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Research Article

Effect of Central Nervous System Metastases on Treatment Discontinuation and Survival in Older Women Receiving Trastuzumab for Metastatic Breast Cancer

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Background. Trastuzumab improves survival in HER2-positive women with metastatic breast cancer (MBC). The consequences of longer survival include a higher likelihood of additional metastases, including those in the central nervous system (CNS). The effect of CNS metastases on both trastuzumab discontinuation and survival in older patients has not been described. *Patients and Methods*. We used the Surveillance Epidemiology and End Results (SEER) Medicare data to identify a cohort of 562 women age 66 or older with MBC who were diagnosed between January 1, 2000 and December 31, 2005, free of CNS metastases, and initiated trastuzumab after MBC diagnosis. Time to discontinuation and time to death were analyzed using proportional hazards models. *Results*. Newly diagnosed CNS metastases were associated with both higher risk of trastuzumab discontinuation (relative hazard [RH] = 1.78, 95% CI 1.11–2.87) and higher risk of death (RH = 2.49, 95% CI 1.84–3.37). The incidence rate of new CNS metastases was comparable among various sites of metastasis (10.7 to 14.7 per 1,000 patient-months), except for bone which was higher (24.1 per 1,000). *Conclusion*. The diagnosis of CNS metastases was associated with an increase in both the likelihood of discontinuing trastuzumab therapy as well as the risk of death.

1. Introduction

Central nervous system (CNS) metastases are common complications after the development of metastatic breast cancer (MBC), occurring in up to 15% of such patients according to observational data [1–4]. Autopsy studies show rates as high as 30% overall, which suggests that a substantial proportion is clinically undetected [5]. In addition, patients with human epidermal growth factor receptor-2 (HER2) positive disease who receive trastuzumab may have lifetime rates of CNS metastases as high as 50% [3].

In HER2-positive MBC, trastuzumab is indicated for use in combination with paclitaxel for first-line treatment, and as a single agent for patients who previously received at least one chemotherapy regimen [6]. While the safety and efficacy of trastuzumab have been evaluated in many clinical trials of women with MBC [7–15], less is known about the epidemiology of metastases in older HER2-positive populations who are more likely to have less aggressive disease and who are less well represented in trials.

Trastuzumab is associated with a significant improvement in mortality, changing the natural history of the disease and allowing patients to live longer. Because CNS metastases tend to appear later in the course of metastatic disease [16], the development of CNS metastases represents a growing challenge in the treatment of MBC, including possibly affecting decisions about discontinuation of therapy. Therefore, it is important to understand and quantify the extent to which the incidence of CNS metastases leads to treatment discontinuation [17].

The purpose of this study was to evaluate factors associated with discontinuation of therapy and with outcomes in HER2-positive older women with metastatic disease treated with trastuzumab. In particular, we sought to determine whether the newly diagnosed CNS metastases might affect both discontinuation of trastuzumab as well as mortality. A secondary objective was to identify other factors associated with discontinuation and mortality in this population.

2. Methods

2.1. Data Source. The source of data for this study was the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) cancer registry linked to Medicare enrollment and claims data (SEER-Medicare data). This database has been described in detail elsewhere [18]. SEER collects and publishes cancer incidence and survival data from 20 population-based cancer registries throughout the United States (US) covering approximately 26% of the US population [19]. The registries collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. Additional data on patterns of care and outcomes other than survival are only available through the incorporation of Medicare claims data. In the SEER-Medicare data, for persons age 65 years or older, 97% are eligible for Medicare, and 93% of patients in the SEER files are matched to the Medicare enrollment file [20]. At the time this study was performed, the SEER-Medicare linkage included all Medicare eligible persons appearing in 16 SEER registries through 2005 and their Medicare claims for Part A (inpatient) and Part B (outpatient and physician services) through 2006. Patients from the Greater Georgia [added in 2010] and Native American registries [Alaska Indian, Cherokee Nation, and Alaska Native] were not available.

