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Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer

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Abstract

IMPORTANCE—Adjuvant chemotherapy improves outcomes of patients with breast cancer. However, the optimal timing of chemotherapy initiation is unknown. Delayed administration can decrease the benefit of cytotoxic systemic therapies.

OBJECTIVE—To identify the determinants in delayed chemotherapy initiation and to determine the relationship between time to chemotherapy (TTC) and outcome according to breast cancer subtype. We hypothesized that prolonged TTC would be associated with adverse outcomes.

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DESIGN, SETTING, AND PARTICIPANTS—In an observational, population-based investigation using data from the California Cancer Registry, we studied a total of 24 843 patients with stage I to III invasive breast cancer diagnosed between January 1, 2005, and December 31, 2010, and treated with adjuvant chemotherapy. Data analysis was performed between August 2014 and August 2015.

MAIN OUTCOMES AND MEASURES—Time to chemotherapy was defined as the number of days between surgery and the first dose of chemotherapy, and delayed TTC was defined as 91 or more days from surgery to the first dose of adjuvant chemotherapy. We evaluated overall survival and breast cancer–specific survival. Logistic regression and Cox proportional hazard models were used.

RESULTS—In all, 24 843 patients were included. Median age at diagnosis was 53 years, and median was TTC was 46 days. Factors associated with delays in TTC included low socioeconomic status, breast reconstruction, nonprivate insurance, and Hispanic ethnicity or non-Hispanic black race. Compared with patients receiving chemotherapy within 31 days from surgery, there was no evidence of adverse outcomes among those with TTC of 31 to 60 or 60 to 90 days. Patients treated 91 or more days from surgery experienced worse overall survival (hazard ratio [HR], 1.34; 95% CI, 1.15-1.57) and worse breast cancer–specific survival (HR, 1.27; 95% CI, 1.05-1.53). In a subgroup analysis according to subtype, longer TTC caused patients with triple-negative breast cancer to have worse overall survival (HR, 1.53; 95% CI, 1.17-2.00) and worse breast cancer–specific survival (HR, 1.53; 95% CI 1.17-2.07).

CONCLUSIONS AND RELEVANCE—For patients with breast cancer, adverse outcomes are associated with delaying initiation of adjuvant chemotherapy 91 or more days. Delayed TTC was particularly detrimental among patients with triple-negative breast cancer. The determinants of delays in chemotherapy initiation appeared to be sociodemographic, and clinicians should provide timelier care to all patients.

In 2015, an estimated 231 840 cases of invasive breast cancer were diagnosed in the United States.[1] Improvements in breast cancer treatment and early detection have resulted in a decrease in the mortality rates of patients with breast cancer in the last decades. Among patients with early-stage breast cancer, the use of adjuvant chemotherapy has had a dramatic effect decreasing the risk of recurrence and improving survival rates.[2]

Most patients with breast cancer start adjuvant chemotherapy within 30 to 40 days of surgery. It is thought that chemotherapy administration delayed beyond this time can decrease the benefit provided by cytotoxic systemic therapies. Possible explanations for these effects include accelerated growth of micrometastases after resection of the primary tumor, increased tumor angiogenesis, or development of primary resistance.[3-6] The optimal time of chemotherapy administration for patients with breast cancer is not precisely defined. Furthermore, it is possible that the time to chemotherapy (TTC) has a different effect according to tumor subtype, tumor stage, and tumor grade.[7,8] Administration of combination systemic chemotherapy within 120 days of diagnosis in women younger than 70 years with T1cN0M0 or stage II or III hormone receptor–negative breast cancer is considered a quality metric by the Centers for Medicare & Medicaid Services. This metric will now be reported

by 11 cancer hospitals as part of the Prospective Payments System-Exempt Cancer Hospital Reporting Program.[9]

The effect of delayed TTC administration has been evaluated retrospectively with contradictory results.[10-18] In a recent study, we reported that a delay of 61 or more days of adjuvant chemotherapy administration was associated with adverse outcomes among patients with stage II and III breast cancer and also among patients with triple-negative and human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu)-positive tumors.[14] Our findings suggest that among these specific patient subgroups, every effort should be made to avoid delayed adjuvant chemotherapy initiation.

