Original Study

Impact of Subtype on Survival of Young Patients With Stage IV Breast Cancer

Rin Ogiya,[1] Yasuaki Sagara,[2] Naoki Niikura,[3] Rachel A. Freedman[4]

Abstract

We used population-based cancer registry data (n = 6,302) to characterize the clinicopathologic features of young patients with stage IV breast cancer and to evaluate overall survival by age in the context of disease subtypes. Compared with patients with breast cancer aged 40 to 59 years, those aged < 40 years experienced significantly longer survival, except in the setting of triple-negative disease.

Background: Although younger age is a negative prognostic factor for patients with early stage breast cancer, data regarding the outcomes of young patients with stage IV disease are limited. We evaluated differences in overall survival (OS) according to age and disease subtype among patients with stage IV breast cancer. **Patients and Methods:** Using Surveillance, Epidemiology, and End Results (SEER) data, we identified 6,302 patients aged < 60 years with de novo stage IV breast cancer between 2010 and 2014. We examined age-specific OS among hormone receptor (HR)-positive (HR$^+$)/human epidermal growth factor receptor 2 (HER2)-negative (HER2$^-$), HR$^+$/HER2-positive (HER2$^+$), HR-negative (HR$^-$)/HER2$^+$, and triple-negative cases using log-rank tests and Cox proportional hazards models, adjusting for relevant clinical and demographic variables. **Results:** Compared with patients aged 40 to 59 years, patients aged < 40 years (n = 944; 15%) had a higher proportion of HER2$^+$ cancers and a lower proportion of HR$^+$/HER2$^-$ disease (P < .001), but a similar proportion of triple-negative disease. Patients aged < 40 years also experienced significantly longer survival, with a median OS of 45 months (vs. 33 months). Further, after stratification by subtype, patients aged < 40 years experienced significantly longer survival, except in the setting of triple-negative disease. These survival differences persisted in adjusted analyses. **Conclusions:** Compared with those aged 40 to 59 years, patients with de novo metastatic breast cancer aged < 40 years experienced significantly longer survival, except in the setting of triple-negative disease. Distinct treatment-related or biological factors may exist between earlier stage and metastatic breast cancers; further examination of the potential reasons for our findings are warranted.

Introduction

Worldwide, breast cancer is the leading cause of cancer-related death among women.[1] Although most patients are diagnosed with early stage disease, 5% of patients in the United States are diagnosed at stage IV, with substantially lower 5-year survival rates (25%) than those diagnosed at earlier stages (82%-98%).[2]

Recent studies have revealed several clinicopathologic prognostic factors for de novo stage IV breast cancer.[3-5] For example, black race, high tumor grade, increasing age, unmarried status, and hormone receptor negativity are independently associated with poor prognosis among these patients.[6] Other studies have suggested that the prognoses of patients with stage IV breast cancer may depend on the metastatic sites involved.[7-9]

Breast cancer is subdivided into 4 clinical subtypes in accordance with hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status: HR-positive (HR$^+$)/HER2-negative (HER2$^-$), HR$^+$/HER2-positive (HER2$^+$), HR$^-$/HER2$^+$, and triple-negative (HR$^-$/HER2$^-$). Systemic treatment approaches for stage IV disease differ across subtypes: triple-negative tumors are primarily treated with chemotherapy, HER2$^+$ tumors are treated with both HER2-directed therapy and chemotherapy, and HR$^+$ tumors are typically treated with endocrine therapy and ultimately chemotherapy following the development of endocrine therapy

[1]Harvard T.H. Chan School of Public Health, Boston, MA
[2]Department of Breast Surgical Oncology, Sagara Hospital, Kagoshima City, Kagoshima, Japan
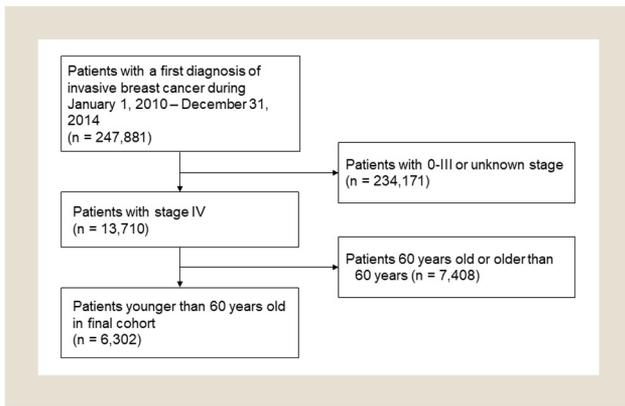[3]Department of Breast and Endocrine Surgery, Tokai University School of Medicine, Isehara City, Kanagawa, Japan
[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Address for correspondence: Rin Ogiya, MD, PhD, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Boston, MA 02115
E-mail contact: rinogiya@gmail.com

edition of the American Joint Committee on Cancer Staging Manual.[21] Patients ≥ 60 years of age were also excluded. Altogether, our study population consisted of 6,302 patients (Figure 1). This study was reviewed and approved by the Institutional Review Board for Clinical Research at Tokai University (17R-340).

