Breast Cancer Research and Treatment (2019) 173:209–216
https://doi.org/10.1007/s10549-018-4968-7

EPIDEMIOLOGY

Association between prolonged metastatic free interval and recurrent metastatic breast cancer survival: findings from the SEER database

Enoch Chang[1] · Sarah S. Mougalian[2,3,4] · Kerin B. Adelson[2,3,4] · Melissa R. Young[1,2,5] · James B. Yu[1,2,3,5]

Received: 26 July 2018 / Accepted: 12 September 2018 / Published online: 21 September 2018

Abstract

Purpose The prevalence of patients living with prolonged interval between initial breast cancer diagnosis and development of subsequent metastatic disease may be increasing with improved treatment. In order to counsel these patients as to their prognosis, we investigated the association between metastatic free interval (MFI) and subsequent survival from newly diagnosed metastatic breast cancer (MBC) in a population-level U.S. cohort.

Methods The Surveillance, Epidemiology and End Results database was used to identify patients with both an initial stage 1–3 breast cancer diagnosis and subsequent MBC diagnosis recorded from 1988 to 2014. Patients were stratified by MFI (< 5 years, 5–10 years, > 10 years). The association between MFI and metastatic breast cancer-specific mortality (MBCSM) was analyzed with Fine–Gray competing risks regression.

Results Five-year recurrent metastatic breast cancer-specific survival rate was 23%, 26%, and 35% for patients with MFI < 5, 5–10, and > 10 years, respectively. Patients with > 10 year MFI were less likely to die of breast cancer when compared with a referent group with < 5 years MFI (standard hazard ratio (SHR) 0.77 [95% CI 0.65–0.90] $P < 0.001$). There was no significant difference for patients with MFI of 5–10 years (SHR 0.92 [95% CI 0.81–1.04, P 0.191]) compared to < 5 years. Other prognostic factors like White race, lower tumor grade, and ER/PR-positive receptors were also associated with improved cancer-specific survival after diagnosis of MBC.

Conclusion Prolonged MFI greater than 10 years between initial breast cancer diagnosis and subsequent metastatic disease was found to be associated with improved recurrent MBC 5-year survival and decreased risk of breast cancer-specific mortality. This has potential implications for counseling patients as to prognosis, choice of treatment, as well as the stratification of patients considered for MBC clinical trials.

Keywords Breast neoplasms · Neoplasm metastasis · Prognosis · Disease-free survival · SEER program

Introduction

With breast cancer death rates falling on average 1.9% each year, patients are living longer after their breast cancer diagnoses [1]. Reflecting this trend, the prevalence of patients living with metastatic breast cancer in the United States has been steadily rising. Currently estimated at 154,794 in 2017, it is projected to increase by 31% from 2010 to 2020 [2]. With improved treatment and higher prevalence, it is also possible that we will observe longer intervals between initial diagnosis and subsequent metastasis. As more patients face this situation, it is important to be able to counsel them on the association between metastatic free interval and their prognosis.

Previous studies of patients treated in Japan [3], the Netherlands [4], Germany, Austria [5] France [6], and Spain [7],

✉ James B. Yu
james.b.yu@yale.edu

1 Yale School of Medicine, New Haven, CT, USA

2 Yale Cancer Center, New Haven, CT, USA

3 Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center at Yale, New Haven, CT, USA

4 Section of Medical Oncology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA

5 Department of Therapeutic Radiology, Yale School of Medicine, New Haven, CT, USA

as well as patients treated at a single institution in the U.S. or enrolled in ECOG clinical trials [8, 9] have found that longer metastatic free interval (MFI) is associated with improved survival after subsequent recurrent metastatic disease diagnosis—perhaps due to differences in tumor biology, staging, size, underlying comorbidities, general health of those qualified for clinical trials, socioeconomic factors, and screening.

Our study expands upon the previous literature by exploring a previously unstudied cohort of patients in the United States using a large population-based registry, which allows for the analysis of greater numbers of patients and the analysis of prolonged MFI greater than 10 years. We analyzed the Surveillance, Epidemiology and End Results (SEER) database to examine our hypothesis that an especially prolonged interval between initial stage 1–3 breast cancer and subsequent metastatic diagnosis would be associated with improved survival.

