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Age and Survival Estimates in Patients Who Have Node-Negative T1ab Breast Cancer by Breast Cancer Subtype

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Abstract

The treatment of tumors ≤1 cm are difficult to treat as recurrence rates are difficult to assess. The purpose of this study was to assess recurrence by underlying triple receptor subtype and by age, both of which had significant impact on outcomes.

Aim—This article evaluates the risk of recurrence for patients who have small node-negative breast cancer by age and tumor subtype.

Methods—One thousand twelve patients with a T1a,bN0 breast cancer diagnosed between 1990 and 2002 who did not receive chemotherapy or trastuzumab were included. Patients and tumor characteristics were compared using the χ^2 or Wilcoxon's rank sum tests. Survival outcomes were estimated with the Kaplan-Meier method and compared using the log-rank statistic. Cox proportional hazards models were used to determine association of breast cancer subtypes and age at diagnosis with other covariates.

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Results—Median age was 51.5 years. There were 771 hormone receptor (HR)-positive, 98 HER2-positive, and 143 triple-negative breast cancers (TNBC). Six hundred ninety-three patients were > 50 years, and 33 patients were ≤ 35 years. For 5-year survival estimates, there were 118 deaths and overall survival was 94.6% (95% confidence interval [CI] = 93.2%, 96.1%). After adjusting for breast cancer subtype and other tumor characteristics, patients ≤ 35 had 2.51 (95% CI = 1.21–5.22) times greater risk of worse recurrence-free survival (RFS), and 2.60 (95% CI = 1.05–6.46) times greater risk of worse distant RFS (DRFS) compared to patients > 50 years old. Compared to patients with HR-positive disease, patients with HER2-positive breast cancer had 4.98 (95% CI = 2.91–8.53) times the risk of worse RFS and 4.70 (95% CI = 2.51–8.79) times greater risk of worse DRFS, and patients with TNBC had 2.71 (95% CI = 1.59–4.59) times greater risk of worse RFS and 2.08 (95% CI = 1.04–4.17) times greater risk of worse DRFS.

Conclusions—In this cohort, patients with T1a,bN0 breast cancer, young age and breast cancer subtype were significantly associated with RFS and DRFS.

Keywords

Distant recurrence-free survival; HER2; Hormone receptor; Recurrence-free survival; Triple-negative breast cancer

Introduction

Approximately 60% of the estimated 209,060 cases of breast cancer that were diagnosed in 2010 were localized to the breast only (without lymph node or distant involvement) with an excellent overall 5-year survival rate of 98%.[1,2] According to the 2010 National Comprehensive Cancer Network Guidelines, small tumors (those less than 0.5 cm in greatest diameter (T1a) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal benefit and is not recommended. These guidelines also state that patients with invasive breast cancers 0.6 to 1 cm in diameter and no lymph node involvement (T1b) may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features (intramammary angiolymphatic invasion, high nuclear grade, high histologic grades, HER2-positive status, and hormone receptor [HR]–negative status) warrant consideration for adjuvant therapy.[3] Despite the overall excellent long-term prognosis for patients with T1a,b breast cancers, recurrences and deaths do occur. The National Surgical Adjuvant Breast and Bowel Project (NSABP) studies B-13, B-19, and B-23 have sequentially evaluated adjuvant chemotherapy in node-negative estrogen receptor–negative tumors and have shown that adjuvant chemotherapy with methotrexate and 5-fluorouracil (MF) is more effective in reducing the risk of relapse than surgery alone (B-13), cyclophosphamide with MF (CMF) is more effective than MF (B-19), and that CMF and doxorubicin with cyclophosphamide (AC) are equally efficacious (B-23).[4–6] Updated findings from these studies demonstrated a 58% reduction in recurrence and a 40% reduction in mortality as a result of chemotherapy through 8 years of follow-up. No outcome differences were noted in age groups.[7] These studies demonstrated that adjuvant chemotherapy, specifically CMF or AC, are of benefit, even in early-stage node-negative breast cancers.

