RESEARCH ARTICLE

Long-Term Survival of Women with Locally Advanced Breast Cancer with ≥10 Involved Lymph Nodes at Diagnosis

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Abstract

Background: Axillary lymph node status at diagnosis remains the strongest predictor of long-term survival in breast cancer. Patients with more than ten axillary lymph nodes at diagnosis have a poor long-term survival. In this single institutional study, we set out to evaluate the prognosis of this high-risk group in the era of multimodality therapy. Materials and Methods: In this retrospective study, we looked at all breast cancer patients with greater than ten axillary lymph nodes diagnosed at Mount Sinai Medical Center (MSMC) from January 1st 1990 to December 31st 2007 (n=161). In the univariate analysis, descriptive frequencies, median survival, and 5- and 10-year survival rates were estimated for common prognostic factors. A multivariate prognostic analysis for time-to-event data, using the extended Cox regression model was carried out. Results: With a median and mean follow-up of 70 and 89.9 months, respectively, the overall median survival was estimated to be 99 months. The five-year disease-free survival (DFS) was 59.3% and the ten-year DFS was 37.9%, whereas the five- and ten-year overall survival (OS) was 66.6% and 43.9%, respectively. Multivariate analysis revealed a significant improvement in DFS among black patients compared to whites (p=0.05), improved DFS and OS among young patients (ages 21-45) compared to elderly patients (age greater than 70) (p=0.00176, p=0.0034, respectively), and improved DFS and OS among patients whose tumors were ER positive (p=0.049, p=0.0034). Conclusions: In this single institution study of patients with greater than 10 positive axillary nodes, black patients had a significantly improved DFS compared with white patients. Young age and ER tumor positivity was associated with improved outcomes. Using multivariate analysis, there were no other variables associated with statistically significant improvements in DFS or OS including date of diagnosis. Further work is needed to improve breast cancer survival in this subgroup of patients.

Keywords: Locally advanced breast cancer - greater than 10 nodes - breast cancer survival

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Introduction

With an estimated 226,870 diagnoses and 39,510 deaths in 2012, breast cancer remains the most commonly occurring and second most lethal cancer among women in the United States (Howlader et al., 2012). Although the prognosis is variable with a five-year survival ranging from 18-95 percent (Ries et al., 2001; Colleoni et al., 2005), axillary lymph node status at diagnosis remains the strongest predictor of long-term survival (Ragaz et al., 1997). Locally advanced breast cancer (LABC) makes up approximately 6.5 % of newly diagnosed breast cancer (VanderWalde et al., 2012). In patients with LABC, the rate of recurrence and associated disease related mortality is high, with an estimated 10-year overall survival (OS) between 24-50% (Woodward et al., 2003; Montero et al., 2005), with inflammatory breast cancer (IBC) having the worst prognosis (Edge et al., 2010, Robertson et al., 2010).

LABC is defined as having one of the following; 1) size greater than 5cm. (T3), 2) greater than or equal to 4 pathologically involved lymph nodes (N2), 3) chest wall or skin (T4) involvement, 4) or inflammatory breast cancer (T4d) (Giordano, 2003; Edge et al., 2010;). Within this group exists a subset of patients, classified as N3, with greater than or equal to ten axillary lymph nodes at diagnosis. Over the past 15 years, many new agents have been incorporated into the breast cancer armamentarium, including taxanes, aromatase inhibitors, and trastuzumab. The purpose of this study was to characterize the prognosis of this high-risk group and compare the long-term survival of patients diagnosed in two different eras of patient diagnosis. We set out to look at our own single institutional experience among breast cancer patients with greater than ten axillary lymph nodes at diagnosis.

