed when comparing the four distinct breast cancer subtypes (P=0.069). Patients with HER2-positive breast cancer demonstrated a significantly shorter BMFS compared with patients with the luminal subtype (hazard ratio, 2.62; 95% CI, 1.19-5.77; P=0.017), irrespectively of whether anti-HER2 therapy was received.
Table I. Baseline characteristics of 1,147 breast cancer patients.

| Characteristic                        | Luminal | HR+/HER2+ | HR-/HER2+ | TN        | P-value |
|---------------------------------------|---------|-----------|-----------|-----------|---------|
| Number of patients (% of total)       | 770 (67.13) | 113 (9.85) | 89 (7.80) | 175 (15.26) | -       |
| Age at diagnosis, years               | <0.001  |           |           |           |         |
| Median                               | 57      | 53        | 50        | 49        |         |
| Interquartile range                   | 47.0-67.0 | 44.5-64.0 | 42.0-61.0 | 38.0-60.0 |         |
| Grade [n (%)]                         | <0.001  |           |           |           |         |
| G1                                    | 78 (10.13) | 1 (0.88)  | 1 (1.12)  | 3 (1.71)  |         |
| G2                                    | 469 (60.91) | 48 (42.48) | 25 (28.09) | 28 (16.00) |         |
| G3                                    | 199 (25.84) | 59 (52.21) | 58 (65.17) | 132 (75.43) |         |
| G4                                    | 0 (0.00)  | 2 (1.77)  | 0 (0.00)  | 5 (2.86)  |         |
| GX                                    | 24 (3.12) | 3 (2.65)  | 5 (5.62)  | 7 (4.00)  |         |
| Histology [n (%)]                     | <0.001  |           |           |           |         |
| Invasive ductal carcinoma             | 596 (77.40) | 104 (92.04) | 81 (91.01) | 145 (82.86) |         |
| Invasive lobular carcinoma            | 118 (15.32) | 6 (5.31)  | 2 (2.25)  | 3 (1.71)  |         |
| Other                                 | 56 (7.27) | 3 (2.65)  | 6 (6.74)  | 27 (15.43) |         |
| pT stage [n (%)]                      | <0.001  |           |           |           |         |
| pT1                                   | 397 (51.56) | 49 (43.36) | 27 (30.34) | 63 (36.00) |         |
| pT2                                   | 208 (27.01) | 29 (25.66) | 28 (31.46) | 52 (29.71) |         |
| pT3                                   | 34 (4.42)  | 2 (1.77)  | 4 (4.49)  | 5 (2.86)  |         |
| pT4                                   | 13 (1.69)  | 2 (1.77)  | 2 (2.25)  | 3 (1.71)  |         |
| Missing/unknown                       | 118 (15.32) | 31 (27.43) | 28 (31.46) | 52 (29.71) |         |
| pN stage [n (%)]                      | <0.001  |           |           |           |         |
| pN0                                   | 402 (52.21) | 39 (34.51) | 25 (28.09) | 72 (41.14) |         |
| pN1                                   | 162 (21.04) | 25 (22.12) | 13 (14.61) | 28 (16.00) |         |
| pN2                                   | 41 (5.32)  | 8 (7.08)  | 10 (11.24) | 13 (7.43)  |         |
| pN3                                   | 38 (4.94)  | 8 (7.08)  | 11 (12.36) | 7 (4.00)  |         |
| Missing/unknown                       | 127 (16.49) | 33 (29.20) | 30 (33.71) | 55 (31.43) |         |
| ypT stage (n=160) [n (%)]             | <0.001  |           |           |           |         |
| ypT0                                  | 6 (3.75)  | 3 (1.88)  | 6 (3.75)  | 17 (10.63) |         |
| ypTis                                 | 3 (1.88)  | 2 (1.25)  | 9 (5.63)  | 2 (1.25)  |         |
| ypT1                                  | 28 (17.50) | 10 (6.25) | 7 (4.38)  | 12 (7.50) |         |
| ypT2                                  | 19 (11.88) | 5 (3.13)  | 0 (0.00)  | 9 (5.63)  |         |
| ypT3                                  | 7 (4.38)  | 1 (0.63)  | 0 (0.00)  | 1 (0.63)  |         |
| ypT4                                  | 4 (2.50)  | 1 (0.63)  | 2 (1.25)  | 3 (1.88)  |         |
| Missing/unknown                       | 1 (0.63)  | 0 (0.00)  | 1 (0.63)  | 1 (0.63)  |         |
| ypN stage (n=147) [n (%)]             | 0.065    |           |           |           |         |
| ypN0                                  | 26 (17.69) | 8 (5.44)  | 16 (10.88) | 31 (21.09) |         |
| ypN1                                  | 16 (10.88) | 9 (6.12)  | 6 (4.08)  | 5 (3.40)  |         |
| ypN2                                  | 13 (8.84) | 3 (2.04)  | 1 (0.68)  | 3 (2.04)  |         |
| ypN3                                  | 3 (2.04)  | 0 (0.00)  | 1 (0.68)  | 1 (0.68)  |         |
| Missing/unknown                       | 3 (2.04)  | 0 (0.00)  | 1 (0.68)  | 1 (0.68)  |         |
| Metastases stage [n (%)]              | 0.032    |           |           |           |         |
| M0                                    | 716 (92.99) | 98 (86.73) | 77 (86.52) | 160 (91.43) |         |
| M1                                    | 46 (5.97)  | 13 (11.50) | 8 (8.99)  | 10 (5.71) |         |
| MX                                    | 8 (1.04)  | 2 (1.77)  | 4 (4.49)  | 5 (2.86)  |         |
| Surgery                               | 0.018    |           |           |           |         |
| No                                    | 29 (3.77) | 5 (4.42)  | 1 (1.12)  | 3 (1.71)  |         |
| Yes                                   | 738 (95.84) | 105 (92.92) | 88 (98.88) | 172 (98.29) |         |
| Unknown                               | 3 (0.39)  | 3 (2.65)  | 0 (0.00)  | 0 (0.00)  |         |
The median duration of SFBM was 246 days (8 months) (95% CI, 128.65-363.35 days) and this differed significantly among the subtypes (P=0.029; Fig. 3A): The median duration of SFBM was 386 days (13 months) (95% CI, 0.00-914.26 days) in luminal, 310 days (10 months) (95% CI, 0.00-658.19 days) in HER2-enriched and 147 days (5 months) (95% CI, 109.64-184.36 days) in TN breast cancer patients.