Historically, young women diagnosed with breast cancer have a worse disease- free survival and breast cancer–specific survival when compared to postmenopausal women. There have been several retrospective studies evaluating age and prognosis.[8] Nixon et al showed that patient age younger than 35 years was a significant predictor for time to recurrence, time to distant failure, and overall mortality.[9] Gnerlich et al found that women younger than 40 years old with stage I or II disease were more likely to die than their counterparts who were older than the age of 40 years.[10] Also, Kwon et al have described that young patients, specifically those 35 years old or younger, have a significantly higher rate of recurrence compared to an older cohort.[11] In addition, newer studies have shown that certain biologic subtypes, including HER2-positive and triple-receptor negative breast cancer (TNBC) tumors, have an increased risk of relapse, despite their small size.[12–16] This analysis evaluates the additional variable of young age, a known poor prognostic factor, when evaluating patients with small tumors, which historically has been a good prognostic feature.

Given all of the above known data about early-stage disease, age at diagnosis, and emerging data about receptor status; the question of whom to treat with adjuvant chemotherapy for small tumors remains controversial. In this study we sought to evaluate outcome differences in T1a and T1b N0M0 tumors by both age and breast cancer subtype to further provide insight into who may have a high enough recurrence risk to potentially benefit from adjuvant therapy.

Materials and Methods

The Breast Cancer Management System database of The University of Texas MD Anderson Cancer Center was searched to identify women who were diagnosed between 1990 and 2002 with node-negative, invasive breast cancers that were 1 cm in diameter or smaller. This database prospectively collects information on patients who present to our institution as part of an Internal Review Board–approved protocol. A separate approval was obtained from our institutional Review Board for this analysis. Additional patients excluded from this study included patients who had received adjuvant systemic therapy other than hormonal therapy, and patients with unknown adjuvant chemotherapy treatment status. From this database, 1102 women were identified. Endocrine therapy was recommended if their tumor was HR-positive as was standard of care at the time of diagnosis. Of note, tamoxifen was not administered routinely to premenopausal women at our institution until 1997. Patients were categorized by triple-receptor subtypes: HR-positive and HER2-negative (HR-positive), HER2-positive, and TNBC. Updates on patient status were extracted from the medical record. For those patients who were not followed-up at our institution, we contacted for updates through our tumor registry and document status on a yearly basis.

Pathologic Methods

Medical records were reviewed and pathologic diagnoses were confirmed by institutional breast pathologists as part of standard care at our institution. Immunohistochemical (IHC) analysis to determine HR status was performed using standard procedures on 4-μm sections of paraffin-embedded tissues stained with monoclonal antibodies for estrogen and progesterone receptors. Nuclear staining ≥ 10% of either estrogen receptor or progesterone

receptor was considered a positive result. HER2 status was evaluated by IHC or by fluorescence in situ hybridization (FISH). HER2 positivity was defined as 3+ receptor over-expression on IHC staining (ie, strong membranous staining in at least 10% of the cells) and/or as gene amplification found on FISH. A gene copy-to-CEP-17 ratio greater than 2.0 was considered amplified. The histologic grade was defined according to the modified Black's nuclear grading system.[17]

Patients were categorized according to the breast cancer subtype and their age at diagnosis.

Statistical Methods

Descriptive statistics were used and patient characteristics were tabulated and described by median and range. Comparisons between groups were made using the χ^2 test or Wilcoxon's rank sum test as appropriate. Time to recurrence was measured from the date of diagnosis to the date of first local or distant disease recurrence or last follow-up. Patients who died before experiencing a disease recurrence were considered censored at their date of death. Similarly, the time to distant recurrence was measured from the date of diagnosis to the date of first distant recurrence or last follow-up. Patients who died before experiencing a distant recurrence were considered censored at their date of death and patients who experienced a local recurrence as their first recurrence were considered censored at their date of local recurrence. Patients who experienced both a local and a distant recurrence at the same time were considered as both events.

Initial analyses revealed an increasing hazard of recurrence over follow-up time. Time to recurrence and to distant recurrence were estimated according to the Kaplan-Meier method and compared between groups by using the log-rank statistic. Cox proportional hazards models were used to determine the association of breast cancer subtype and age at diagnosis with the risk of recurrence after adjustment for other patient and tumor characteristics. Each model contained terms for tumor subtypes, age at diagnosis, nuclear grade, T stage, and hormonal therapy. All terms were retained in the models due to clinical significance, regardless of statistical significance in univariate model. Two sided *P* values of less than .05 were considered statistically significant. Analyses were performed by using SAS 9.1 (SAS Institute, Cary, NC) and R 2.7.0(R Development Core Team, available at: http://www.r-project.org/).