To provide data that is more generalizable and to clarify this important clinical problem, we evaluated whether TTC is associated with survival in a large population-based study using the California Cancer Registry (CCR) database. In addition, we evaluated the determinants of delayed chemotherapy administration.

Methods

Study Population and Variables

We used data from the CCR, a population-based registry that has been collecting information on all cancer cases in California since 1988. Breast cancer case ascertainment is 99% complete.[19] The CCR started collecting data on hormone receptor status (both estrogen receptor [ER] and progesterone receptor [PR]) in 1990 and began collecting information on ERBB2 status in 1999. However, information on ERBB2 breast cancer status did not become consistently available until 2005.[20,21] The Cancer Prevention Institute of California institutional review board oversaw the study, and the University of Texas MD Anderson Cancer Center institutional review board considered the study exempt under Category 4 of the Code of Federal Regulations.

We identified 41 194 patients with stage I to III primary breast cancer diagnosed between January 1, 2005, and December 31, 2010, who underwent surgery and were treated with chemotherapy. Patients with inflammatory breast cancer, unknown tumor size or surgery type, or incomplete or unknown chemotherapy or surgery dates, were excluded (n = 9843). Patients with incomplete treatment dates (n = 9048) were more likely to be diagnosed in earlier years, have more advanced cancer, and have Medicare and/or Medicaid coverage (P < .001 for all cases). Patients treated with neoadjuvant chemotherapy (n = 4046) were also excluded. The final study cohort included 24 843 patients, and data analysis was performed between August 2014 and August 2015.

Patient information, including demographic characteristics and variables related to the cancer diagnosis and treatment, were abstracted from medical records by tumor registrars as part of routine registry procedures. From the CCR, we obtained the following patient characteristics: date of diagnosis, age, marital status, insurance type (private, Medicaid, Medicare, military, not insured or self-pay, unknown), race (non-Hispanic whites, non-Hispanic blacks, Hispanics, Asian or Pacific Islander, non-Hispanic American Indian, other, or unknown), type of breast surgery (mastectomy or breast conserving), whether

reconstructive surgery was performed, and whether the patient received radiation therapy. We also obtained data on tumor ER, PR, and ERBB2 status, and we categorized patients into subgroups according to breast cancer subtype. The hormone receptor–positive subgroup was characterized by ER-positive (ER+) and/or PR-positive (PR+) and ERBB2-negative (ERBB2−) breast cancer; ERBB2-positive (ERBB2+) breast cancer was characterized by the presence of ERBB2 regardless of ER or PR status; and triple-negative breast cancer (TNBC) was characterized as ER–negative (ER−), PR– negative (PR−), and ERBB2−. To ascertain socioeconomic status (SES), residential addresses at the time of diagnosis were geocoded to correspond with census block groups. For cases diagnosed in 2005, we used a measure of neighborhood-level SES incorporating block group level data from the 2000 Census reporting income, education, housing costs, and occupation.[22] For cases diagnosed from 2006 to 2010, we used data from the 2007 to 2011 American Community Survey of the US Census to derive a similar SES index.[23] We identified patients seen at NCI-designated cancer centers.[24]

Statistical Analysis

Patients were categorized according to TTC categories, and this variable was calculated from the date of definitive surgery to the date that the first dose of adjuvant chemotherapy was administered. Patients TTC categories were 30 days or less, 31 to 60 days, 61 to 90 days, or 91 or more days, and delay in chemotherapy administration was defined as 91 or more days. Descriptive statistics were used to evaluate the characteristics of the patient population according to TTC, and the distribution was compared using χ^2 test. A multivariable logistic regression model was used to identify factors associated with delay in chemotherapy administration. Variables in the multivariable model were selected a priori and included age, sex, race/ethnicity, year of diagnosis, SES, breast cancer stage, breast cancer subtype, marital status, type of breast surgery, whether reconstructive surgery was performed, primary payer, and whether the patient was treated at a NCI–designated cancer center.