Outcome Measure

The primary outcome of interest was OS, which was defined as the date of diagnosis until the last date for which vital status data were available (date of death, date last known to be alive, or December 31, 2015). We verified deaths and causes thereof from the National Death Index data provided with the SEER files. Although 90% of the deaths in our cohort were related to breast cancer, to confirm findings, we also examined breast cancer-specific survival (BCSS).

Assembly of Key Variables

A data table composed of individual patient records was created using the case listing sessions in SEER*Stat software, version 8.3.5. The following variables were abstracted: year of diagnosis, age, gender, race (black, non-black, and unknown), marital status (married, single/separated/divorced/widowed, and unknown), tumor grade (I-III and unknown), disease subtype, metastatic sites at diagnosis (bone, brain, liver, and lung), surgery for primary site, cause-specific death classification, and survival month. We defined the "young age" group as patients under the age of 40 years at breast cancer diagnosis.[22] Given that our analyses focused on young patients, and that prior work has demonstrated that patients aged 40 to 59 often have the most optimal cancer outcomes,[19] we used the latter category as the reference group in our analysis. The disease subtype variable was classified as $HR^+/HER2^-$, $HR^+/HER2^+$, $HR^-/HER2^+$, or triple-negative ($HR^-/HER2^-$). For HR status, estrogen receptor-positive and/or progesterone receptor-positive disease was classified as HR^+ disease, whereas estrogen receptor-negative and progesterone receptor-negative disease was classified as HR^- disease. We defined the "bone-only metastases" variable according to the site of visceral metastasis (bone metastases: "Yes"; brain/liver/lung metastases: "No" or "unknown").

Statistical Analysis

All analyses were performed for both the entire cohort and after stratifying by age (< 40 years vs. 40-59 years) and/or disease subtype. Patient characteristics across age groups, disease subtypes, and metastatic sites were compared using χ^2 testing.

The OS (and BCSS) hazard ratios for young patients were compared with those of patients aged 40 to 59 years, and were evaluated using Kaplan-Meier curves, log-rank tests, and Cox regression models. For our primary analysis, we utilized multivariable Cox proportional hazards models, adjusting for age, race, tumor grade, disease subtype, and bone metastases ("only" or "not"). In addition, owing to the relatively limited demographic profile of patients that typically undergo surgery, we reasoned that receipt of surgery may bias outcomes towards improved survival. We, therefore, performed a sensitivity analysis wherein we adjusted our models for receipt of breast surgery. Interaction terms between age category and disease subtypes were included to investigate the survival impact of age in each disease subtype.

resistance.[10,11] With appropriate treatment, patients with HR^+ and/or $HER2^+$ breast cancer have substantially better prognoses than those diagnosed with metastatic triple-negative breast cancer.[11-13]

Although young age has not been associated with a worse prognosis among patients with stage IV disease specifically, many studies have identified young age as a generally unfavorable breast cancer prognostic factor.[14,15] For example, young patients are more likely to have node-positive, high-grade, HR^-, and $HER2^+$ tumors.[16,17] Young patients (≤ 40 years) with early stage breast cancer also experienced shorter survival periods than middle-aged patients (51-60 years), particularly in the setting of the $HR^+/HER2^-$ subtype.[18,19] In another report, young age was related to shorter survival compared with the older population only in early stage breast cancer, and this relationship was reversed in stage IV breast cancer. However, factors that may explain the differential relationship between age and stage-specific survival have not been widely studied. Moreover, we are unaware of any reports examining associations between age- and subtype-specific survival in the de novo metastatic setting, including information on the HER2 status and metastatic sites of disease. To this end, we used population-based cancer registry data to characterize the clinicopathologic features of young patients with stage IV breast cancer, and to evaluate overall survival (OS) by age in the context of disease subtypes.