2.2. Patient Eligibility. Two groups of women with metastatic disease were included in this study: those who were first diagnosed with Stage IV breast cancer between 2000 and 2005 (hereafter referred to as "incident" patients) and those who were diagnosed with Stage 0–III breast cancer between 2000 and 2005 and who were later diagnosed with a distant recurrence before the end of their Medicare claims (hereafter referred to as "recurrent" patients). Patients were included if they first received trastuzumab after diagnosis of MBC. In addition, we required that women be enrolled in Medicare Parts A and B, with no health maintenance organization (HMO) coverage for 12 months prior to diagnosis of MBC to ensure the availability of claims information to estimate baseline comorbidity burden. Women were excluded if they died during the month of diagnosis or if they had less than 12 months of Medicare participation before MBC diagnosis.

In addition, because our primary aim was to evaluate the effect of CNS metastases emerging after initiation of trastuzumab, women with CNS metastases at the time of trastuzumab initiation were excluded from the cohort and primary analyses. However, a sensitivity analysis was conducted by adding these women back into the cohort (see Section 2.7).

2.3. Timing of Exposures and Outcomes. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) procedure codes [21] and Healthcare Common Procedure Coding System (HCPCS) codes [22] within Medicare claims were used to identify intravenous chemotherapy agents and trastuzumab administered during the observation period. Medicare Part D (prescription drug coverage) data were not available; consequently, antiestrogen or other oral therapy could not be identified. For confidentiality reasons, SEER provides only the calendar month in which cancer was diagnosed, so for incident patients, the date of MBC diagnosis was defined as the first day of the diagnosis month. For recurrent patients, the date of diagnosis was defined as the date of the first Medicare claim indicating distant recurrence. The observation period began on the day trastuzumab was initiated (the index or baseline date).

The date of death was assigned by using the Medicare date. In cases where the Medicare date was missing, the SEER date was used. All other patients were assumed to be alive at the end of the analysis period (December 31, 2006), except for those switching from fee-for-service to HMO coverage who were censored at the time of the change in coverage. Discontinuation was defined as a period of at least 60 days with no trastuzumab treatment and no reinitiation, using the first day of the interval as the discontinuation date. As a result, patients were not at risk of discontinuation within 60 days of the end of observation, and death was not counted as discontinuation.

2.4. Patient Characteristics. Patients were described according to their demographic and clinical characteristics at the time MBC was diagnosed. Patient age at MBC diagnosis was stratified into five groups: 66–69, 70–74, 75–79, 80–84, and ≥85. Requiring eligible patients to have at least one year of Medicare enrollment prior to diagnosis ensured that the minimum age in the cohort was 66 years. Race/ethnicity was defined using the SEER recoded race variable as white, black, Hispanic, and other (which consists predominantly of American Indian/Native Alaskan, Native Hawaiian or Other Pacific Islander, and Asian) [23].

Medicare claims for inpatient, outpatient, and physician services were used to calculate an NCI Comorbidity Index for each patient [24–26]. The algorithms used to identify these conditions reflect the Deyo et al. [27] adaptation of the Charlson Comorbidity Index [28] and include several procedure codes from the Romano et al. [29] adaptation. A weight was assigned to each condition, and the weights were summed to obtain the index for each patient.

2.5. Identification of Recurrence and Metastases. For recurrent patients, distant recurrence was identified by an ICD-9-CM code in the medical claims for secondary cancer (197.XX–198.XX), excluding breast (198.81, 198.82) and lymph node (196.XX) [30, 31]. The number and location of metastases were identified using the specific ICD-9-CM

diagnosis codes for recurrence. Based on a recent validation study of CNS metastases in lung cancer patients, a single occurrence of ICD-9-CM code 198.3 was used to indicate the presence of a metastasis to the brain or spinal cord (hereafter referred to as CNS metastasis) [32]. All other metastases were identified and grouped into the following categories based on the specific codes: Bone, Lung/Chest, Liver, and Other. The first occurrence within each site category was recorded for each patient (see Section 2.6), and each was classified as being present either at the time of trastuzumab initiation (baseline) or afterward. Patients with more than one site of metastasis were not identified as unique groups because of the potentially large number of such groups.