Follow-up was calculated using the reverse censored Kaplan-Meier method. Survival time was calculated in days from the date of breast cancer diagnosis to the date of last contact. The CCR regularly updates vital patient status information and active hospital follow-ups through linkages with state and national databases. Patients who were known to be alive at the study cutoff date of December 31, 2012, were censored on that date. For BCSS, deceased patients whose underlying cause of death was not breast cancer were censored at time of death. Univariate survival analyses according to TTC were performed using the Kaplan-Meier method, and the log-rank test was used to compare differences between groups. Using a multivariable Cox proportional hazard model, we examined the effect of TTC as a continuous (in weeks) and as a categorical variable for OS and BCSS. The proportional hazards assumption was assessed using Schoenfeld residuals and also by examining log-log plots. Breast cancer subtype violated the proportional hazards assumption. Therefore, the models were stratified according to the breast cancer subtype variable. Results are expressed in hazard ratios (HR) and 95% CIs. The following variables were included in the final model: TTC, age, sex, race/ethnicity, marital status, SES, stage,

primary payer; type of surgery, breast reconstruction, and whether the patient was treated at a NCI-designated cancer center.

Statistical analyses were performed with deidentified data from the CCR using SAS version 9.3 software (SAS Institute Inc). All tests were 2-sided, and $P \leq .05$ was considered statistically significant.

Results

Among the 24 843 patients included in our study, the median age at diagnosis was 53 years, and the median TTC was 46 days. A total of 5224 (21.0%) patients started chemotherapy within fewer than 31 days; 12 432 (50.0%) between 31 and 60 days; 4765 (19.2%) between 61 and 90 days; and 2422 (9.8%) started chemotherapy 91 or more days after surgery. Patient characteristics according to TTC are presented in eTable 1 in the Supplement. When evaluating the factors associated with a delay in adjuvant chemotherapy administration with a multivariable model, we observed that compared with either stage I patients, those with stage II and III were less likely to have delays in chemotherapy administration (odds ratio [OR], 0.69; 95% CI, 0.63-0.76, and OR, 0.59; 95% CI, 0.52-0.67, respectively). Patients with TNBC were also less likely to have delays (OR, 0.72; 95% CI, 0.63-0.81) compared with patients with hormone-receptor positive tumors. On the other hand, age, reconstructive surgery, and sociodemographic factors were associated with longer TTC. Compared with non-Hispanic whites, non-Hispanic blacks and Hispanics were significantly more likely to receive chemotherapy 91 or more days after surgery (OR, 1.38; 95% CI, 1.19-1.60, and OR, 1.15; 95% CI, 1.03-1.29, respectively). A similar phenomenon was observed for SES. Compared with the highest quintile, those in the lowest quintile were more likely to receive delayed chemotherapy (OR, 1.40; 95% CI, 1.21-1.62). The complete multivariable model for the determinants of delay in TTC is shown in Table 1.

Median follow-up was 62.7 months. Survival analysis using the Kaplan-Meier method for OS according to TTC demonstrated that patients who received chemotherapy 91 or more days after surgery had worse OS ($P < .001$). In the analysis according to tumor subtype, we observed that among patients with hormone-receptor positive tumors ($P = .002$) and TNBC ($P<.001$) those treated with chemotherapy 91 or more days had worse OS. The same phenomenon was not observed among patients with ERBB2+ tumors ($P = .18$) (eFigure in the Supplement). Similar results were seen when evaluating BCSS (data not shown).

The multivariable analyses for OS and BCSS are shown in Table 2. After adjusting for important confounders, we observed that a 7-day delay in initiation of adjuvant chemotherapy increased the risk of death by 1% (HR, 1.01; 95% CI, 1.01-1.01). Using a reference of TTC less than 31 days from surgery in the analysis, we observed that receiving treatment between 31 and 60 days or 61 and 90 days was not associated with worse OS. However, patients in the category of 91 or more days had a 34% increase in the risk of death (HR, 1.34; 95% CI, 1.15-1.57). Other factors associated with worse OS included older age, advanced stage breast cancer, non-Hispanic black ethnicity, and lower SES. Compared with patients with private insurance, those with Medicare and Medicaid coverage had worse OS. Patients treated at NCI-designated cancer centers had improved OS. In the analysis

according to BCSS, we observed similar findings. While TTC 31 to 60 and 60 to 90 days was not associated with adverse outcomes, patients with TTC 91 or more days had a 27% increase in the risk of breast cancer death (HR, 1.27; 95% CI, 1.05-1.53). The factors associated with worse BCSS included older age, advanced stage breast cancer, non-Hispanic black ethnicity, and lower SES. In a stratified model including a term for radiation therapy, we observed similar results (data not shown), and inclusion of contralateral breast cancer in the model did not change our results (data not shown).