Materials and Methods

Data Source and Study Population

We performed a retrospective longitudinal cohort study using data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database (www.seer.cancer.gov). We used the SEER 18 dataset, which contains demographic, tumor, treatment, and survival data collected from 18 United States population-based cancer registries. Cases in this dataset were diagnosed between 2000 and 2014,[20] and 247,881 patients with first breast cancer diagnosed between January 1, 2010 (when information on HER2 status became available) and December 31, 2014 were identified. We excluded cases diagnosed in 2015 so that at least 1 year of follow-up data were available for survival analyses. We also excluded patients with stage 0 to III disease, as well as those with breast cancer of unknown stage, using SEER codes from the seventh

Table 1 Patient Characteristics by Age Group

	All Ages N = 6302		< 40 Years N = 944		40-59 Years N = 5358		P Value
	N	%	N	%	N	%	
Age, y							
Median (IQR)	51 (44-55)		35 (32-38)		52 (47-56)		
Gender							
Female	6246	(99)	937	(99)	5309	(99)	.60
Male	56	(1)	7	(1)	49	(1)	
Race							
Non-black	5000	(79)	721	(76)	4279	(80)	.05
Black	1281	(20)	219	(23)	1062	(20)	
Unknown	21	(0)	4	(0)	17	(0)	
Married							
Yes	3043	(48)	477	(51)	2566	(48)	.12
No	2918	(46)	427	(45)	2491	(47)	
Unknown	341	(5)	40	(4)	301	(6)	
Grade							
I	384	(6)	39	(4)	345	(6)	**< .0001**
II	1658	(26)	254	(27)	1404	(26)	
III	2078	(33)	377	(40)	1701	(32)	
Unknown	2182	(35)	274	(29)	1908	(36)	
Subtype							
HR$^+$/HER2$^-$	3085	(49)	413	(44)	2672	(50)	**< .0001**
HR$^+$/HER2$^+$	1122	(18)	223	(24)	899	(17)	
HR$^-$/HER2$^+$	636	(10)	117	(12)	519	(10)	
Triple-negative	838	(13)	136	(14)	702	(13)	
Unknown	621	(10)	55	(6)	566	(11)	
Bone only							
Yes	2149	(34)	325	(34)	1824	(34)	.82
No	4153	(66)	619	(66)	3534	(66)	
Bone metastasis							
No	2077	(33)	316	(34)	1761	(33)	.69
Yes	4103	(65)	614	(65)	3489	(65)	
Unknown	122	(2)	14	(2)	108	(2)	
Brain metastasis							
No	5587	(89)	856	(91)	4731	(88)	.12
Yes	492	(8)	65	(7)	427	(8)	
Unknown	223	(4)	23	(2)	200	(4)	
Liver metastasis							
No	4216	(67)	596	(63)	3620	(68)	**.004**
Yes	1912	(30)	330	(35)	1582	(30)	
Unknown	174	(3)	18	(2)	156	(3)	
Lung metastasis							
No	4389	(70)	690	(73)	3699	(69)	.08
Yes	1688	(27)	227	(24)	1461	(27)	
Unknown	225	(4)	27	(3)	198	(4)	
Surgery for primary site							
Yes	2243	(36)	402	(43)	1841	(34)	**< .0001**
No	4013	(64)	532	(57)	3481	(65)	
Unknown	46	(1)	10	(1)	36	(1)	

Table 1	Continued						
		All Ages		**< 40 Years**		**40-59 Years**	
		N = 6302		**N = 944**		**N = 5358**	
		N	**%**	**N**	**%**	**N**	**%**	**P Value**
Vital status, cause of death							
Alive		3016	(48)	548	(58)	2468	(46)	**< .0001**
Dead, breast cancer		2988	(48)	366	(39)	2622	(49)	
Dead, other		298	(5)	30	(3)	268	(5)	

Total percentages may not equal 100% because of rounding.
P values marked in bold indicate a statistically significant difference (*P* < .05).
Abbreviations: − = negative; + = positive; bone only = bone metastases without liver/lung/brain metastases; IQR = interquartile range; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Two-tailed *P* values were reported for all analyses, and $\alpha < .05$ was considered statistically significant. All analyses were performed using IBM SPSS, version 25 (Armonk, NY).