2.6. Statistical Analysis. Cumulative incidence was estimated using Kaplan-Meier methods to account for censoring and death. Cumulative incidence rates were reported at 36 months when only 6% of the original cohort was still alive. Incidence rates were estimated across all time of observation and expressed in terms of cases per patient-month of observation.

Cox proportional hazards modeling was used to identify factors associated with time to trastuzumab discontinuation and time to death. Because trastuzumab therapy was a criterion for inclusion in this study, death could not have occurred until after trastuzumab was initiated. Therefore, to avoid immortal time bias [33], the index (baseline) date for these analyses was the date of the first claim for trastuzumab. An independent variable was included to account for the time (in days, transformed using the natural logarithm) from MBC diagnosis to initial trastuzumab, and this was evaluated in sensitivity analyses.

In the models of time to discontinuation, the sites of metastases were indicated both at baseline and as time-vary ing covariates after baseline (i.e., reflecting new metastases not present at the time of trastuzumab initiation). In addition, hospitalization (all-cause) was included as a time-varying covariate. Other patient and tumor characteristics were included as baseline covariates. In the models of time to death, the covariates were the same, except for the addition of a time-varying covariate indicating the discontinuation of trastuzumab. Analyses were not adjusted for multiple comparisons.

2.7. Sensitivity Analyses. Sensitivity analyses were conducted to test the robustness of the results to variations in model specification. This included adding patients with CNS metastases diagnosed before trastuzumab initiation to the cohort and including the presence of CNS metastases as a baseline covariate, as well as using a delayed entry approach to change the time scale of the models to time since MBC diagnosis rather than time since trastuzumab initiation. The latter approach more precisely controls for the time between MBC diagnosis and trastuzumab initiation by only including patients who survived the same length of time since diagnosis in the risk set [34].

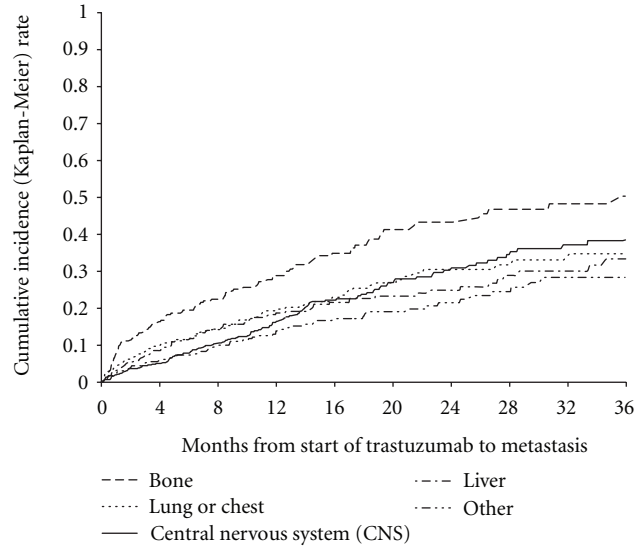

Figure 1: Cumulative incidence of metastases in women with metastatic breast cancer receiving trastuzumab over 36 months. Note: Data truncated at 36 months because only 6% of the cohort was available for additional followup. Incidence rates estimated in patients who were free of the particular metastasis at baseline. See Table 2 for number at risk for each site of metastasis.

3. Results

3.1. Characteristics of Patients at Trastuzumab Initiation. There were 562 patients who met the study inclusion criteria (Table 1). Sixty percent were diagnosed with recurrent disease, while the remaining patients were diagnosed with incident disease. The mean age was 76 years. Bone metastases were present at baseline in almost half of patients (48%) with other sites of metastasis present in 29% to 33% of patients. The average time of observation (from start of trastuzumab to death, the end of eligibility, or the end of observation) was 527 days. The median was 416 days, (interquartile range 199 to 712 days).

3.2. Incidence of Metastases. In women with recurrent disease ($n = 336$), the 5-year cumulative incidence of CNS metastases after starting trastuzumab was 37% (95% CI 27–49%) using the Kaplan-Meier estimator. In women with incident disease ($n = 226$), the 5-year cumulative incidence of CNS metastases after starting trastuzumab was 53% (95% CI 41–67%). The log-rank test for differences between the recurrent and incident groups was not significant ($P = 0.17$).