We evaluated whether TTC had a different effect according to breast cancer subtype and observed that TTC 91 or more days was associated with worse OS among patients with TNBC (HR, 1.53; 95% CI, 1.17-2.00) but had no significant effect among those with hormone receptor–positive (HR, 1.25; 95% CI, 0.98-1.59) or ERBB2+ (HR, 1.28; 95% CI, 0.93-1.75) tumors. The effect of SES in OS was much stronger among patients with hormone receptor–positive and ERBB2+ tumors and patients with Medicaid had worse OS in these 2 tumor subtypes (Table 3).

Similar results were seen when evaluating BCSS (eTable 2 in the Supplement). Time to chemotherapy 91 or more days was associated with an increased risk in breast cancer death among patients with TNBC (HR, 1.53; 95% CI, 1.17-2.07) but had no significant effect among patients with hormone receptor– positive (HR, 1.23; 95% CI, 0.92-1.66) or ERBB2+ (HR, 1.02; 95% CI, 0.68-1.53) tumors. The effect of SES on outcome was statistically significant among patients with hormone receptor-positive and ERBB2+ tumors.

Discussion

In this large, population-based study, we observed that a delay in initiation of adjuvant chemotherapy of 91 or more days after surgery was associated with worse OS and BCSS among patients with breast cancer. Furthermore, our study suggests that the adverse outcomes associated with delays in TTC are particularly important among patients with TNBC.

The optimal time to start adjuvant chemotherapy remains a topic of fundamental clinical importance. Given the nature of the question, clinical trials addressing this issue will not be undertaken since they will be considered to be unfeasible and unethical. Reports are conflicting since some studies have found no relationship between TTC and outcome.[11,15,25] However, these studies[11,15,25] were small, reported on single-institution data, and do not reflect contemporary breast cancer systemic management.

The notion that a delay in adjuvant chemotherapy is associated with adverse outcomes is supported by preclinical data that identified a phase of accelerated growth of the microscopic residual disease after initial surgical resection and by mathematical models demonstrating the development of chemotherapy resistance.[3-6,8] In this study, we observed that delays in TTC 91 or more days are associated with poorer outcomes. Our results are consistent with previous reports, including 2 large meta-analyses. Yu et al[26] identified 34 097 patients from 7 different studies and observed that OS decreased by 15% for every additional 4-week delay in initiation of adjuvant chemotherapy (HR, 1.15; 95% CI, 1.03-1.28). Applying these

results, a 12-week delay in TTC would be associated with an approximately 30% increase in the risk of death, which is consistent with the 34% increased risk that we observed in our study for patients with TTC 91 or more days. In the second meta-analysis, Biagi et al[10] evaluated TTC as a continuous variable among 15 327 breast cancer patients. They observed that each 4-week increase in TTC was associated with a 6% increase in the risk of all-cause mortality, similar to the 4% increase in mortality for every 4-week delay observed in our analysis using TTC as a continuous variable.