Results

Patient Characteristics

Among the 6,302 patients < 60 years of age who were diagnosed with stage IV breast cancer from 2010 to 2014, 944 (15%) were aged < 40 years, and 5,358 (85%) were aged 40 to 59 years. Patient clinicopathologic characteristics differed by age group and are presented in Table 1. Patients aged < 40 years were more likely to have high-grade (40% vs. 32%; *P* < .0001) and HER2$^+$ tumors (36% vs. 27%) and less likely to have HR$^+$/HER2$^−$ tumors (44% vs. 50%; *P* < .0001). Patients aged < 40 years were also more likely to have undergone surgical excision of the primary tumor compared with those aged 40 to 59 years (43% vs. 34%; *P* < .0001).

Among patients with HR$^+$/HER2$^−$ and triple-negative disease, young patients had a higher proportion of high-grade tumors compared with those aged 40 to 59 years (*P* = .006 and *P* = .039, respectively) (see Supplemental Figure 1 in the online version). Compared with patients aged 40 to 59 years, patients aged < 40 years with HR$^+$/HER2$^−$ disease also experienced a higher prevalence of bone (*P* = .04) and liver (*P* = .04) metastases, whereas those < 40 years with HR$^+$/HER2$^+$ disease experienced a higher prevalence of bone-only metastases (*P* = .03). On the other hand, among patients with HR$^+$/HER2$^+$ disease, patients aged < 40 years had a lower prevalence of lung metastases compared with patients aged 40 to 59 years (*P* = .002) (Figure 2).

Survival Analysis

Over a median follow-up period of 23 months from the date of diagnosis (interquartile range, 13-38 months), there were 3,286 (52.1%) death events, with a median OS of 35 months (range, 1-60 months) among all patients. There were 396 (41.9%) and 2,890 (53.9%) death events among patients aged < 40 years and 40 to 59 years, respectively.

Kaplan-Meier curves comparing the OS of patients within each age group are shown in Figure 3. Patients aged < 40 years experienced significantly increased survival compared with those aged 40 to 59 years, with median OS periods of 45 and 33 months, respectively (log-rank test, *P* < .0001). This statistically significant difference persisted after adjusting for other clinical and demographic variables (adjusted hazard ratio [HR] for patients aged < 40 years vs. aged 40-59 years, 0.65; 95% confidence interval [CI], 0.57-0.75) (Figure 4, Table 2). In a sensitivity analysis including the term for receipt of breast surgery, the result also persisted similarly (adjusted HR for patients aged < 40 years vs. aged 40-59 years, 0.67; 95% CI, 0.58-0.77). The significant survival difference was also observed with BCSS (adjusted HR for patients aged < 40 years vs. aged 40-59 years, 0.65; 95% CI, 0.56-0.75) (see Supplemental Table 1 in the online version). Other factors that were significantly associated with OS included race, marital status, tumor grade, disease subtype, and the presence of bone-only metastases (vs. not) (Figure 4).

Kaplan-Meier curves comparing age-specific OS within each disease subtype category are shown in Figure 5. Patients aged < 40 years experienced significantly longer survival than patients aged 40 to 59 years across all disease subtypes (Figures 5A-C), except for in the setting of triple-negative disease (Figure 5D). These statistically significant differences persisted in adjusted analyses (Table 2). The survival difference observed with BCSS was similar (see Supplemental Table 1 in the online version). The interaction term for age category and disease subtype was statistically significant for OS in a multivariable model (*P* = .001).