Methods

Data source and cohort selection

We performed a retrospective cohort study using the NCI-sponsored SEER database [10]. Capturing 97% of incident cancers through 18 tumor registries, the SEER Program collects and publishes cancer incidence, survival, and treatment data for 28% of the US population [11].

As shown in Fig. 1, we started with a national cohort of 1,465,100 breast cancer cases (primary site = C500-C506, C508-C509) diagnosed between 1973 and 2014. Of these, we included only the 52,917 cases of metastatic breast cancer diagnosed between 1988 and 2014 (AJCC 6th M = M1). Then we excluded 44,374 cases recorded as the first sequential diagnosis of cancer (sequence < = 1: de novo metastatic cases), leaving 8543. Furthermore, we excluded 5782 cases without a previous stage 1–3 breast cancer diagnosis recorded in SEER, leaving 2761. Of these, 488 cases were excluded because of discordant dates of diagnosis (date of metastatic disease was recorded prior to date of first primary), leaving 2313. Our final cohort included 2308 cases with known survival times.

Construction of variables

The primary independent variable of interest in this study was metastatic free interval (MFI)—the time between initial breast cancer diagnosis and subsequent recurrent metastatic cancer diagnosis, categorized as < 5 years, 5–10 years, > 10 years.

Using characteristics recorded at the time of metastatic diagnosis, we categorized: race as White, Black, or other; marital status as married, unmarried, or other; grade as well differentiated (1), moderately differentiated (2), or poorly differentiated or anaplastic (3 and 4); histologic type as ductal, lobular, or other; ER and PR status as positive, negative, borderline/unknown (which includes all cases prior to 1990, as this variable was not recorded prior to then); tumor laterality as left, right, unknown; year of metastatic diagnosis as pre-2000 or post-2000. We included age at metastatic diagnosis as a continuous variable. We were not able to include information on site of metastasis or HER2 status because this information was not recorded in SEER prior to 2010 [12].

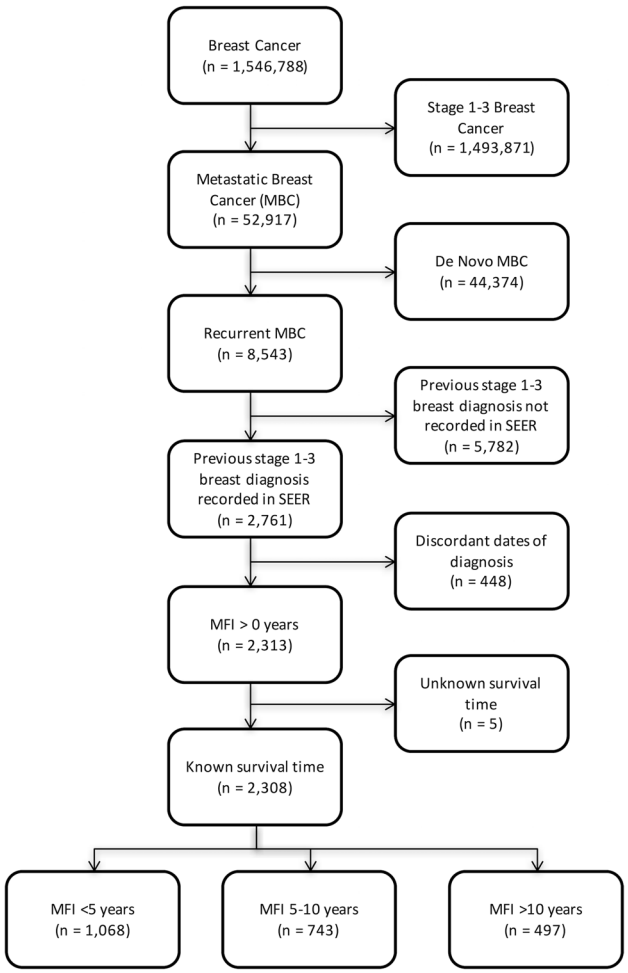

Fig. 1 Selection criteria

Statistical analysis

We compared baseline patient characteristics across MFI categories with the chi-squared test or Fisher's exact test (categorical) or Kruskal–Wallis test (continuous). Unadjusted survival analysis was first performed by the log-rank test, and unadjusted overall survival estimates were generated by the Kaplan–Meier method.