The optimal time to initiation of adjuvant chemotherapy has been evaluated using clinical trial data. No survival differences were observed among participants of Danish Breast Cancer Cooperative group trials.[12] Given the nature of the study, the authors were not able to evaluate the effect of delays beyond 90 days, since 98% of the patients started adjuvant chemotherapy within 3 months after surgery. In an analysis including 1788 premenopausal patients participating in the IBIS (International Breast Cancer Intervention Study) I, II, and VI trials, a differential effect in TTC according to tumor subtype was observed but adverse outcomes owing to a delay in TTC were only observed among patients with ER− tumors.[13] In our study, an analysis according to tumor subtype suggests that the effect of delays in TTC is of particular relevance among patients with TNBC. This is not surprising considering the rapid proliferation rate of these tumors. Also, the proportional benefit provided by chemotherapy among high-grade tumors with an aggressive biology is expected to be greater.[27-29] Our group recently reported a large single-institution study[14] including 6827 patients, and in this selected patient population, TTC 61 or more days after surgery was associated with adverse outcomes, particularly among patients with TNBC and those with ERBB2+ tumors that received trastuzumab-based therapy. In the present study, we did not observe a statistically significant detrimental effect in OS or BCSS among patients with ERBB2+ tumors with TTC 91 or more days; however, the direction of the estimate was parallel with those with TNBC. It is possible that the lack of statistical significance was the product of the small number of patients in the ERBB2+ category or to the heterogeneous use of trastuzumab-based therapy in our cohort.

Other population-based studies have addressed the topic of TTC postsurgery with results that are consistent with our findings. Data from British Columbia[16] including 2594 patients with stage I and II breast cancer suggests that OS and relapse-free survival are compromised when adjuvant chemotherapy is administered more than 12 weeks after surgery. In a large study including 14 380 breast cancer SEER-Medicare participants (data collected 1992-2005), Nurgalieva et al[28] observed that patients with TTC greater than 90 days had a statistically significant increase in overall risk of death (HR, 1.53; 95% CI, 1.32-1.80) and breast cancer-specific death (HR, 1.83; 95% CI, 1.31-2.47) compared with patients treated within a month of surgery. In this study, African American or Hispanic race/ethnicity was a significant factor associated with delays in TTC. Hershman et al[30] evaluated 5003 patients using the same SEER-Medicare database and reported that a delay in TTC greater than 90 days in patients older than 65 years was associated with worse OS (HR, 1.46; 95% CI, 1.21-1.75) and BCSS (HR, 1.69; 95% CI, 1.31-2.19). The study by Hershman et al also identified that delays in TTC were associated with increased age, rural location residence, being unmarried, earlier-stage breast cancer, hormone receptor-positive tumors, and patients undergoing mastectomy.

Our study is unique and adds to the available literature. We report results from a large, population-based cohort that reflects general practice patterns, allowing generalization of our results. Given the recent years of inclusion, the patients in our cohort were treated with contemporary systemic regimens, and we were able to perform subgroup analysis according to breast cancer subtype.

In addition to evaluating the relationship between TTC and corresponding outcomes, we were also able to identify that the main determinants of delaying TTC are sociodemographic in nature. Similar to what others have described,[17,30-36] we observed that Hispanics, non-Hispanic blacks, unmarried patients, patients with low SES, patients with Medicare, Medicaid, or military insurance, and patients who are not insured or are self-paid are more likely to experience delayed initiation of adjuvant chemotherapy. On the other hand, patients with TNBC and those with stage II or III breast cancer were less likely to have delays in treatment, probably because such characteristics are associated with poor prognosis. In the analysis according to breast cancer subtype, payment coverage method and SES were significantly associated with OS and BCSS among patients with hormone receptor-positive and ERBB2+ tumors. This finding is likely associated with the financial burden from health care costs and that the treatment duration is longer among these patients. It has been demonstrated that the out-of-pocket cost of adjuvant endocrine therapy is associated with treatment adherence and compliance, therefore affecting outcomes.[37-39] Unfortunately, in the CCR data on type, duration, or adherence to endocrine therapy is not available, and we could not include this important confounder in our analyses.

Our study is limited by its retrospective nature. However, that we are aware of, this study is the largest published cohort of patients with breast cancer of known breast cancer subtype treated with contemporary regimens. We acknowledge that in clinical practice a number of factors determine the optimal TTC, and that in many cases, this time frame is determined by comorbidities or complications associated with surgery.[40] Unfortunately, data concerning comorbidities and complications with surgery are not available in the CCR database, and we cannot exclude that the factors associated with delays in chemotherapy administration are not also related to worse outcomes. However, the fact that we observed consistent results in our OS and BCSS risk estimates makes this scenario unlikely. In addition, we acknowledge that the potential determinants of chemotherapy initiation include the recommendation of the medical oncologist and the entire multidisciplinary team. Additionally, from the patient-centered care perspective, a patient's preferences are likely to play a role, which we were unable to take into account.