Discussion

In this population-based study of approximately 6300 patients with de novo stage IV breast cancer, we observed significantly longer survival periods for those aged < 40 years compared with those aged 40 to 59 years, a finding that is consistent with previous studies when looking at overall outcomes, although the age cutoff points and adjusting confounding factors were different.[19,23] In addition, we observed differences in OS by age within all disease subtype categories except for triple-negative disease, with patients aged < 40 years having significantly longer survival times than those aged 40 to 59 years. Interestingly, we also observed variability in the distribution of metastatic sites by age and subtype. Compared with patients aged 40 to 59 years, a higher prevalence of liver and bone metastases was observed in patients aged < 40 years with HR$^+$/HER2$^−$ disease, whereas a higher prevalence of bone-only metastases was observed in patients aged < 40 years with HR$^+$/HER2$^+$ disease. However, despite a previous study demonstrating that liver and brain metastases are poor prognostic factors for patients with stage IV breast cancer[5] and the high proportions of tumors with
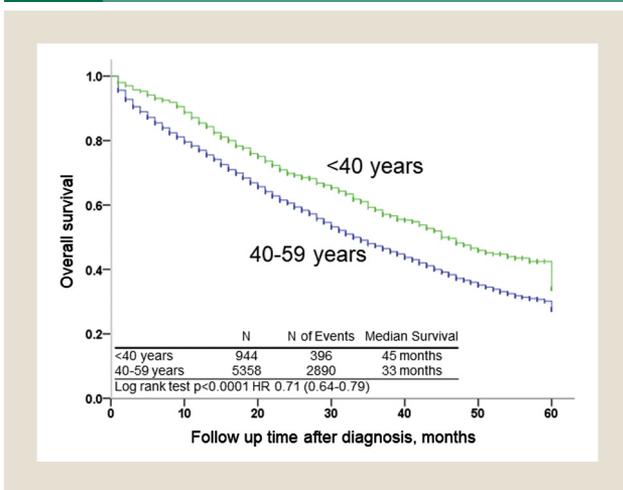
Figure 2 — Subtype-specific Distributions of Metastatic Site Stratified by Age. *P < .05
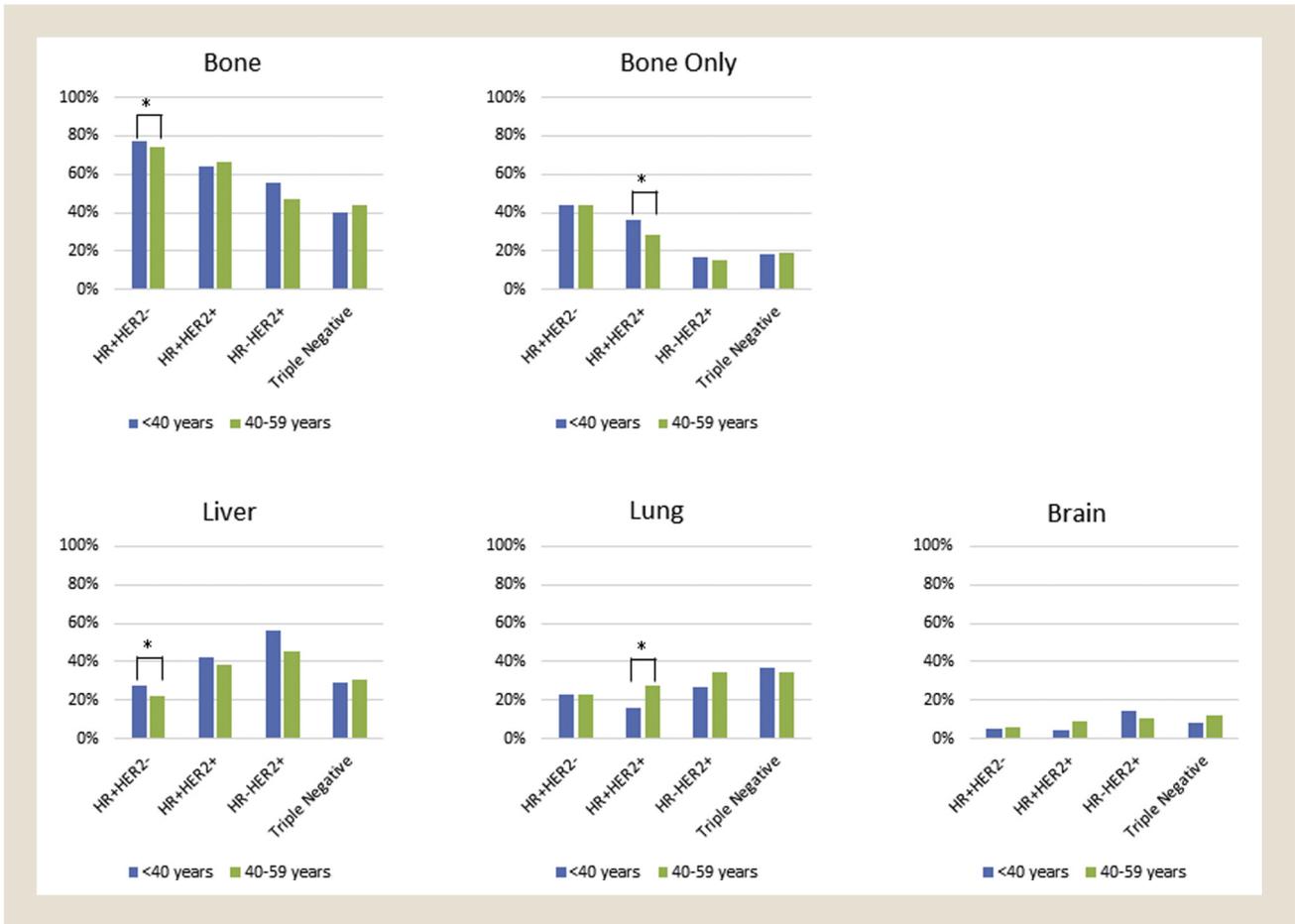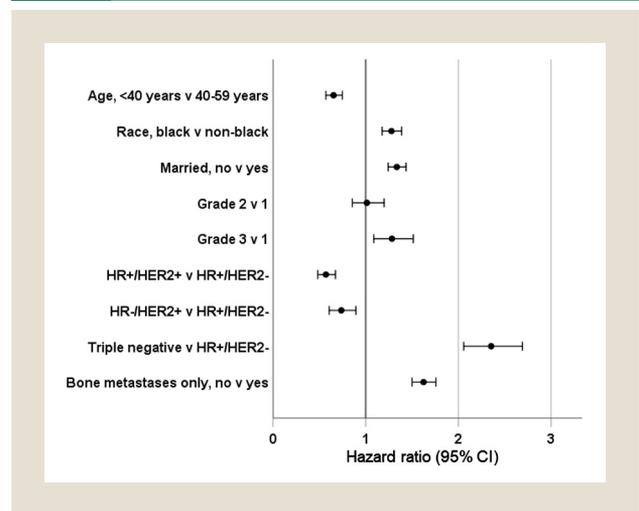