We performed stepwise multivariable Fine and Gray competing risks regression analysis to determine metastatic breast cancer-specific mortality (MBCSM) as a function of categories of MFI, taking into account the competing risk of non-breast cancer death [13]. These categories of MFI (< 5 years, 5–10 years, and > 10 years) were defined prior to competing risks regression after reviewing the distribution of MFI within our sample. In the preliminary multivariate model, we selected all co-variables with $P < 0.10$ from univariate Fine–Gray competing risks analysis. We subsequently excluded all co-variables with $P > 0.10$ in the preliminary multivariate model. The final multivariable model was adjusted for the demographics of race, grade, ER status, PR status, and year of metastatic diagnosis. We also generated a cumulative incidence plot from the Fine–Gray analysis.

After determining favorable prognostic factors from competing risks regression, we also compared a subset of patients with those prognostic factors against a subset without the favorable prognostic factors using unadjusted overall survival estimates generated by the Kaplan–Meier method.

We determined statistical significance with 2-sided P values and a threshold of 0.05, performing all statistical analyses using STATA 13.0.

Results

Baseline patient characteristics

We identified 2308 patients whose prior stage 1–3 breast cancer diagnosis and subsequent metastatic disease were both recorded in SEER. There were 1068 patients with MFI < 5 years, 743 with MFI of 5–10 years, and 497 patients with MFI > 10 years. As shown in Table 1, age at metastatic diagnosis, grade, ER status, PR status, and year of metastatic diagnosis were statistically different when compared across the three MFI categories (< 5 years, 5–10 years, > 10 years).

Of note, patients were older with increasing MFI (median age 59 vs. 62 vs. 66 years, $P < 0.001$). With respect to race, as MFI increased, higher percentages of White (72.57% vs. 76.46%) or other race (7.40% vs. 8.85%) patients were found, while a lower percentage of Black patients (20.04% vs. 14.69%) was found ($P = 0.056$). Patients with longer MFI had the highest percentage of low-grade tumors (7.44%), while those with shorter MFI had the highest percentage of high-grade tumors (40.36%) ($P = 0.002$). Patients with longer MFI had the highest rate of ER- and PR-positive status (68.81%, 55.13%), while those with shorter MFI had a higher rate of ER- and PR-negative status (27.25%, 38.58%) (both $P < 0.001$).

Median follow-up, median overall survival, and 5-year breast cancer-specific survival

The median follow-up after metastatic recurrence using all patients was 15 months (IQR 5–30 months) for those with MFI < 5 years, 19 months (IQR 6–40 months) for those with MFI 5–10 years, and 17 months (IQR 6–37 months) for those with MFI > 10 years.

The median overall survival after recurrent metastatic breast cancer diagnosis was 25 months (range 1–221 months, Fig. 2). Median overall survival for patients with MFI < 5 years was 20 months, while for patients with MFI > 10 years it was 35 months. Five-year recurrent metastatic breast cancer-specific survival rate was 23%, 26%, and 35% for patients with MFI < 5, 5–10, and > 10 years, respectively. Breast cancer was the cause of death for the majority of patients (58%, Table 2). Interestingly, Table 2 also shows a lower percentage of patients with MFI > 10 years died of breast cancer compared to those with MFI 5–10 years and MFI < 5 years (45% vs. 56% and 65%).

Association between MFI and metastatic breast cancer-specific mortality (MBCSM)

Taking into account non-cancer death, cumulative incidence estimates (Fig. 3) of metastatic breast cancer-specific mortality (MBCSM) after a subsequent metastatic diagnosis were significantly higher among patients with shorter MFI (< 5 years) than for those with longer MFI (> 10 years), ($P < 0.001$).