Incidence rates for the diagnosis of new metastases were comparable for CNS, lung/chest, and liver at approximately 14 per 1,000 patient years (Table 2 and Figure 1). The rate for bone metastases was higher at 24 per 1,000 patient-years, and lower for all other sites combined at 11 per 1,000 patient-years. At 24 months, the cumulative incidence of metastasis was as follows for each site: bone (43%, 95% CI 36%–51%), lung/chest (31%, 95% CI 25%–37%), CNS (31%, 95% CI 26%–37%), liver (25%, 95% CI 20%–31%), and other (22%, 95% CI 17%–28%).

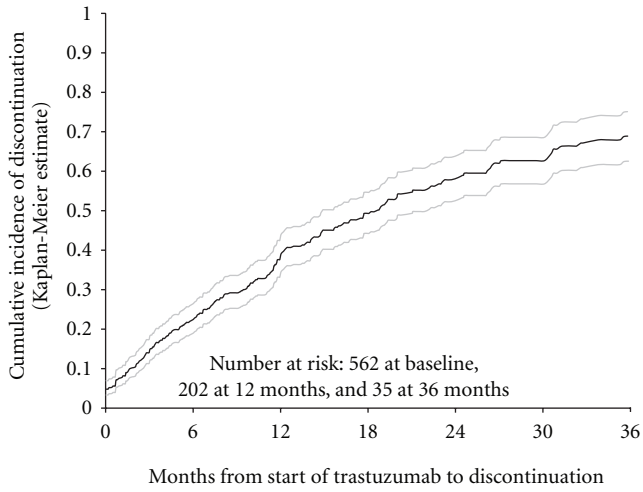

Figure 2: Cumulative rate of trastuzumab discontinuation in women with metastatic breast cancer. Note: Light gray bars represent 95% confidence interval bands.

3.3. Trastuzumab Discontinuation. The rate of trastuzumab discontinuation was estimated to be 37 per 1,000 patient-months with 58% (95% CI 52%–64%) of those still alive having discontinued by 24 months (Figure 2). In the model of time to trastuzumab discontinuation, none of the metastases present at baseline were associated with discontinuation (Table 3). The presence of newly identified CNS metastases after diagnosis was associated with a 1.78-fold higher risk of trastuzumab discontinuation (95% CI 1.11–2.87); no other newly identified sites of metastases were associated with discontinuation. The only other factor associated with discontinuation was that incident patients were 35% (95% CI 12%–52%) less likely to discontinue treatment compared to recurrent patients. See Table 3 for full model results.

3.4. Time to Death. Median survival from the time of trastuzumab initiation was 19 months (95% CI 15–22). In the multivariate proportional hazards model of time to death, the presence of liver metastases at baseline was associated with a 2-fold increase in risk, while baseline lung/chest metastases were associated with a 1.4-fold increase (Table 4). The diagnosis of new liver and CNS metastases over the follow-up period were associated with 2.5-fold and 2.8-fold increases in risk, respectively. Hospitalization for any reason and new cardiovascular disease were also strong independent predictors of death. Finally, the discontinuation of trastuzumab was also associated with death (HR = 2.44, 95% CI 1.90–3.15).

3.5. Sensitivity Analyses. When patients with CNS metastases at baseline (time of trastuzumab initiation) were added to the cohort ($n = 48$), the results did not change in any meaningful way and the presence of CNS metastases was not associated with a significantly different risk of discontinuation or death (results not shown). In addition, changing the time scale of the models to reflect time since diagnosis (rather than time since trastuzumab initiation) using a delayed entry approach also did not change the results.