Abbreviations: ⁻ = negative; ⁺ = positive; bone only = bone metastases without liver/lung/brain metastases; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Figure 3 — Kaplan-Meier Estimates of Overall Survival Stratified by Age

Abbreviation: HR = hazard ratio.

Figure 4 — Forest Plot of Adjusted Overall Survival Hazard Ratios

Abbreviations: ⁻ = negative; ⁺ = positive; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Table 2 Subtype-specific Unadjusted and Adjusted Hazard Ratios for Overall Survival Between Patients Aged < 40 and 40 to 59 Years

|	Univariable Analysis		Multivariable Analysis[a]	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All	0.71 (0.64-0.79)	< .0001	0.65 (0.57-0.75)	< .0001
HR⁺/HER2⁻	0.78 (0.66-0.91)	.001	0.75 (0.64-0.88)	< .0001
HR⁺/HER2⁺	0.49 (0.37-0.66)	< .0001	0.5 (0.37-0.67)	< .0001
HR⁻/HER2⁺	0.65 (0.5-0.93)	.02	0.65 (0.46-0.93)	.02
Triple-negative	1.01 (0.82-1.24)	.92	0.99 (0.8-1.22)	.91

Abbreviations: ⁻ = negative; ⁺ = positive; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.
[a]Adjusted for race, marital status, tumor grade, disease subtype and bone metastases (only or not).

higher-risk features such as high grade and more visceral disease in the present study, OS among patients aged < 40 years was significantly better than that of patients aged 40 to 59 years across all subtypes, except for triple-negative disease.

The reasons for which young patients may experience relatively low survival rates in the setting of early stage breast cancer, yet relatively high survival rates in the context of stage IV disease, are not clear and cannot be evaluated in our registry-based study. One possible explanation is that young patients may be more likely than older patients to receive more aggressive or novel treatments, given minimized concerns about comorbidities or potential toxic effects of treatments. However, it is unclear if comorbidities differed by age in our study.