On multivariable Fine–Gray competing risks regression (Table 3), as MFI increased, risk of MBCSM decreased: patients with 5–10 year or > 10 year MFI had a reduced risk of MBCSM compared with a referent group of patients with < 5 years MFI [standard hazard ratio (SHR) 0.92, 95% CI 0.81–1.04; and SHR 0.77, 95% CI 0.65–0.90; $P = 0.191$ and < 0.001, respectively].

Association between other variables and breast cancer-specific mortality after diagnosis of metastatic breast cancer

In multivariate analysis, Black patients had a higher risk of MBCSM (SHR 1.24, 95% CI 1.08–1.44, $P = 0.004$) compared with a referent group of White patients after a diagnosis of metastatic breast cancer. Patients with higher tumor grade (Grade 2 vs. Grade 1 SHR 1.27, 95% CI 0.99–1.63, $P = 0.062$; and Grade 3,4 vs. Grade 1 SHR 1.60, 95% CI 1.25–2.05, $P < 0.001$), ER-negative status (vs. ER-positive status SHR 1.40, 95% CI 1.17–1.67, $P < 0.001$), and PR-negative status (vs. PR-positive status SHR 1.25, 95% CI 1.07–1.46, $P = 0.006$) also had a higher risk of MBCSM. Finally, patients with a metastatic diagnosis post-2000 had a

Table 1 Patient demographics

Characteristic	MFI < 5 years	MFI 5–10 years	MFI > 10 years	*P*
Number of patients	1068	743	497	
Median age (IQR), years	59 (49–71)	62 (53–74)	66 (59–76)	< 0.001*
Marital status				
Married	510 (47.75%)	334 (44.95%)	229 (46.08%)	0.316
Unmarried	506 (47.38%)	356 (47.91%)	237 (47.69%)	
Unknown	52 (4.87%)	53 (7.13%)	31 (6.24%)	
Race				
White	775 (72.57%)	568 (76.45%)	380 (76.46%)	0.056
Black	214 (20.04%)	119 (16.02%)	73 (14.69%)	
Other	79 (7.40%)	56 (7.54%)	44 (8.85%)	
Grade				
1	62 (5.81%)	52 (7.00%)	37 (7.44%)	0.002
2	281 (26.31%)	230 (30.96%)	153 (30.78%)	
3 and 4	431 (40.36%)	403 (35.98%)	329 (37.47%)	
N/A	294 (27.53%)	228 (30.69%)	152 (30.58%)	
Histologic type				
Ductal	686 (64.23%)	481 (64.74%)	331 (66.60%)	0.331
Lobular	123 (11.52%)	101 (13.59%)	51 (10.26%)	
Other	259 (24.25%)	161 (21.67%)	115 (23.14%)	
ER status				
Positive	531 (49.72%)	489 (65.81%)	342 (68.81%)	< 0.001
Negative	291 (27.25%)	141 (18.98%)	94 (18.91%)	
Borderline/unknown/not 1990 + Breast	246 (23.03%)	113 (15.21%)	61 (12.27%)	
PR status				
Positive	393 (36.8%)	359 (48.32%)	274 (55.13%)	< 0.001
Negative	412 (38.58%)	255 (34.32%)	156 (31.39%)	
Borderline/unknown/not 1990 + Breast	263 (24.63%)	383 (25.62%)	287 (17.31%)	
Tumor laterality				
Right-sided	491 (45.97%)	345 (46.43%)	223 (44.87%)	0.090
Left-sided	512 (47.94%)	334 (44.95%)	226 (45.47%)	
Unknown	65 (6.09%)	64 (8.61%)	48 (9.66%)	
Year of metastatic diagnosis				
Pre-2000	169 (15.82%)	42 (5.65%)	< 10 (< 2%)	< 0.001
Post-2000	899 (84.18%)	701 (94.35%)	> 490 (> 98%)	

Year of metastatic diagnosis reported as < 10 to protect patient confidentiality

*Kruskal–Wallis

lower risk of MBCSM when compared to those with a metastatic diagnosis pre-2000 (SHR 0.77, 95% CI 0.65–0.92, $P = 0.004$).