Conclusions

In our cohort, the median time between diagnosis and surgery was 26 days. We observed adverse outcomes among patients with TTC 91 or more days. Our findings support the notion that TTC should be used as a quality measure as has been proposed recently by the Centers for Medicare & Medicaid Services. Given the results of our analysis, we would suggest that all breast cancer patients that are candidates for adjuvant chemotherapy should receive this treatment within 91 days of surgery or 120 days from diagnosis. Administration of chemotherapy within this time frame is feasible in clinical practice under most clinical

scenarios, and as medical oncologists, we should make every effort not to delay the initiation of adjuvant chemotherapy. Furthermore, determinants of delay in TTC were sociodemographic in nature; better understanding and removing barriers to access of care in vulnerable populations should be a priority.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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At a Glance

- The relationship between time to chemotherapy (TTC) and outcomes for subgroups of patients with breast cancer receiving adjuvant chemotherapy were determined, as well as the determinants in delayed chemotherapy initiation.
- Compared with patients receiving adjuvant chemotherapy within 31 days of surgery, there was no evidence of adverse outcomes among patients who received chemotherapy 31 to 90 days after surgery.
- Patients treated 91 or more days from surgery experienced worse overall survival (hazard ratio [HR], 1.34; 95%CI, 1.15-1.57) and worse breast cancer–specific survival (HR, 1.27; 95%CI, 1.05-1.53).
- Among patients with triple-negative breast cancer, longer TTC had a significant effect on overall survival (HR, 1.53; 95%CI, 1.17-2.00) and breast cancer–specific survival (HR, 1.53; 95%CI, 1.17-2.07).
- Factors associated with delays in TTC included low socioeconomic status, breast reconstruction, nonprivate insurance, and Hispanic ethnicity or non-Hispanic black race.

Table 1

Logistic Regression of Factors Associated With Delayed TTC[a,b]

Characteristic	Odds Ratio (95% CI)
Age at diagnosis, y	
<40	0.93 (0.80-1.08)
41-59	0.97 (0.87-1.07)
60-79	1 [Reference]
≥80	1.36 (0.95-1.96)
Sex	
Female	1 [Reference]
Male	0.51 (0.27-0.98)
Race/ethnicity	
Non-Hispanic white	1 [Reference]
Non-Hispanic black	1.38 (1.19-1.60)
Hispanic	1.15 (1.03-1.29)
Asian/Pacific Islander	1.07 (0.94-1.21)
Non-Hispanic American Indian/other/unknown	1.29 (0.88-1.89)
SES quintile	
1 (lowest)	1.40 (1.21-1.62)
2	1.24 (1.09-1.42)
3	1.24 (1.09-1.41)
4	1.20 (1.06-1.35)
5 (highest)	1 [Reference]
AJCC stage at diagnosis	
I	1 [Reference]
II	0.69 (0.63-0.76)
III	0.59 (0.52-0.67)
Breast cancer subtype	
Hormone receptor–positive	1 [Reference]
ERBB2+	1.04 (0.95-1.15)
TNBC	0.72 (0.63-0.81)
Unknown	1.02 (0.88-1.19)
Marital status	
Not currently married	1.24 (1.14-1.35)
Married	1 [Reference]
Unknown	1.03 (0.77-1.37)
Surgery	
Mastectomy	1 [Reference]
Breast conserving surgery	0.90 (0.82-0.99)

Characteristic	Odds Ratio (95% CI)
Primary payer/insurance	
Private	1 [Reference]
Medicare	1.53 (1.30-1.82)
Military	1.74 (1.26-2.41)
Medicaid	2.19 (1.97-2.43)
Not insured/self-pay	1.66 (1.13-2.43)
Unknown	1.03 (0.80-1.34)
Breast reconstruction	
Yes	1.51 (1.31-1.74)
No	1 [Reference]
NCI-designated cancer center	
Yes	1.17 (1.00-1.37)
No	1 [Reference]

Abbreviations: AJCC, American Joint Committee on Cancer; ERBB2+, human epidermal growth factor receptor 2-positive; NCI, National Cancer Institute; SES, socioeconomic status; TNBC, triple negative breast cancer; TTC, time to chemotherapy.