Figure 5 Kaplan-Meier Estimates of Overall Survival Among HR⁺/HER2⁻ (A), HR⁺/HER2⁺ (B), HR⁻/HER2⁺ (C), and Triple-negative Cases (D). *Median Overall Survival Had Not Been Reached
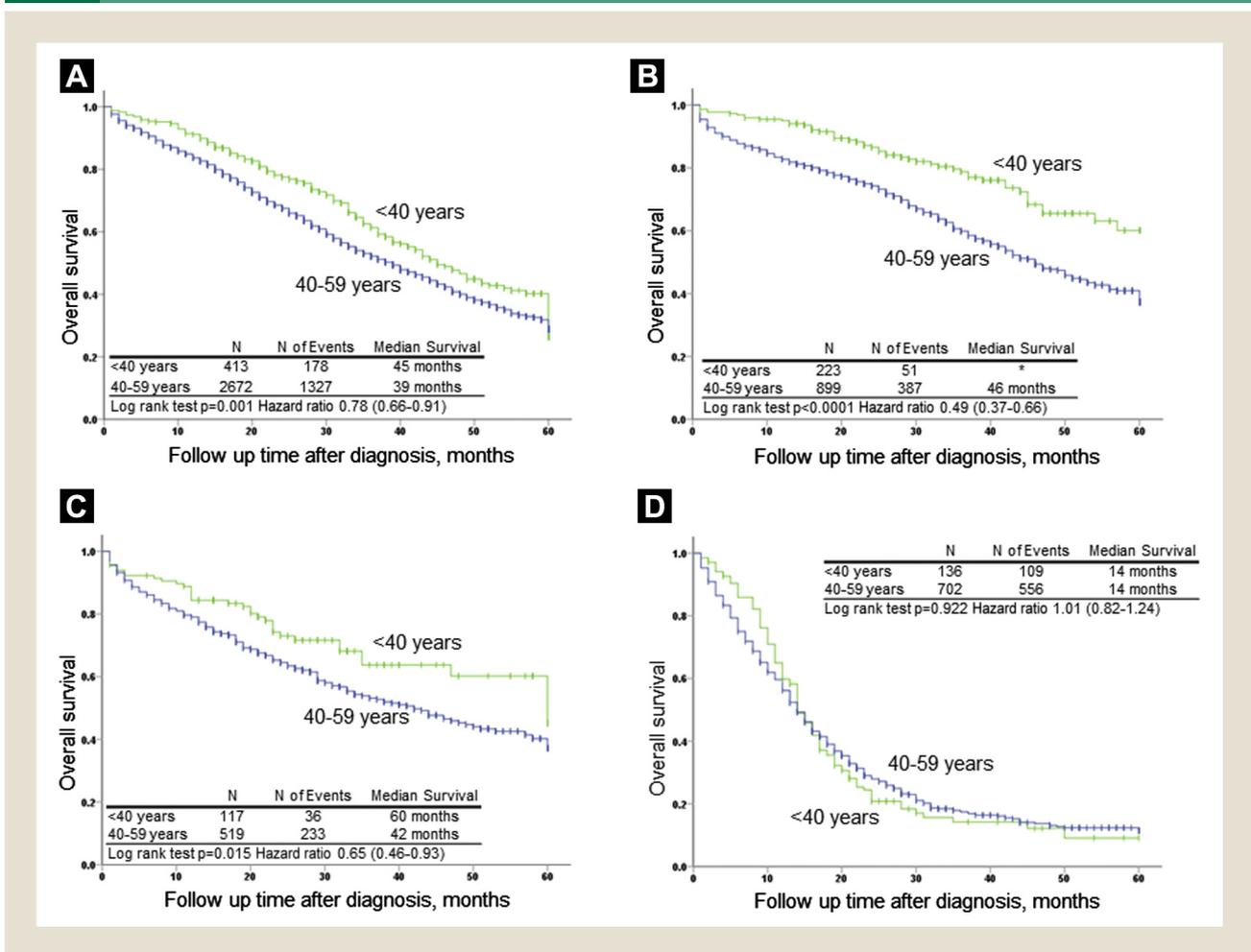
Abbreviations: ⁻ = negative; ⁺ = positive; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Another possible explanation may relate to the variability in treatment protocols delivered in the setting of metastatic disease, wherein regimens may be less standardized and more nuanced than in the neo/adjuvant setting.[24] This variability may be most relevant to HR[+] and/or HER2^{+} cancers, the subtypes for which we observed survival differences by age. Unfortunately, however, data pertaining to the types of treatments received, the utilization of clinical trials, and time-to-treatment progression was unavailable. A third possible explanation for our findings may relate to the presence of age-related genomic or biologic differences in de novo metastatic disease, perhaps with longer time-to-treatment-resistance among young patients. Previous genomic studies have shown that breast cancers of young patients have unique oncogenic signaling pathways,[25,26] and that the poor prognosis of young patients with early stage disease may be mediated by tumor-intrinsic molecular features.[27] Future studies that include granular patient, tumor, genomic, treatment, and adherence data will be required in order to optimally address the reasons for the observed differences in survival outcomes.