Subset analysis: prognostic factors

The median overall survival of patients after recurrent breast cancer metastasis with favorable prognostic factors (longer MFI, ER/PR positive, lower grade, White race) was 40 months compared to a median survival of 8 months for those with less favorable prognostic factors (shorter MFI, ER/PR negative, higher grade, Black race).

Discussion

Metastatic free interval of greater than 10 years was significantly associated with improved recurrent metastatic breast cancer 5-year survival and decreased breast cancer-specific mortality. Our study is unique in that it was based on US population-level data and accounted for prolonged metastatic free interval of 10 years and beyond as opposed to a 2- or 5-year MFI cut-off more commonly used in previous studies [3–9]. As expected, we also confirmed clinical and demographic variables associated with survival. Thus, our analysis is consistent with previous studies and adds further insights for patients who develop metastatic disease.

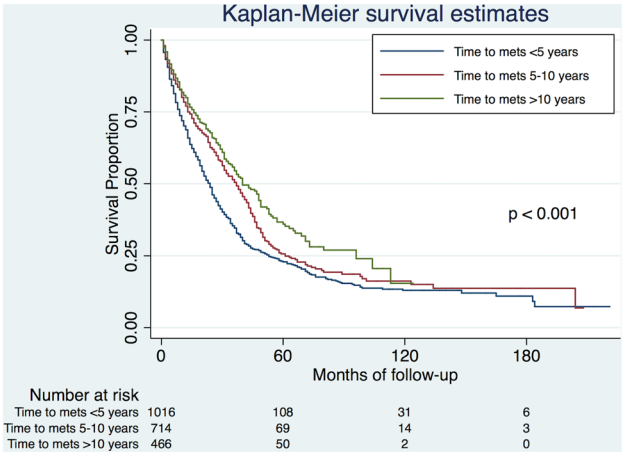

Fig. 2 Overall survival

Although we cannot definitively explain why longer MFI is associated with improved survival, we found that multiple positive prognostic factors are associated with a longer time to metastasis (lower grade of tumor and ER/PR-positive status), consistent with other studies [3–9]. Therefore, it is likely that long MFI is a prognostic marker because it indicates more indolent disease even after diagnosis of metastatic disease. Thus, for patients who are faced with the devastating news that they have metastatic breast cancer, a longer MFI may indicate that their disease may progress more slowly than others with metastatic disease.

This also has implications for stratification of patients in clinical trials. Studies of a cohort that is enriched with patients with long MFI may be biased towards longer survival. These findings could also influence treatment strategies; for example, patients with longer MFI could be candidates for initial treatment with single-agent endocrine therapy (i.e., an aromatase inhibitor (AI)) rather than combination therapy with an AI and CDK4/6 inhibitor, thereby reserving the more toxic combination for the second line following progression.

Regarding race, it has been found previously that Black patients are more likely to be diagnosed with ER−/PR− disease, which has a worse prognosis [14–19]. Other factors, such as delayed diagnosis and delayed treatment of Black patients may also contribute to the observed trends [20]. This may explain the higher percentage of Black patients with shorter observed MFI. The initial breast cancer might be diagnosed at a higher stage with further progression, leading to a higher risk of MBCSM upon a subsequent metastatic diagnosis.

Regarding year of metastatic diagnosis, the decreased risk of MBCSM in patients with metastatic diagnosis post-2000 may be associated with the improvement in therapeutic agents [21].