Results

Patient characteristics according to breast cancer subtypes and age are shown in Table 1. Ninety-eight (9.68%) patients had HER2-positive tumors, 771 (76.19%) patients had HR-positive tumors, and 143 (14.13%) patients had TNBC. Compared to HR-positive and TNBC, patients with HER2-positive tumors tended to be younger, have T1a tumors more frequently, and also have a higher nuclear grade disease. The cohort was divided into the following age groups: 33 (3.26%) patients were 35 years old or younger, 286 (28.26%) patients were between 35 and 50 years old, and 693 (68.48%) patients were older than 50 years. There were more HER2-positive andTNBCbreast cancers in the less than 35-years-old group, than in the > 50-year-old group. Patients younger than 35-years-old had the highest percentage of T1a tumors among different age groups (45.45% in the ≤ 35-years-old

age group versus 38.81% in the 35- to 50-years-old age group and 30.45% in the > 50-years-old group, $P = .013$).

Recurrence-free survival estimates (RFS) are summarized in Table 2. The 5-year RFS estimate for the entire population was 91.5% (95% confidence interval [CI]: 89.7–93.3%). The 5-year RFS estimates according to breast cancer subtype were 94.5% for HR-positive, 77.2% for HER2-positive, and 84.9% for TNBC, $p < 0.0001$) (Figure 1). Patients that were 35 years or younger at the time of diagnosis had lower RFS estimates (75.1%), compared to patients diagnosed in a later age (85.7% if diagnosed between 36–50 years old, and 94.6% if diagnosed after 50-years old; $P < .0001$; Figure 1). When studying RFS estimates by breast cancer subtype and age, patients 35-years old or younger had the worst outcomes across all breast cancer subtypes. The group of patients with the lowest 5-year RFS estimate was the group of 35-years-old or younger patients with HER2-positive tumors (42.9%), However, given the small numbers of patients, this point estimate has a wide confidence interval. (Table 2).

Distant recurrence-free survival (DRFS) estimates are summarized in Table 2. The 5-year DRFS estimate for the entire population was 96.3% (95% CI: 96.3–97.5%). The 5-year DRFS estimates according to breast cancer subtype were 97.5% for HR-positive, 86.9% for HER2-positive, and 96.3% for TNBC ($P < .0001$; Figure 1). Patients diagnosed at 35-years old or younger had lower RFS estimates (87.7%) compared to patients diagnosed when they were older (RFS was 94.2% if diagnosed between 36- and 50-years old, and 97.5% if diagnosed after 50-years old; $P < .0001$; Figure 1). When studying DRFS estimates by breast cancer subtype and age, again, patients 35-years old or younger had the worst outcomes in all breast cancer subtypes. The group of patients with the lowest 5-year DRFS estimate was in the group of patients 35-years old or younger with HER2-positive tumors (71.4%; Table 2).

Table 3 shows the results of the multivariable models for RFS and DRFS with respect to age and breast cancer subtype. After adjusting for breast cancer subtype and other tumor characteristics, patients 35-years old or younger had 2.51 (95% CI = 1.21–5.22) times greater risk of RFS, and 2.60 (95% CI = 1.05–6.46) times greater risk of DRFS compared to patients older than 50 years. Compared to patients with HR-positive disease, patients with HER2-positive breast cancer had 4.98 (95% CI = 2.91–8.53) times greater risk of RFS, and 4.70 (95% CI = 2.51–8.79) times greater risk of DRFS. Patients with TNBC had 2.71 (95% CI = 1.59–4.59) times greater risk of RFS, and 2.08 (95% CI = 1.04–4.17) times greater risk of DRFS compared to patients with HR-positive tumors..

Discussion

In this single-institution, retrospective study, we observed that both age at diagnosis and breast cancer subtype were significantly associated with patient outcomes among patients with T1a,bN0M0 tumors. Younger age, HER2-positivity, and TNBC status correlated with worse RFS as well as DRFS rates. These findings could have significant implications when formulating treatment recommendations.