[a] Delayed TTC is defined as 91 or more days.

[b] Year of diagnosis was included as a covariate in the model.

Table 2

Multivariable Cox Proportional Hazards Model for OS and BCSS[a]

	HR (95% CI)	
Characteristic	**BCSS**	**OS**
TTC, d		
<31	1 [Reference]	1 [Reference]
31-60	0.98 (0.87-1.09)	0.99 (0.86-1.12)
61-90	1.01 (0.88-1.16)	1.00 (0.85-1.18)
≥91	1.34 (1.15-1.57)	1.27 (1.05-1.53)
Age at diagnosis, y		
<40	0.84 (0.72-0.98)	1.15 (0.97-1.37)
41-59	0.65 (0.59-0.72)	0.81 (0.72-0.92)
60-79	1 [Reference]	1 [Reference]
≥80	2.19 (1.70-2.82)	1.99 (1.42-2.78)
Sex		
Female	1 [Reference]	1 [Reference]
Male	1.37 (0.87-2.16)	0.96 (0.49-1.85)
Race/ethnicity		
Non-Hispanic white	1 [Reference]	1 [Reference]
Non-Hispanic black	1.26 (1.08-1.46)	1.30 (1.09-1.54)
Hispanic	0.84 (0.75-0.96)	0.84 (0.72-0.97)
Asian/Pacific Islander	0.78 (0.66-0.91)	0.79 (0.66-0.95)
Non-Hispanic American Indian/other/unknown	1.02 (0.65-1.61)	0.93 (0.53-1.60)
SES quintile		
1 (lowest)	1.46 (1.25-1.72)	1.42 (1.17-1.71)
2	1.39 (1.20-1.61)	1.35 (1.14-1.60)
3	1.32 (1.15-1.51)	1.37 (1.17-1.61)
4	1.21 (1.06-1.39)	1.27 (1.08-1.49)
5 (highest)	1 [Reference]	1 [Reference]
AJCC stage at diagnosis		
I	1 [Reference]	1 [Reference]
II	1.97 (1.71-2.26)	2.54 (2.11-3.05)
III	5.16 (4.47-5.95)	8.21 (6.82-9.88)
Marital status		
Married	1 [Reference]	1 [Reference]
Not currently married	1.07 (0.98-1.18)	1.01 (0.90-1.13)
Unknown	1.14 (0.83-1.57)	1.25 (0.88-1.78)
Primary payer/insurance		
Medicare	1.40 (1.20-1.64)	1.29 (1.05-1.57)

	HR (95% CI)	
Characteristic	**BCSS**	**OS**
Military	0.82 (0.45-1.49)	0.70 (0.33-1.46)
Not insured/self-pay	1.14 (0.71-1.85)	1.30 (0.78-2.17)
Private	1 [Reference]	1 [Reference]
Medicaid	1.48 (1.32-1.66)	1.39 (1.22-1.60)
Unknown	0.87 (0.66-1.14)	0.84 (0.62-1.15)
NCI-designated cancer center		
No	1 [Reference]	1 [Reference]
Yes	0.66 (0.53-0.82)	0.73 (0.58-0.93)

Abbreviations: AJCC, American Joint Committee on Cancer; BCSS, breast cancer–specific survival; HR, hazard ratio; NCI, National Cancer Institute; OS, overall survival; SES, socioeconomic status; TTC, time to chemotherapy.

[a]Model was stratified according to breast cancer subtype, and year of diagnosis was also included in the model.