Our study has several limitations. SEER does not actively follow patients other than to determine vital status [12]. Thus, recurrent metastasis is often not recorded in SEER unless a patient receives treatment for the recurrent disease. This results in under-reporting of metastatic recurrence because older patients often decline or do not receive treatment [22]. It is unclear whether under-ascertainment of metastatic disease would create a systematic bias that would impact the conclusions of our study. The fact that we confirm many elements of prior analyses gives us confidence as to the validity of our findings. Another limitation of our study is that we could not include site of recurrent metastasis or HER2 status, which have been found to be significant prognostic factor in previous studies [5, 6, 23, 24]. Furthermore, we did not include initial tumor information in our model. Rather, we focused on the clinical factors of the disease at time of metastasis so that patients can be

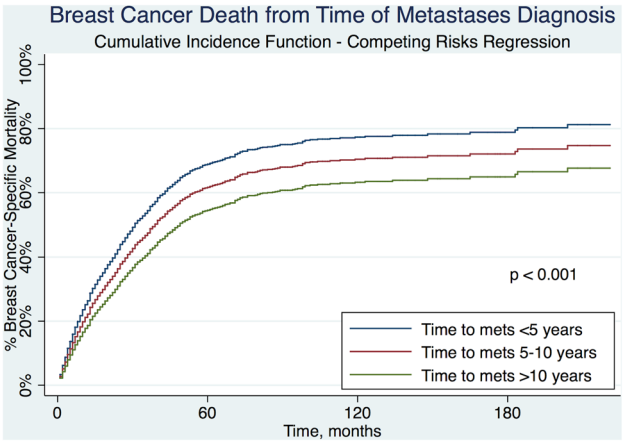

Fig. 3 Competing risks regression—cumulative incidence of breast cancer death, taking into account the competing risk of non-breast cancer death

Table 2 Causes of death

Cause of death	Overall	MFI < 5 years	MFI 5–10 years	MFI > 10 years
Alive	722 (31.28%)	230 (21.54%)	272 (36.61%)	220 (44.27%)
Breast cancer death	1338 (57.97%)	699 (65.45%)	414 (55.72%)	225 (45.27%)
Other cancer death	111 (4.81%)	70 (6.55%)	20 (2.69%)	21 (4.23%)
Heart disease	44 (1.91%)	20 (1.87%)	14 (1.88%)	10 (2.01%)
Other non-cancer death	93 (4.03%)	49 (4.59%)	23 (3.1%)	21 (4.23%)

Table 3 Multivariable Fine and Gray competing risks regression for breast cancer-specific mortality among patients with subsequent metastatic breast cancer

Characteristic	Univariate analysis		Multivariate analysis	
	SHR (95% CI)	*P*	SHR (95% CI)	*P*
Metastatic free interval				
<5 years	1.0 (ref)		1.0 (ref)	
5–10 years	0.82 (0.73–0.93)	< 0.001	0.92 (0.81–1.04)	0.191
>10 years	0.65 (0.56–0.76)	< 0.001	0.77 (0.65–0.90)	< 0.001
Age (per year increase)	1.00 (0.99–1.00)	0.172	*	
Marital status				
Married	1.0 (ref)		*	
Not married	1.10 (0.99–1.23)	0.087	*	
Unknown	1.17 (0.93–1.47)	0.179	*	
Race				
White	1.0 (ref)		1.0 (ref)	
Black	1.30 (1.13–1.49)	< 0.001	1.24 (1.08–1.44)	0.003
Other	1.05 (0.85–1.30)	0.629	1.11 (0.90–1.38)	0.332
Grade				
1	1.0 (ref)		1.0 (ref)	
2	1.34 (1.04–1.71)	0.022	1.27 (0.99–1.63)	0.062
3 and 4	2.00 (1.57–2.55)	< 0.001	1.60 (1.25–2.05)	< 0.001
N/A	1.47 (1.15–1.89)	0.002	1.24 (0.96–1.59)	0.099
Histologic type				
Ductal	1.0 (ref)		*	
Lobular	0.94 (0.80–1.09)	0.404	*	
Other	0.99 (0.86–1.13)	0.874	*	
ER status				
Positive	1.0 (ref)		1.0 (ref)	
Negative	1.90 (1.66–2.18)	< 0.001	1.40 (1.17–1.67)	< 0.001
Borderline/unknown/not 1990 + Breast	1.59 (1.37–1.84)	< 0.001	1.75 (1.18–2.61)	0.005
PR status				
Positive	1.0 (ref)		1.0 (ref)	
Negative	1.67 (1.48–1.89)	< 0.001	1.25 (1.07–1.46)	0.006
Borderline/unknown/not 1990 + Breast	1.58 (1.36–1.83)	< 0.001	0.90 (0.61–1.33)	0.613
Tumor laterality				
Right-sided	1.0 (ref)		*	
Left-sided	1.01 (0.90–1.12)	0.916	*	
Unknown	0.77 (0.61–0.97)	0.026	*	
Year of metastatic diagnosis				
Pre-2000	1.0 (ref)		1.0 (ref)	
Post-2000	0.67 (0.57–0.79)	< 0.001	0.77 (0.65–0.92)	0.004

