

Clinical outcomes after a diagnosis of brain metastases in patients with estrogen- and/or human epidermal growth factor receptor 2-positive versus triple-negative breast cancer

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Background: Women with triple-negative (TN) breast cancer are at increased risk of distant metastases and have reduced survival versus other breast cancer patients. Relative survival of women with TN breast cancer who develop brain metastases is unknown.

Methods: Patients with breast cancer who developed brain metastases at our institution from 1993 to 2006 were reviewed. Four survival time intervals were compared in patients with TN disease and those with non-TN disease: initial diagnosis to distant metastases, distant metastases to brain metastases, brain metastases to death, and overall diagnosis to death.

Results: One hundred and eighteen patients were identified. Fifty-one (50%) of 103 were estrogen receptor positive, 26 (39%) of 67 were human epidermal growth factor receptor 2 positive, and 20 (22%) of 91 were TN. Survival times were shorter for TN patients, with overall survival of 26 months in TN patients versus 49 months for non-TN patients. In TN patients, time to development of distant metastases, brain metastases, and death after brain metastases was shorter than in non-TN patients.

Conclusion: Patients with TN disease were more likely to develop distant metastases earlier than non-TN patients, developed brain metastases sooner, and had shorter overall survival.

Key words: brain metastasis, brain tumors, breast cancer, hormonal therapy, survival, triple-negative breast cancer

introduction

Molecular and gene expression profiling has shown that breast cancers are a heterogeneous group of tumors with several subtypes, including the luminal subtypes (hormone receptor positive), the human epidermal growth factor receptor 2 (HER2)-positive subtype (*ERBB2* positive), and the basal subtype [1–3]. Basal subtype breast cancers, commonly referred to as triple-negative (TN) tumors, are estrogen receptor (ER), progesterone receptor (PR), and HER2 negative and account for 15% of all newly diagnosed breast cancers [1]. These tumors are typically high grade and are often associated with *TP53* mutations, HER1, basal cytokeratins, and *c-kit* overexpression. TN disease is more likely to develop in two subsets of patients, those with *BRCA1* mutations [2–4] and young women of African-American descent [5]. Targeted therapies such as trastuzumab or antiestrogen agents (such as tamoxifen or aromatase inhibitors) have reduced the recurrence rate and

improved survival in patients with HER2- or hormone receptor-positive disease [6]. Patients with TN tumors, however, have no specifically targeted therapy available that can improve long-term survival and are at increased risk for distant metastases and poor survival [2, 5, 7].

The incidence of brain metastases in patients with breast cancer has been estimated historically at between 10% and 16% [8]. Once brain metastases develop, survival is limited, with a 1-year survival of ~20% [8]. Patients who undergo no further treatment are likely to succumb to the disease within weeks. Treatment options, including surgical excision, whole-brain radiotherapy, stereotactic radiosurgery, or a combination of therapies, may improve survival in patients with brain metastases [8–10]. The benefit of targeted systemic therapy is less consistent because trastuzumab does not effectively cross the blood–brain barrier, and data with lapatinib show modest benefit, even in patients whose tumors are HER2 positive [11–13]. Therefore, the clinical implications of TN disease, for which there is no specifically targeted therapy, on the presence of brain metastases, as well as its impact on survival, is unknown. The purpose of this study was to

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determine if the survival of patients with TN breast cancer differs from that in other, non-TN breast cancer patients with brain metastases.

methods

data collection

The electronic medical record system was accessed to obtain all medical records of breast cancer patients with brain metastases who were seen at Mayo Clinic in Jacksonville, FL, from 1993 to 2007. Information obtained from these records was entered into an electronic spreadsheet for analysis. Data extracted included the patients' demographic information, age at diagnosis, tumor histology, biological marker status, including ER, PR, and HER2; staging information and grade; treatment; survival status; and dates of initial diagnosis, distant metastasis, brain metastasis, and death (if applicable). This study was conducted with the approval of the Mayo Clinic Institutional Review Board.

statistical analysis

Cox proportional hazards analysis was used to analyze the effects of molecular marker status on four time intervals: time from diagnosis to distant metastases, time from distant metastases to brain metastases, time from brain metastases to death, and time from diagnosis to death [14]. Specifically, patients with TN disease were compared with patients with ER/PR-positive tumors (defined as >5% of nuclei staining) or HER2-positive tumors (defined as 3+ by immunohistochemistry or a score of >2.0 by FISH). The validity of the proportional hazards assumption was assessed using log-log survival plots, and Kaplan–Meier survival curves were produced to illustrate differences in survival between the comparison groups. Results were judged to be statistically significant for $P < 0.05$ according to the Wald test, and no adjustments were made for multiple hypothesis tests in this exploratory retrospective analysis. All analyses were carried out using SAS version 9.1 (SAS Institute Inc, Cary, NC).