Table 3

Multivariable Cox Proportional Hazards Model OS According to Breast Cancer Subtype[a]

	Breast Cancer Subtype, HR (95% CI)		
Characteristic	**Hormone Receptor Positive**	**ERBB2+**	**TNBC**
TTC, d			
<31	1 [Reference]	1 [Reference]	1 [Reference]
31-60	0.90 (0.75-1.08)	0.97 (0.77-1.24)	1.09 (0.90-1.31)
61-90	0.95 (0.77-1.18)	1.03 (0.76-1.38)	1.08 (0.85-1.36)
≥91	1.25 (0.98-1.59)	1.28 (0.93-1.75)	1.53 (1.17-2.00)
Age at diagnosis, y			
0-40	0.90 (0.70-1.15)	0.64 (0.47-0.88)	0.90 (0.70-1.15)
41-59	0.62 (0.53-0.73)	0.58 (0.47-0.72)	0.73 (0.61-0.88)
60-79	1 [Reference]	1 [Reference]	1 [Reference]
≥80	2.94 (1.89-4.59)	2.11 (1.33-3.36)	2.05 (1.35-3.11)
Sex			
Female	1 [Reference]	1 [Reference]	1 [Reference]
Male	1.73 (1.02-2.94)	1.12 (0.42-3.01)	0.46 (0.06-3.34)
Race/ethnicity			
Non-Hispanic white	1 [Reference]	1 [Reference]	1 [Reference]
Non-Hispanic black	1.21 (0.94-1.57)	1.36 (0.98-1.89)	1.26 (1.01-1.57)
Hispanic	0.76 (0.63-0.93)	0.86 (0.67-1.11)	0.92 (0.75-1.13)
Asian/Pacific Islander	0.72 (0.56-0.92)	0.83 (0.61-1.12)	0.85 (0.64-1.12)
Non-Hispanic American Indian/other/unknown	1.58 (0.89-2.80)	0.36 (0.09-1.46)	0.89 (0.37-2.16)
AJCC stage at diagnosis			
I	1 [Reference]	1 [Reference]	1 [Reference]
II	1.56 (1.24-1.95)	2.59 (1.87-3.59)	2.08 (1.68-2.58)
III	3.76 (3.00-4.72)	7.46 (5.41-10.3)	5.72 (4.56-7.18)
Neighborhood SES			
1 (lowest)	1.60 (1.25-2.06)	1.66 (1.18-2.32)	1.22 (0.94-1.58)
2	1.57 (1.26-1.96)	1.53 (1.12-2.09)	1.11 (0.87-1.41)
3	1.31 (1.06-1.63)	1.43 (1.06-1.93)	1.22 (0.97-1.53)
4	1.35 (1.10-1.66)	1.20 (0.88-1.63)	1.04 (0.83-1.31)
5 (highest)	1 [Reference]	1 [Reference]	1 [Reference]
Marital status			
Married	1 [Reference]	1 [Reference]	1 [Reference]
Not currently married	1.08 (0.93-1.24)	1.03 (0.85-1.26)	1.10 (0.94-1.29)
Unknown	0.97 (0.57-1.65)	1.93 (1.05-3.56)	0.98 (0.58-1.68)
Primary payer/insurance			
Medicare	1.82 (1.45-2.29)	1.19 (0.84-1.68)	1.11 (0.84-1.46)

	Breast Cancer Subtype, HR (95% CI)		
Characteristic	**Hormone Receptor Positive**	**ERBB2+**	**TNBC**
Military	0.51 (0.16-1.59)	1.12 (0.41-3.03)	1.09 (0.41-2.94)
Not insured/self-pay	1.60 (0.79-3.23)	0.97 (0.36-2.62)	0.90 (0.37-2.19)
Private	1 [Reference]	1 [Reference]	1 [Reference]
Medicaid	1.76 (1.47-2.10)	1.44 (1.15-1.81)	1.20 (0.99-1.47)
Unknown	0.90 (0.56-1.44)	0.79 (0.46-1.33)	0.85 (0.56-1.30)
NCI-designated cancer center			
No	1 [Reference]	1 [Reference]	1 [Reference]
Yes	0.61 (0.44-0.86)	0.69 (0.44-1.08)	0.74 (0.53-1.04)

Abbreviations: AJCC, American Joint Committee on Cancer; ERBB2+, human epidermal growth factor receptor 2-positive; HR, hazard ratio; NCI, National Cancer Institute; OS, overall survival; SES, socioeconomic status; TTC, time to chemotherapy.

[a]Models adjusted for individual year of diagnosis.