*Not included in multivariate model

informed of prognosis even when not much is known about their prior tumor—whether they cannot recall or the records are lost over time.

An additional limitation is that our cohort included only 212 patients with a metastatic diagnosis before the year 2000 compared with 2096 after the year 2000. Thus, our length of follow-up for patients with MFI > 10 years was limited past 5 years. One explanation is that SEER included fewer registries before 2000, thus capturing fewer patients [25]. However, that our patients were skewed to more recent years improves the contemporary nature of our findings. Finally, we emphasize the importance of distinguishing clinical significance from statistical significance, as clinicians and patients must discern whether these statistically significant findings are clinically meaningful. We acknowledge that treatment strategies may not change based on these differences at this time.

Conclusion

In conclusion, patients with a new diagnosis of metastatic breast cancer with very prolonged MFI (> 10 years) have higher breast cancer-specific 5-year survival compared to those with shorter MFI. These patients have more favorable prognostic factors as well. These findings can be used to counsel patients and inform interpretation of clinical trials.

Author contributions Enoch Chang: Conceptualization, data curation, formal statistical analysis and interpretation of data, funding acquisition, investigation, methodology, software, validation, visualization, writing—original draft, and writing—review and editing. Sarah S. Mougalian: Analysis and interpretation of data, writing—review and editing. Kerin B. Adelson: Analysis and interpretation of data, writing—review and editing. Melissa R. Young: Analysis and interpretation of data, writing—review and editing. James B. Yu: Conceptualization, data curation, formal statistical analysis and interpretation of data, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing—original draft, and writing—review and editing.

Funding Enoch Chang was supported by the NIDDK of the NIH under Award Number T35DK104689. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Conflict of interest Sarah S. Mougalian MD: Consulting role with Eisai. Stocks: Gilead, Coronado Biosciences, Roche. Research funding from Genentech, Pfizer; Kerin B. Adelson MD: Immediate family member is employed with Lyra Health; Consulting role with Wellpoint; Travel, Accommodations, Expenses from Genentech; Honoraria from Genentech; James B. Yu MD, MHS: Consulting role with Augmenix. Research funding from twenty-first Century Oncology.