results

One hundred and eighteen breast cancer patients with brain metastases were identified as eligible for analysis. Partial or complete biological marker status was available for 103 patients: 51 (50%) of 103 patients typed for ER were positive; 40 (41%) of 98 patients typed for PR were positive; and 26 (39%) of 67 typed for HER2 were positive. Of these, sufficient information was available for ascertainment of tumor receptor status in 91 patients, who constituted the final analysis group. Twenty (22%) of these 91 patients had TN tumors.

The length of follow-up ranged from 3 to 302 months, with a median follow-up time of 42 months, and 79% of the patients were deceased. The median age at initial diagnosis was 52 years (range 30–86 years) and did not differ notably according to TN status (TN, 50 years; non-TN, 52 years). Of the 107 patients for whom race was known, 94 (88%) were white, five (5%) African-American, six (5%) Hispanic, and two (2%) Asian. Of all patients with TN disease, only three were Hispanic, accounting for 50% of the Hispanic patients in the study group and 19% of patients with TN disease. Only one African-American woman had sufficient molecular marker information to determine tumor subtype, and this patient's tumor was ER positive.

A majority of the TN tumors [11 of 17 (65%)] were grade 3, with six (35%) of 17 grade 2 and no grade 1 tumors (0 of 17)

identified (Table 1). Of the 16 TN patients with lymph node staging information, nine (56%) initially presented with positive lymph nodes at the time of surgery, compared with 25 (47%) of 53 non-TN patients. Stage N0 disease occurred in seven (44%) of 16 TN patients and 28 (53%) of 53 non-TN patients. Finally, seven (28%) of 16 TN patients were staged as having T1 disease compared with 22 (43%) of 51 non-TN patients.

Median survival times were shorter for patients with TN disease than for patients with other breast cancers, with a median time from initial diagnosis to death of 26 months (range 3–109 months) in TN patients and 49 months (range 4–302 months) in non-TN patients. Other time subintervals were shorter in TN patients as well, including the time from diagnosis to distant metastases, time from distant metastases to brain metastases, and time from brain metastases to death (Table 2).

When the times spent in each cancer development phase were compared between patients with TN disease and those who were positive for ER, PR, or HER2, the time from brain metastases to death was the only time that did not differ significantly between marker status categories (Table 3, Figure 1). Within the other time intervals, including the overall time from initial diagnosis to death, TN patients had ~1.70 to 2.44 times the hazard of progressing to the next disease stage compared with non-TN patients.

discussion

Patients with TN breast cancer and brain metastases had a significantly shorter overall survival than patients who were

Table 1. Grade, staging, and lymph node status at initial diagnosis^a

Characteristic	ER, PR, or HER2 positive	Triple negative
Grade		
1	1/47 (2%)	0/17
2	7/47 (15%)	6/17 (35%)
3	38/47 (81%)	11/17 (65%)
4	1/47 (2%)	0/17
LN positive	25/53 (47%)	9/16 (56%)
T staging		
T1	22/51 (43%)	5/18 (28%)
T2	20/51 (39%)	8/18 (44%)
T3	5/51 (10%)	2/18 (11%)
T4	4/51 (8%)	3/18 (17%)
N staging		
N0	28/53 (53%)	7/16 (44%)
N1	15/53 (28%)	2/16 (12%)
N2	5/53 (9%)	3/16 (19%)
N3	3/53 (6%)	2/16 (13%)
NX	2/53 (4%)	2/16 (13%)

^aAll variables are reported as fraction (percentage). Missing data were not distributed equally for all variables. Total percentages may exceed 100% due to rounding.

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node.

Table 2. Median (range) time (months) spent in each disease progression stage

Disease progression stage	ER, PR, or HER2 positive	Triple negative
Diagnosis to distant metastases	24 (0–263)	15 (0–54)
Distant metastases to brain metastases	11 (0–175)	3 (0–70)
Brain metastases to death ^a	7 (0–111)	7 (0–20)
Diagnosis to death ^a	49 (4–302)	26 (3–109)

^aThe date of death was not known for three patients.