4. Discussion

Based on these analyses of older women (≥66 years of age) with MBC, the diagnosis of CNS metastases was an independent risk factor associated both with the discontinuation of trastuzumab and with mortality. In addition, new liver and "other" metastases were also associated with a 2-3-fold increased risk of death. Based on these data, the risk of death in women taking trastuzumab who developed new CNS metastases appeared to be comparable to new liver metastases. This is a particularly interesting finding given the fact that women with CNS metastases were more likely to discontinue their trastuzumab therapy, but women with liver metastases were not.

This differential in discontinuation rates by site of metastasis suggests that risk of death is not the sole criterion used to determine discontinuation. One factor that may explain part of this differential is that, because trastuzumab does not easily cross the blood-brain barrier, clinicians may assume that trastuzumab is no longer effective and discontinue therapy. However, there is evidence that trastuzumab may still be effective in these patients, so it is not clear that discontinuation is the optimal approach [35].

The related question of whether the discontinuation of trastuzumab after CNS metastasis caused the higher mortality risk cannot be answered from this study design. This is because therapy discontinuation is confounded by the clinician's perception of the patient's prognosis. Without detailed clinical information, one can only approximate prognosis using the variables available in the data (e.g., hospitalization, new metastases, cardiovascular disease, etc.). This high correlation between an intervention and a patient's prognosis, sometimes referred to as "confounding by indication," is the most likely explanation for the higher mortality risk associated with trastuzumab discontinuation. In fact, a related limitation of these analyses is that we cannot distinguish trastuzumab discontinuation from discontinuation of chemotherapy because 85% of women receiving chemotherapy who discontinued trastuzumab also discontinued their chemotherapy at the same time.

In older women taking trastuzumab, metastases in the CNS developed at a rate that was similar to those for other sites (Figure 1 and Table 2). Furthermore, the linear nature of the cumulative incidence plot for all sites of metastasis through 36 months illustrates that, despite therapy with trastuzumab, MBC continued to progress over time with a fairly uniform risk of metastasis to other sites. Bone metastases were the most common occurrence, with much of the difference resulting from diagnoses made in the two months after trastuzumab initiation. This may reflect the availability of effective therapy for preventing skeletal-related events, and therefore a higher likelihood of having medical claims for this condition, rather than a higher incidence rate. Figure 1 suggests that CNS metastases were more commonly diagnosed in later in the course of metastatic disease rather than earlier, as suggested by others [16].

Table 1: Characteristics of patients without CNS metastases at the time of starting trastuzumab for metastatic breast cancer.

Characteristic		All Patients ($N = 562$)
Age at start of trastuzumab (years), Median (IQR)		75 (71–79)
Months from diagnosis to trastuzumab, Median (IQR)		2 (1–6)
Age category, *n* (%)	66–69	94 (17)
	70–74	181 (32)
	75–79	148 (26)
	≥80	139 (25)
Race/ethnicity, *n* (%)	White	455 (81)
	Black	62 (11)
	Hispanic	23 (4)
	Other	22 (4)
Year trastuzumab therapy started, *n* (%)	2000	19 (3)
	2001	47 (8)
	2002	68 (12)
	2003	89 (16)
	2004	119 (21)
	2005	136 (24)
	2006	84 (15)
Comorbidity score at start of trastuzumab, *n* (%)	0	495 (88)
	1	45 (8)
	≥2	22 (4)
Stage at initial diagnosis, *n* (%)	Recurrent Stage 0–III	336 (60)
	Incident Stage IV	226 (40)
ER/PR Status, *n* (%)	Both ER and PR positive	143 (25)
	Either ER or PR positive	91 (16)
	Both ER and PR negative	251 (45)
	Unknown	77 (14)
Metastases at start of trastuzumab, *n* (%)	Bone	269 (48)
	Liver	172 (31)
	Lung/Chest	184 (33)
	All Other	162 (29)

Note: IQR: interquartile range, ER: estrogen receptor, PR: progesterone receptor.

Table 2: Incidence rates for metastases by site.

Site of metastasis	Number starting trastuzumab without indicated metastasis	Number developing indicated metastasis	Incidence rate (95% CI)
CNS	562	125	14.1 (11.9–16.9)
Bone	293	101	24.1 (19.8–29.3)
Liver	390	86	13.5 (11.0–16.7)
Lung/Chest	378	82	14.7 (11.8–18.2)
All Other	400	68	10.7 (8.5–13.6)

Note: Rates estimated over all follow-up time and reported per 1,000 person-months of follow-up.