References

1. SEER Cancer stat facts: female breast cancer [https://seer.cancer.gov/statfacts/html/breast.html]. Accessed Mar 2017
2. Mariotto AB, Etzioni R, Hurlbert M, Penberthy L, Mayer M (2017) Estimation of the Number of Women Living with Metastatic Breast Cancer in the United States. Cancer Epidemiol Biomarkers Prev 26(6):809–815
3. Nakano M, Fujisue M, Tashima R, Okumura Y, Nishiyama Y, Ohsako T, Toyozumi Y, Arima N, Nishimura R (2015) Survival time according to the year of recurrence and subtype in recurrent breast cancer. Breast 24(5):588–593
4. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, van de Wouw AJ, Peters FP, van Riel JM, Peters NA et al (2015) Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? Br J Cancer 112(9):1445–1451
5. Regierer AC, Wolters R, Ufen MP, Weigel A, Novopashenny I, Kohne CH, Samonigg H, Eucker J, Possinger K, Wischnewsky MB (2014) An internally and externally validated prognostic score for metastatic breast cancer: analysis of 2269 patients. Ann Oncol 25(3):633–638
6. Largillier R, Ferrero JM, Doyen J, Barriere J, Namer M, Mari V, Courdi A, Hannoun-Levi JM, Ettore F, Birtwisle-Peyrottes I et al (2008) Prognostic factors in 1,038 women with metastatic breast cancer. Ann Oncol 19(12):2012–2019
7. Puente J, Lopez-Tarruella S, Ruiz A, Lluch A, Pastor M, Alba E, de la Haba J, Ramos M, Cirera L, Anton A et al (2010) Practical prognostic index for patients with metastatic recurrent breast cancer: retrospective analysis of 2,322 patients from the GEICAM Spanish El Alamo Register. Breast Cancer Res Treat 122(2):591–600
8. Dawood S, Broglio K, Ensor J, Hortobagyi GN, Giordano SH (2010) Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 21(11):2169–2174
9. Tevaarwerk AJ, Gray RJ, Schneider BP, Smith ML, Wagner LI, Fetting JH, Davidson N, Goldstein LJ, Miller KD, Sparano JA (2013) Survival in patients with metastatic recurrent breast cancer after adjuvant chemotherapy: little evidence of improvement over the past 30 years. Cancer 119(6):1140–1148
10. Surveillance E, Results E (SEER) (2016) Program (http://www.seer.cancer.gov): Research Data (1973–2014), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2017, based on the November submission
11. Number of Persons by Race and Hispanic Ethnicity for SEER Participants (2010 Census Data) https://seer.cancer.gov/registries/data.html. Accessed Mar 2017
12. Healthcare Delivery Research Program: Measures that are limited or not available in the data [https://healthcaredelivery.cancer.gov/seermedicare/considerations/measures.html]. Accessed May 2017
13. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94(446):496–509
14. Harper S, Lynch J, Meersman SC, Breen N, Davis WW, Reichman MC (2009) Trends in area-socioeconomic and race-ethnic disparities in breast cancer incidence, stage at diagnosis, screening, mortality, and survival among women ages 50 years and over (1987–2005). Cancer Epidemiol Biomarkers Prev 18(1):121–131
15. Ooi SL, Martinez ME, Li CI (2011) Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat 127(3):729–738
16. Curtis E, Quale C, Haggstrom D, Smith-Bindman R (2008) Racial and ethnic differences in breast cancer survival: how much is explained by screening, tumor severity, biology, treatment, comorbidities, and demographics? Cancer 112(1):171–180
17. Dunnwald LK, Rossing MA, Li CI (2007) Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 9(1):R6
18. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, Lickley LA, Rawlinson E, Sun P, Narod SA (2007) Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res 13(15 Pt 1):4429–4434
19. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong YN, Blayney DW, Niland JC, Winer EP, Weeks JC (2012) Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer 118(22):5463–5472
20. Gorin SS, Heck JE, Cheng B, Smith SJ (2006) Delays in breast cancer diagnosis and treatment by racial/ethnic group. Arch Intern Med 166(20):2244–2252
21. Chia SK, Speers CH, D'Yachkova Y, Kang A, Malfair-Taylor S, Barnett J, Coldman A, Gelmon KA, O'Reilly SE, Olivotto IA (2007) The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer 110(5):973–979
22. Warren JL, Mariotto A, Melbert D, Schrag D, Doria-Rose P, Penson D, Yabroff KR (2016) Sensitivity of medicare claims to

identify cancer recurrence in elderly colorectal and breast cancer patients. Med Care 54(8):e47–e54
23. Kennecke H, Yerushalmi R, Woods R, Cheang MC, Voduc D, Speers CH, Nielsen TO, Gelmon K (2010) Metastatic behavior of breast cancer subtypes. J Clin Oncol 28(20):3271–3277
24. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, Smilde TJ, van de Wouw AJ, Peters FP, van Riel JM, Peters NA et al (2013) Prognosis of metastatic breast cancer subtypes: the hormone receptor/HER2-positive subtype is associated with the most favorable outcome. Breast Cancer Res Treat 141(3):507–514
25. SEER Registry Groupings for Analyses [https://seer.cancer.gov/registries/terms.html]. Accessed Dec 2017