With regard to luminal, HR+/HER2+, HR-/HER2+ and TN breast cancer subtypes, the median durations of SFBM were 386 days (13 months) (95% CI, 0.00-914.26 days), 837 days (28 months) (95% CI, 0.00-2,301.57 days), 310 days (10 months) (95% CI, 227.49-392.51 days) and 147 days (5 months) (95% CI, 109.64-184.36 days), respectively (P=0.042; Fig. 3B). Patients with TN cancer had a significantly
shorter SFBM compared with that of HER2-positive patients (P=0.013; hazard ratio, 2.66; 95% CI, 1.23–5.73), particularly those with the HR+/HER2+ subtype (P=0.013; hazard ratio, 4.44; 95% CI, 1.36–14.49).

OS in the 54 patients with brain metastases did not differ significantly between breast cancer subtypes (P=0.180). The median OS times were 1,282 days (43 months) (95% CI, 817.03–1,746.97 days) in patients with HER2-enriched breast cancer, 664 days (22 months) (95% CI, 338.79–989.21 days) in patients with TN breast cancer and 1,690 days (56 months) (95% CI, 1,038.21–2,341.79 days) in patients with luminal breast cancer.

### Discussion

The incidence of brain metastasis detection in breast cancer is increasing due to advances in imaging technologies and the introduction of novel therapies resulting in longer survival...
time (9,19). In-depth understanding of the natural history of brain metastases can aid in the optimization of treatment and follow-up strategies.