It is known that HER2 positivity is associated with a more aggressive clinical presentation in early-stage breast cancer.[16] Patients with HER2-positive breast cancers have a significant improvement in both disease-free survival and overall survival after treatment with traztuzumab.[18–22] Recent data also suggests that traztuzumab may be of benefit in reducing both early recurrence and mortality in HER2-positive tumors that are ≤ 1cm suggesting that these patients should be included in future clinical trials to evaluate adjuvant anti-HER2 therapy.[12] Patients with TNBC are also known to have significantly higher rates of both local and distant recurrence.[11,15] Our data show that age ≤ 35-years old is a worse prognostic factor, indicating higher disease recurrence; this is consistent with historical data.

There is a paucity of data guiding clinicians on how to proceed with patients who present with small, node-negative breast cancers. However, as more information regarding these aggressive biological subtypes emerge, planning systemic treatment based on stage alone appears to lead to worse outcomes. Taking into account aggressive biological subtypes such as TNBC and HER2-positive breast cancers, as well as age at diagnosis, may better aid the patient and clinician in forming an individualized treatment plan.

Several limitations of this study should be considered when interpreting its results. This is a retrospective single-institution cohort, which lends inherent bias. Because clinicians may have been biased to treat T1b tumors with aggressive biology, patients who received systemic chemotherapy or trastuzumab therapy were excluded from this cohort. This may account for the more frequent T1a tumors in this analysis. However, this may provide further support for the need to consider the higher recurrence risks for these small tumors.

Our study lends insight into the natural history of early-stage node-negative breast cancers based on both age and biologic markers. Despite the overall excellent prognosis of these cancers, certain subgroups are emerging with notably higher recurrence rates. Both age at diagnosis and triple-receptor subtype were significantly associated with patient outcomes in T1a, bN0M0 tumors. Thus, despite small tumors, biologically more aggressive traits such as HER2 positivity, triple-negative status, and young age at diagnosis should be considered when counseling patients about treatment interventions and when developing clinical trials to prospectively evaluate treatment options in women with small but high-risk tumors.

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Clinical Practice Points

- It has been well described that breast cancer patients with young age and aggressive tumor subtypes such triple receptor negative disease (TN) or HER2-positive disease have worse outcomes when gone untreated. Additionally including patients with small tumors in treatment clinical trials is often limited.
- This study evaluated outcomes in women who had tumors ≤1 cm, node negative and looked at recurrence by both underlying tumor subtypes and by age. The women may have received adjuvant endocrine therapy but did not receive trastuzumab or chemotherapy.
- The study showed that young age, HER2 positive disease and TN disease had worse outcomes. Women with TN disease had worse outcomes regardless of age of diagnosis, although this was mostly with local recurrences.
- Women with small tumors and with aggressive underlying biology such as TN or HER2 positive should be considered for inclusion in treatment protocols to evaluate extent of therapeutic benefits.