Women who were incident metastatic patients were 35% less likely to discontinue trastuzumab than those who were recurrent. While this same characteristic was not associated with a statistically significant change in mortality, the results suggest that continuing therapy is viewed differently in recurrent MBC compared to incident MBC. Finally, we also showed that many other factors aside from CNS metastases are associated with increased mortality risk in women with MBC, most notably hospitalization.

The incidence of CNS metastases in women receiving trastuzumab can be challenging to identify in the literature. While many studies report cumulative proportions of patients who develop metastases of 25% to 40%, most do not use methods that account for the duration of follow up, and

Table 3: Adjusted model for risk of permanent discontinuation of trastuzumab.

Characteristic		Adjusted HR (95% CI)	*P*-Value
Metastases present at trastuzumab initiation	Bone	0.96 (0.72–1.27)	0.76
	Liver	0.93 (0.68–1.27)	0.65
	Lung/chest	0.86 (0.63–1.16)	0.32
	Other	1.02 (0.74–1.40)	0.93
Diagnosed with metastases after start of trastuzumab*	CNS	1.78 (1.11–2.87)	0.02
	Bone	1.17 (0.75–1.84)	0.49
	Liver	1.08 (0.66–1.78)	0.76
	Lung/Chest	0.76 (0.46–1.26)	0.29
	Other	1.58 (0.95–2.64)	0.08
Hospital inpatient*	No	1.00 (ref)	0.49
	Yes	1.34 (0.59–3.06)	
Age at start of trastuzumab	66–69	1.00 (ref)	
	70–74	1.04 (0.70–1.54)	0.86
	75–79	0.95 (0.63–1.44)	0.81
	≥80	1.23 (0.81–1.87)	0.33
Need line above race/ethnicity	White	1.00 (ref)	0.20
	Non-White	1.24 (0.89–1.72)	
Time from MBC diagnosis to trastuzumab initiation	Per ln (days)	1.00 (0.92–1.09)	0.99
NCI comorbidity score at start of trastuzumab	0	1.00 (ref)	
	1	0.99 (0.62–1.60)	0.98
	≥2	1.68 (0.91–3.08)	0.10
Stage at initial diagnosis	Recurrent Stage 0–III	1.00 (ref)	0.005
	Incident Stage IV	0.65 (0.48–0.88)	
ER/PR Status	Hormone Positive	1.00 (ref)	
	Hormone Negative	1.05 (0.79–1.40)	0.73
	Unknown	1.14 (0.76–1.72)	0.53

Note: Asterisk (*) indicates time varying covariate. All listed covariates were included in one model. Nonwhite race includes Black, Hispanic, and Other as a combined category. Baseline defined as the date of trastuzumab initiation. Additional covariates in model that are not shown include a time-varying covariate for new cardiovascular disease and year of trastuzumab initiation (neither of which was statistically significant). Reference group for each metastasis covariate is the absence of the condition (HR = 1.0).

for losses to follow-up from death and the end of observation (e.g., using Kaplan-Meier or competing risk methods) [36–38]. However, at least three studies report 1-year Kaplan-Meier cumulative incidence estimates for CNS metastases in women receiving trastuzumab. These estimates, 26%, 27% and 30%, are closer to our 2-year estimate of 31% [39–41]. This suggests that the incidence of CNS metastases may be lower in older women, a finding consistent with findings from a large meta-analysis using competing risk methods [42]. One other challenge in comparing our results to those from other studies is that many focus on new CNS metastases without regard to other new sites of metastasis. Hence, it is impossible to discern whether the CNS metastases develop at a different rate than those at other sites. Therefore, in our study, we incorporated all sites of metastases to provide a more complete picture of their emergence over time.