It is accepted that the risk of metastasis and the survival times vary significantly among breast cancer subtypes, which was confirmed in the current single-institution cohort study. Patients with TN breast cancer had a significantly decreased OS compared with those with luminal or HER2-positive breast cancer subtypes. However, no significant difference in OS was identified between luminal and HER2-positive breast cancer, which is most likely attributable to the fact that the majority of HER2-positive patients that were included in this study received HER2-targeted treatment.

Due to the limited number of patients in the current study, OS did not significantly differ among patients with brain metastases with different intrinsic subtypes. However numerically, OS was longest in patients with luminal breast cancer [1,690 days (56 months)] compared with patients with HER2-enriched [1,282 days (43 months)] and TN cancers [664 days (22 months)]. These differences may be explained, in part, by the differences in BMFS; metastases of luminal breast cancer occur rather late in the course of the disease (4,20). In fact, it was demonstrated that BMFS varies significantly between breast cancer subtypes, with luminal breast cancer patients showing the most favorable outcome. The median BMFS was 33 months in luminal compared to 17 months in HER2-enriched and 15 months in TN breast cancer patients (P=0.045).

SFBM significantly differed in the current study cohort (P=0.042). TN patients had the poorest survival time (5 months) compared with luminal (13 months), HR+/HER2+ (28 months) and HR-/HER2+ (10 months) tumors, respectively. These findings are consistent with previous reports demonstrating that the median length of SFBM is <6 months in patients with TN breast cancers (21-23). This indicates that treatment strategies for TN patients with brain metastases should be carefully selected and should acknowledge the limited prognosis. By contrast, SFBM was doubled in HER2-enriched cancer cases (10 months) compared with TN breast cancers (5 months), despite similar BMFS times; this may reflect the high efficiency of HER2-targeted treatment strategies (21,24).

With regard to brain metastases in cases of the luminal subtype, data varies among studies; certain authors have reported a median SFBM similar to that of TN patients (22), speculating that the lack of further treatment options later in the course of the disease could explain the poor prognosis. By contrast, the present data and that of Niwińska et al (23) demonstrated median SFBMs in luminal tumors of 13 months and 15 months, respectively. In the present study, the survival time of this subgroup was longer than that of patients with TN or HR-/HER2+ breast cancer.

In the past, HER2-positive breast cancer has been considered as a single disease entity. However, there is mounting evidence to suggest that HER2-positive breast cancers are clinically and biologically heterogeneous (18). This is recognized by the St. Gallen's criteria, which divide HER2-positive disease into two groups: ER+/HER2+ and ER-/HER2+ (25). In the present study, ~75% of the patients with HER2-positive breast cancer received HER2-targeted treatment. The OS in HR+/HER2+ patients was significantly shorter compared with that of patients with luminal breast cancer (P=0.049; hazard ratio, 1.58; 95% CI, 1.00-2.49). By contrast, the OS of HR+/HER2+ patients was comparable to that of luminal breast cancer. These findings are in line with previous studies, which have shown that adjuvant treatment with trastuzumab is associated with a 40% increase in disease-free survival and OS times in HR+/HER2+ cancers as compared with HR+/HER2+ cancers (26,27).

There are several limitations of the present study. All patients included in this retrospective analysis were treated at a single institution between 2004-2010, and only 54 patients with brain metastases met all inclusion and exclusion criteria of the study. Therefore, subgroup analysis must be interpreted with caution. Due to the small and varying subgroup sizes of the patients with brain metastases, a distinct multivariate analysis was not appropriate. In addition, immunohistochemical staining and FISH analysis were used to define subtypes of breast cancer, rather than gene expression analysis. However, considerable efforts have been made to ensure the high-quality of immunohistochemical analysis of steroid hormone receptors and HER2 status (28). Despite these efforts, immunostaining remains only a surrogate marker of...
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