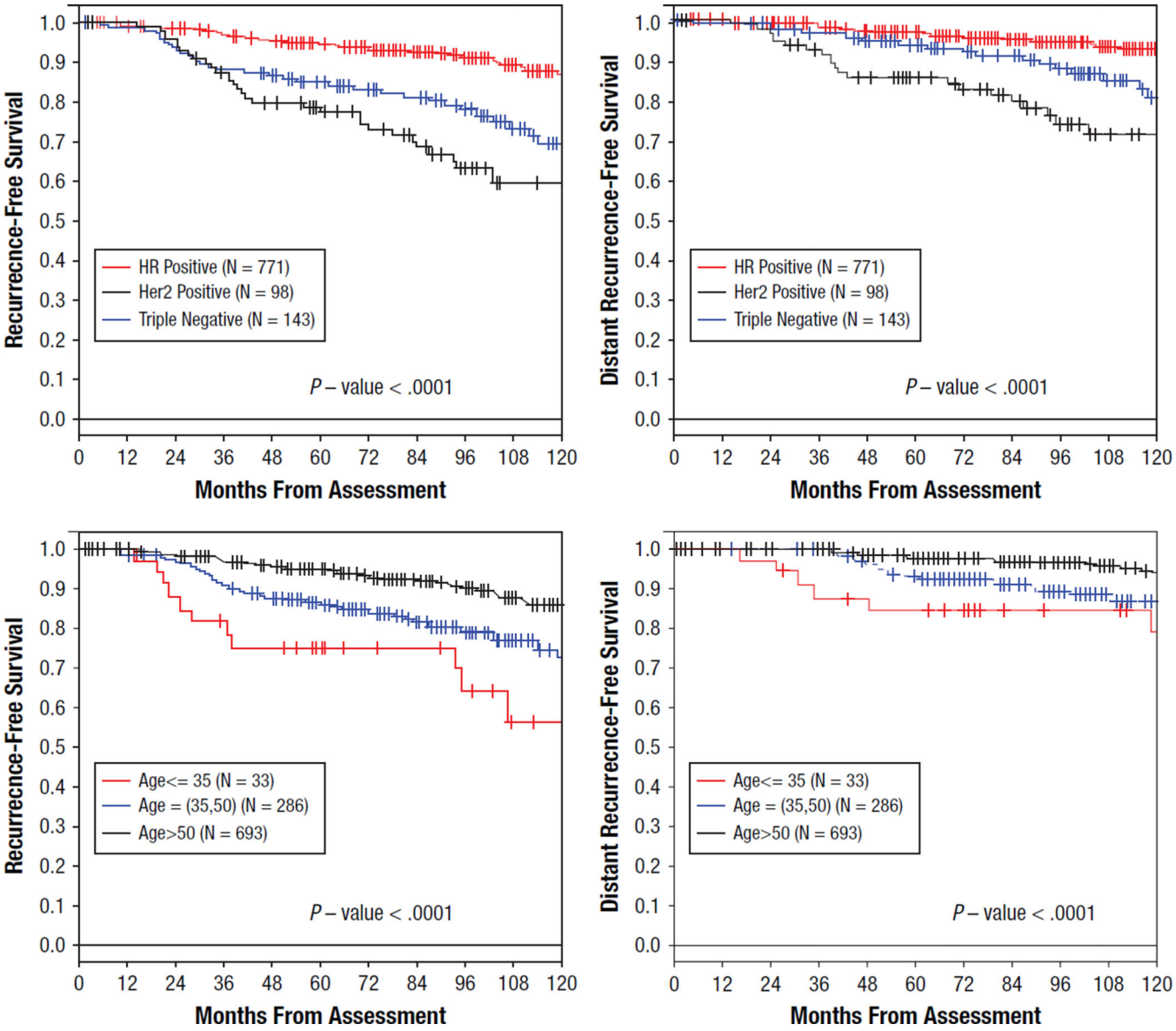

Figure 1.

(A) Recurrence-Free Survival by Breast Cancer Subtype. (B) Distant Recurrence-Free Survival by Breast Cancer Subtype. (C) Recurrence-Free Survival by Age at Diagnosis. (D) Distant Recurrence-Free Survival by Age at Diagnosis

Table 1

Patient Characteristics by Patient Cancer Subtype and Age at Diagnosis

By Breast Cancer Subtype							
N	**Her2PN 98**	**%**	**HRPN 771**	**%**	**TRNN 143**	**%**	***P* Value**
Age							
Min	28	–	26	–	32	–	
Median	51.5	–	57	–	55	–	
Max	78	–	87	–	85	–	<.0001
Race							
Black	9	9.18	54	7.00	12	8.39	
Hispanic	10	10.20	68	8.82	13	9.09	
White	75	76.53	622	80.67	107	74.83	
Other	4	4.08	27	3.50	11	7.69	.3397
Menopausal Status							
Pre	43	43.88	176	22.83	38	26.57	
Post	55	56.12	594	77.04	105	73.43	<.0001
Histology							
Ductal	90	91.84	589	76.39	113	79.02	
Other	8	8.16	182	23.61	30	20.98	.0022
T Stage							
A	43	43.88	241	31.26	53	37.06	
B	55	56.12	530	68.74	90	62.94	.0261
Nuclear Grade							
1	1	1.02	113	14.66	5	3.50	
2	17	17.35	370	47.99	30	20.98	
3	49	50.00	125	16.21	57	39.86	.0214
Hormonal Therapy							
Yes	45	45.92	469	60.83	30	20.98	
No	53	54.08	296	38.39	112	78.32	<.0001