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 3. Hazard ratios for the effect of triple-negative status by each disease progression stage

Disease progression stage	Sample no. (no. censored)	Hazard ratio (95% CI)	P value ^a
Diagnosis to distant metastases	91 (0)	1.81 (1.08–3.02)	0.02
Distant metastases to brain metastases	91 (0)	1.70 (1.02–2.83)	0.04
Brain metastases to death ^b	88 (19)	1.78 (0.98–3.24)	0.06
Diagnosis to death ^b	88 (19)	2.44 (1.34–4.45)	0.004

^aP values were obtained using Cox proportional hazards analysis.

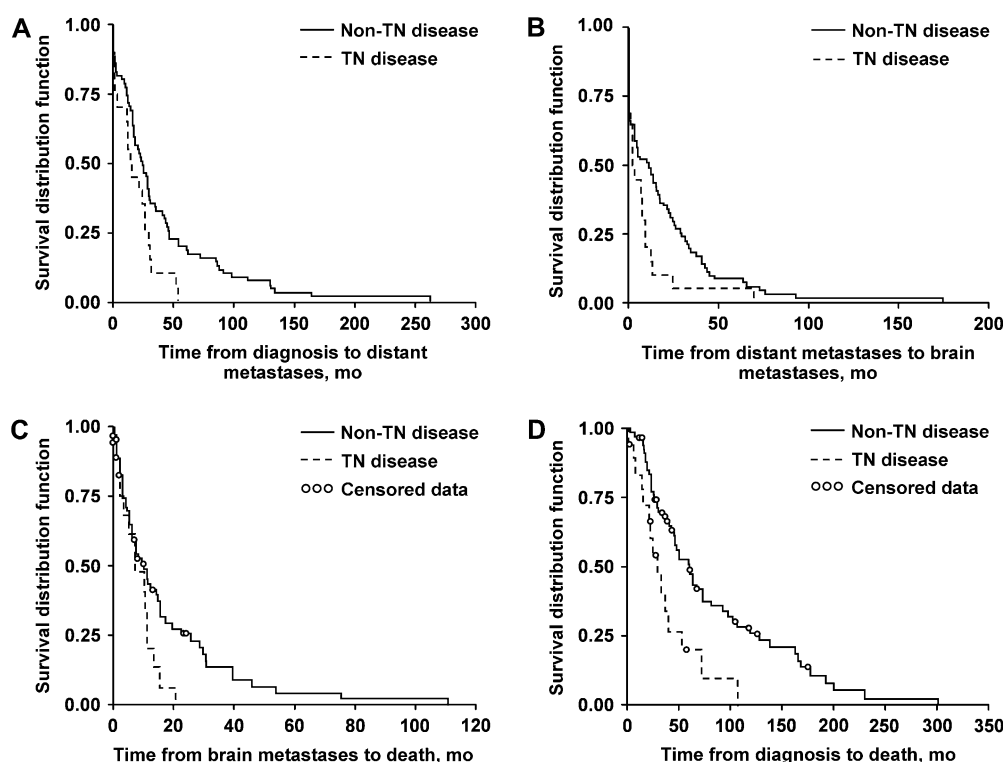
^bThe date of death was not known for three patients.

CI, confidence interval.

ER, PR, or HER2 positive. This reduction in survival is attributable to the significantly shorter time from initial diagnosis to distant metastases and distant metastases to brain metastases in patients with TN disease. The median time from brain metastases to death was 7 months for both groups, although the range was narrower in the TN patients.

These findings are consistent with several previously published reports that document an increase in the risk of distant metastases and a reduced cause-specific mortality in patients with TN disease compared with those who are ER, PR, or HER2 positive [5, 7]. Haffty et al. [7] found that TN patients have a reduced nodal relapse-free time, reduced distant metastases-free survival, and reduced survival compared with non-TN patients. TN status was also an independent predictor of distant metastases, with a hazard ratio of 2.15. Bauer et al. [5] also reported poorer survival in women with TN breast cancers, with 77% of women surviving 5 years after diagnosis compared with 93% 5-year survival in women with other breast cancers. Others [15, 16] have attempted to identify subgroups of women at higher risk of developing brain metastases and have reported that ER-negative tumors are more likely than ER-positive tumors to lead to brain metastases.

The survival difference may be related to the high-grade characteristics of TN disease, larger primary tumor size at diagnosis, or the initial lymph node status. Sixty-five percent of TN patients in this study had grade 3 disease, with 35% having grade 2 and none with grade 1 tumors. This observation is consistent with findings from Evans et al. [15] and Pestalozzi

**Figure 1.** Kaplan–Meier survival curves for the analyses of times from diagnosis to distant metastases (A), distant metastases to brain metastases (B), brain metastases to death (C), and diagnosis to death (D). Survival curves distinguish between patients with TN disease and those who are ER, PR, or HER2 positive.

et al. [16] that indicate that grade 3 tumors were a factor predictive of central nervous system (CNS) metastatic disease.