There are limitations to these analyses what should be kept in mind. First, these were analyses of observational data. The identification of sites of metastases was based on diagnosis codes as recorded in administrative billing (i.e., claims) data, which may have limited sensitivity and specificity. In a validation study in non-small cell lung cancer using claims data, the use of a single diagnosis code for CNS and spinal cord metastases was associated with 100% sensitivity (i.e., all patients with CNS metastases were correctly identified) and with 97% specificity (some false positives were also captured) [31]. Similarly, a study by Lamont in breast cancer showed that using diagnosis codes for metastasis was associated with 100% sensitivity and 97% specificity in an analysis of progression-free survival (using clinical trial data as the gold standard) [32]. While supportive of our approach, these studies were generally small and it is possible that the sensitivity and specificity are not as high in our data. Importantly, other than the validation study for CNS metastases, there is no data to estimate the sensitivity or specificity of identifying specific sites of metastasis. Hence, these rates should be interpreted cautiously. Furthermore, as noted above regarding bone metastases, the rates of diagnosis of these metastases are likely to reflect both screening practices as well as available interventions.

Table 4: Adjusted model for risk of death.

Characteristic		Adjusted HR (95% CI)	*P*-Value
Metastases present at trastuzumab initiation	Bone	1.17 (0.75–1.84)	0.49
	Liver	2.03 (1.55–2.64)	<0.001
	Lung/chest	1.36 (1.04–1.78)	0.02
	Other	0.72 (0.53–0.96)	0.03
Diagnosed with metastases after start of trastuzumab*	CNS	2.49 (1.84–3.37)	<0.001
	Bone	1.34 (0.93–1.94)	0.12
	Liver	2.72 (1.93–3.84)	<0.001
	Lung/Chest	1.39 (0.98–1.97)	0.07
	Other	1.91 (1.31–2.78)	0.001
Discontinued trastuzumab therapy*	No	1.00 (ref)	<0.001
	Yes	2.44 (1.90–3.15)	
Hospital inpatient*	No	1.00 (ref)	<0.001
	Yes	7.04 (5.32–9.32)	
Age at start of trastuzumab	66–69	1.00 (ref)	
	70–74	1.17 (0.80–1.69)	0.42
	75–79	1.17 (0.80–1.72)	0.42
	≥80	1.24 (0.84–1.81)	0.28
Race/ethnicity	White	1.00 (ref)	0.22
	Non-White	1.21 (0.89–1.63)	
Time from MBC diagnosis to trastuzumab initiation	Per ln (days)	1.07 (0.98–1.15)	0.12
NCI comorbidity score at start of trastuzumab	0	1.00 (ref)	
	1	1.27 (0.80–2.01)	0.31
	≥2	0.95 (0.48–1.85)	0.87
Cardiovascular disease*	Yes	3.23 (2.43–4.30)	<0.001
Stage at diagnosis	Recurrent Stage 0–III	1.00 (ref)	0.23
	Incident Stage IV	0.86 (0.66–1.10)	
ER/PR Status	Hormone Positive	1.00 (ref)	
	Hormone Negative	1.06 (0.81–1.40)	0.67
	Unknown	1.40 (0.96–2.05)	0.08

Asterisk (*) indicates time varying covariate. All listed covariates were included in one model. Nonwhite race includes Black, Hispanic and Other as a combined category. Baseline defined as the date of trastuzumab initiation. Year of trastuzumab initiation (not significant) was also included as a covariate but results are not shown. Discontinuation was defined to be at least 60 days with no therapy. Reference group for cardiovascular disease and for each metastasis covariate is the absence of the condition (HR = 1.0).

In addition, we did not have access to data on oral therapies. While only 41% of the cohort was known to be hormone positive, information about hormonal therapy that might have been used in this subset of patients could have affected the results. Also, our data are relevant to older women with MBC and may not reflect the experiences of younger patients. Finally, our data reflect practice patterns from 2000 through 2006 and may not reflect current patterns of care.

5. Conclusion

The diagnosis of CNS metastases was associated with both discontinuation of trastuzumab therapy as well as with mortality. The rate of metastasis development appeared to be linearly related to survival time and appeared comparable among various sites of recurrence, with the possible exception of metastasis to the bone.

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