By Breast Cancer Subtype							
N	**Her2P N 98**	**%**	**HRP N 771**	**%**	**TRN N 143**	**%**	***P* Value**
By Age at Diagnosis							
		≤35		**(35,50)**		**>50**	
		N 33	**%**	**N** 286	**%**	**N** 693	**%**
Breast Cancer Subtype							
Her2- positive	7	21.21	41	14.34	50	7.22	
Hormone receptor–positive	18	54.55	200	69.93	553	79.80	
Triple- negative	8	24.24	45	15.73	90	12.99	<.0001
Race							
Black	5	15.15	30	10.49	40	5.77	
Hispanic	7	21.21	29	10.14	55	7.94	
White	17	51.52	212	74.13	575	82.97	
Other	4	12.12	15	5.24	23	3.32	<.0001
Menopausal Status							
Pre	30	90.91	207	72.38	20	2.89	
Post	3	9.09	78	27.27	673	97.11	<.0001
Histology							
Ductal	27	81.82	229	80.07	536	77.34	
Other	6	18.18	57	19.93	157	22.66	.5663
T Stage							
A	15	45.45	111	38.81	211	30.45	
B	18	54.55	175	61.19	482	69.55	.0133
Nuclear Grade							
1	1	3.03	22	7.69	96	13.85	
2	13	39.39	108	37.76	296	42.71	
3	13	39.39	99	34.62	119	17.17	.0617
Hormonal Therapy							
Yes	19	57.58	136	47.55	389	56.13	

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By Breast Cancer Subtype							
N	**Her2P N 98**	**%**	**HRP N 771**	**%**	**TRN N 143**	**%**	***P* Value**
No	14	42.42	148	51.75	299	43.15	.0445
	33		286		693		

Abbreviations: Her2P = HER2 positive; HRP = hormone receptor positive; TRN = triple negative.

Table 2

Recurrence-Free Survival and Distant Recurrence-Free Survival by Age and Triple Receptor Subtype

Recurrence-Free Survival					
Triple Receptor Subtype	**Age**	**N Events**	**5-Year Estimate**	**95% Confidence Interval**	***P* Value**
HER2-Positive					
	≤35	5	42.9%	(18.2%, 100%)	
	35–50	15	70.5%	(57.2%, 86.9%)	
	>50	12	87.7%	(78.9%, 97.4%)	.0027
Hormone Receptor-Positive					
	≤35	3	88.9%	(75.5%, 100%)	
	35–50	27	90.3%	(86.1%, 94.7%)	
	>50	35	96.2%	(94.6%, 97.9%)	.0030
Triple-Negative Breast Cancer					
	≤35	4	75.0%	(50.3%, 100%)	
	35,–50	14	79.5%	(68.3%, 92.4%)	
	>50	20	88.6%	(82.1%, 95.5%)	.146
Distant Recurrence-Free Survival					
HER2-Positive					
	≤35 35–50	2 7	71.4% 86.0%	(44.7%, 100%) (75.4%, 98.2%)	
	>50	6	89.7%	(81.6%, 98.7%)	.341
Hormone Receptor-Positive					
	≤35	3	88.9%	(75.5%, 100%)	
	35–50	13	95.6%	(92.6%, 98.6%)	
	>50	15	98.4%	(97.3%, 99.5%)	.0008
Triple-Negative Breast Cancer					
	≤35	2	100%	(100%, 100%)	
	35–50	4	95.2%	(89.0%, 100%)	
	>50	6	96.5%	(92.7%,100%)	.332

Table 3

Multivariable Model

	Recurrence-Free Survival			Distant Recurrence-Free Survival		
	Hazard Ratio	**95% Confidence Interval**	***P* Value**	**Hazard Ratio**	**95% Confidence Interval**	***P* Value**
Breast Cancer Subtype						
Hormone receptor–positive	1			1		
HER2-positive	4.98	(2.91,8.53)	<.001	4.70	(2.51,8.79)	<.001
Triple negative	2.71	(1.59,4.59)	<.001	2.08	(1.04,4.17)	.039
Age at Diagnosis						
>50	1			1		
≤35	2.51	(1.21,5.22)	.013	2.60	(1.05,6.46)	.04
(35, 50]	1.53	(1.01,2.33)	.045	2.01	(1.20,3.37)	.008
Grade						
Grade 1 or 2	1			1		
Grade 3	1.13	(0.73,1.75)	.58	1.00	(0.58,1.73)	.99
T Stage						
T1a	1			1		
T1b	1.31	(0.86,1.97)	.21	1.45	(0.86,2.44)	.16
Hormonal Therapy						
No	1			1		
Yes	0.92	(0.60,1.40)	.69	1.19	(0.71,2.02)	.51