Findings from this study also suggest that women with TN disease who subsequently developed brain metastases were also more likely to present initially with a higher T stage on initial pathology, with 13 (72%) of 18 women with TN tumors having a T2 or greater tumor. This finding is consistent with the report by Haffty et al. [7] that patients with TN disease are more likely to have a higher pathologic T stage, as well as with the finding by Pestalozzi et al. [16] that tumors >2 cm are more likely to be associated with CNS metastases. The women with TN disease in this study were also more likely to present with a higher N stage, with nine (56%) of 16 women presenting with positive lymph nodes at the time of surgery, despite other reports that patients with TN disease have a decreased likelihood of nodal disease [4].

The specific time interval from brain metastases to death was shorter in patients with TN disease, although it was not statistically significantly shorter. This lack of statistical significance may be due to advancements in the treatment of patients with metastatic brain disease as most patients underwent surgical excision, whole-brain radiation, stereotactic radiosurgery, or a combination of these treatments. However, this difference in survival may be underestimated, given our small sample size and subsequent limited power to calculate the difference in survival.

The differences in survival may also be due in part to the availability of targeted systemic therapy. ER-positive tumors have been treated with tamoxifen, aromatase inhibitors, or both, which have proven to reduce recurrence rates and distant metastases and to improve survival. Tamoxifen has also been reported to cross the blood–brain barrier [17], which may help explain the improved survival in patients with ER-positive disease. Trastuzumab has been shown to reduce recurrence rates and improve survival in patients with HER2-positive disease, although the drug's molecule is thought to be too large to effectively cross the blood–brain barrier [11]. Therefore, its effect on metastatic brain disease in these women is less clear. Unfortunately, TN breast cancer patients are not candidates for the currently available targeted therapies that can reduce the risk of recurrence and improve survival in those with luminal or HER2 subtype disease, although this is the subject of many ongoing trials. This is another factor that may influence the difference in overall survival, although ongoing research into various molecular markers may help identify new targets for therapy.

Several studies have attempted to improve the characterization of TN breast cancer on the basis of gene and molecular profiling. Specific genetic expression patterns such as the luminal, *ERBB2*-positive, and basal subtypes have been described and correlated to specific molecular subtypes. Luminal subtypes are characterized by ER-positive tumors; HER2 subtypes by *ERBB2* positivity; and basal subtypes by the lack of ER or *ERBB2* expression [1–3]. Most TN breast cancers are basal subtype carcinomas on the basis of gene profiling [18]. Although the clinical implications of TN disease in patients with brain metastases has not been described previously, these tumors are characterized by frequent *TP53* mutations and higher expression of basal cytokeratins [1–5]

and are generally positive for HER1 expression, basal cytokeratins, and *c-kit*.

Despite the lack of a proven targeted therapy for TN disease, research is currently aimed at identifying biological therapies to the molecular markers specific to the TN breast cancer cells. Possible areas of future therapy include the evaluation of potential differential efficacy of different chemotherapy drugs, epidermal growth factor receptor antibodies such as cetuximab, *c-kit* growth factor receptor inhibitors such as imatinib, or a multitargeted kinase inhibitor such as dasatinib [19–21]. Other agents are being tested for possible inhibition of other components of the signal transduction cascade, including inhibitors of Ras, mTOR, and HSP90 [19].

study limitations

Our study has several limitations. Our small sample size likely contributed to limited power and imprecise effect estimates. This was also a retrospective study, lacking detailed molecular profiling and a hierarchical cluster analysis of the tissue, although previous studies have reported a high level of concordance between genetic profiles and the molecular profiles used in this review.

Despite these limitations, this exploratory study supports the hypothesis that patients with TN breast disease have a poorer prognosis than patients with non-TN breast disease, even after they develop brain metastasis. These findings emphasize that novel treatments should be separately developed for these patients because of the poor prognosis and unique biological characteristics of TN disease. It is imperative that prospective studies be conducted in these patients to fully determine the most appropriate diagnostic and therapeutic approaches.

conclusion

Patients with TN breast cancer have a higher rate of metastases, shorter time to development of metastases, and shorter survival after a diagnosis of brain metastases than patients with other types of breast cancer.

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