We acknowledge several study limitations. First, we used a population-based cancer registry that lacked tumor biology and treatment data, information pertaining to insurance and access to care, and sociodemographic characteristics beyond race.[28] Second, SEER data only includes de novo breast cancer cases, so it may not be possible to generalize our results to patients with recurrent disease. Third, follow-up times were limited for some patients; however, by using a diagnostic cutoff date of 2014, all patients had at least 1 year of follow-up data available. This length of follow-up is particularly relevant in the setting of HR[+] and HER2^{+} disease, wherein patients often live for several years after diagnosis. Further, the heterogeneity present across disease subtypes implies that vastly different tumor behaviors and treatment sensitivities may exist among patients.

Conclusions

In summary, the OS and BCSS of patients with de novo stage IV breast cancer were significantly longer in patients aged < 40 years than in those aged 40 to 59 years, except for in the setting of triple-negative disease. Further understanding of the clinical and biologic underpinnings of metastatic disease, as well as mechanisms by which we may mitigate poor outcomes in those at risk for shortened survival times is crucial and may help direct patients (of all ages) to the most relevant and tailored therapies or clinical trials, and perhaps improve referral times for patients in need of palliative and hospice care.

Clinical Practice Points

- Knowing the age-specific survival among patients with stage IV breast cancer may help patients to access the most relevant and tailored therapies or clinical trials.
- In addition, this knowledge could aid in improving referral times for patients in need of palliative and hospice care.

Acknowledgments

Disclosure

Supplemental Data

Supplemental figure and table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.01.005.

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Supplemental Data

Supplemental Figure 1	Subtype-specific Proportions of Histologic Grade Among Tumors Within Each Age Group
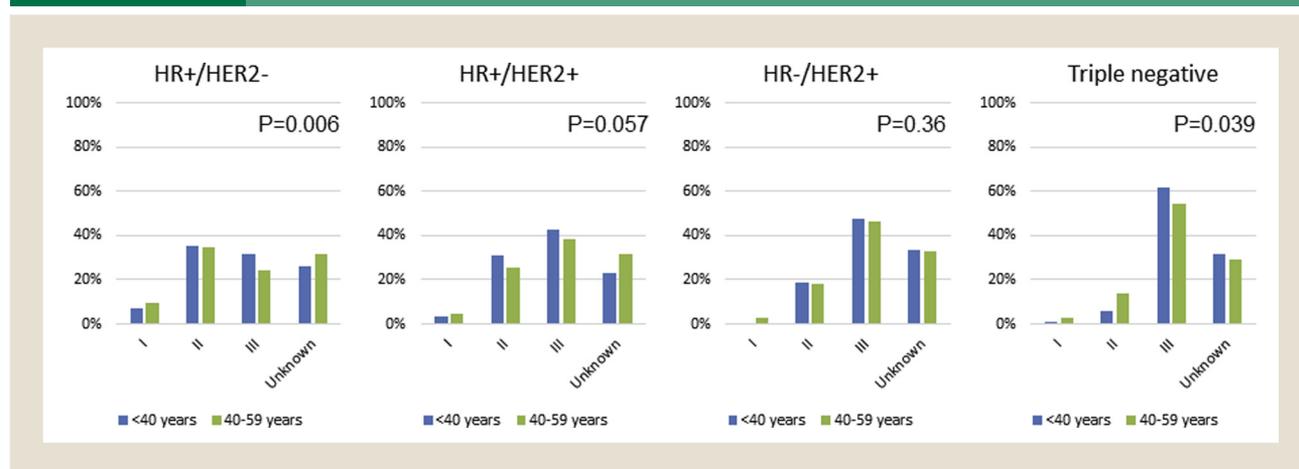
Abbreviations: ⁻ = negative; ⁺ = positive; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.

Supplemental Table 1	Subtype-specific Unadjusted and Adjusted Hazard Ratios for Breast Cancer-specific Survival Between Patients Aged < 40 and 40 to 59 Years

	Univariable Analysis		Multivariable Analysis[a]	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
All	0.73 (0.65-0.81)	< .0001	0.65 (0.56-0.75)	< .0001
HR⁺/HER2⁻	0.82 (0.70-0.97)	.02	0.80 (0.68-0.94)	.006
HR⁺/HER2⁺	0.47 (0.34-0.64)	< .0001	0.47 (0.35-0.65)	< .0001
HR⁻/HER2⁺	0.67 (0.47-0.96)	.03	0.67 (0.47-0.97)	.03
Triple-negative	0.98 (0.79-1.22)	.83	0.95 (0.76-1.19)	.66

Abbreviations: ⁻ = negative; ⁺ = positive; CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.
[a]Adjusted for race, marital status, tumor grade, disease subtype, and bone metastases (only or not).