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Materials and Methods

In this retrospective study, we looked at all breast cancer patients with greater than ten axillary lymph nodes diagnosed at Mount Sinai Medical Center (MSMC) from January 1st 1990 to December 31st 2007 (n=161), with a follow-up until December 31st 2012. The minimum follow-up time was 5 years, while the maximum follow-up was 23 years. The mean follow-up time was 89 months. Excluded patients included those with de-novo metastatic disease, men, secondary cancers, bilateral breast cancers, 2nd primary breast cancers, inflammatory breast cancers, those lost to follow-up, and those who only received a one-time consult. The number of involved lymph nodes was determined by pathologic analysis after definitive surgery. The results were presented in descriptive frequencies, using means and standard deviation for continuous variables while for the other types of variables we used frequencies and percentages. The study consisted in two parts: the univariate and the multivariate analyzes. In the univariate section, the studied factors were analyzed through the time-to-event endpoints, in two ways: first, overall survival (OS) where deaths from any cause were included, while all other events were considered censored; second, disease-free survival (DFS) where the relapses and deaths from any cause were included, while all other events were censored. For both types of endpoints the median survival, the 5- and 10-years survival rates were estimated for all analyzed factors (i.e., adjuvant treatment types, race, ethnicity, age at diagnosis, year at diagnosis, pathologic subtype, tumor size, number of metastatic nodes, hormone receptor status, HER2-neu status, etc.). The survival rates were estimated using the Kaplan Meier method and the survivorships were compared using nonparametric survival comparisons. For both endpoints, the survival time was calculated from the date of diagnosis to the time-to-event (i.e. relapse, or death). The simple Cox proportional hazards models were also use to estimate the crude hazard ratios (HR) along with their corresponding 95% confidence intervals and the Wald test for significance (Suciu et al., 2004). The multivariate section consisted in the analysis of all prognostic factors significant at 0.25 level in the univariate analysis. We used the multiple Cox proportional hazards regression for this purpose, were the estimated hazard ratios were considered significant at the level of 0.10. We increased the error margins since the sample size was small.

Results

Of the 161 patients in the cohort, the median age at diagnosis was 61. The majority of patients were Caucasian (85.7%) and non-Hispanic (76.4%) and were aged 56-70 at diagnosis (39.8%; Table 1). We had two timeframe cohorts, those patients who were diagnosed between 1990-1999 (58.9%), and those diagnosed between 2000-2007 (41.1%). The second cohort corresponded approximately to the timeframe in which taxanes, aromatase inhibitors, and trastuzumab became commonly used within the community. The majority of the tumors were invasive ductal (56.5%), sized 2-5cm (61.4%), with 10-15 involved lymph nodes (54.1%), and ER positivity (64.4%). Almost half of the patients had HER2 positive tumors (47.4%). The majority of patients in our cohort received mastectomy (79.9%), radiation (59.0%), and adjuvant (as opposed to neo-adjuvant) chemotherapy (80%), consisting of anthracyclines (87.7%) and taxanes (68.1%). Roughly equivalent number of ER positive patients received tamoxifen (55.3%) and aromatase inhibitors (44.7%). Of

Table 1. Baseline Descriptive Statistics of 161 Breast Cancer Patients, with ≥10 Lymph Nodes at Diagnosis, Mount Sinai Medical Center from 1990-2007

Category		Mean/ Median (n)	Standard Deviation (%)
Age at Diagnosis		61	13.6
Race	White	138	85.7
	Black	23	14.3
Ethnicity	Hispanic	38	23.6
	Non-Hispanic	123	76.4
Age Range	21-45	26	16.2
	46-55	35	21.7
	56-70	64	39.8
	>70	36	22.4
Year of Diagnosis	1990-1999	94	58.4
	2000-2007	67	41.6
Pathologic Subtype	Invasive Ductal	91	56.5
	Lobular	32	19.9
	Mixed	20	12.4
	Other	18	11.2
Size at Diagnosis	0-2cm.	33	21.6
	2-5cm.	94	61.4
	>5cm.	26	17
Positive Nodes	10 to 15	92	54.1
	>15	69	42.9
ER status	Positive	76	64.4
	Negative	42	35.6
	Unknown	43	
HER-2 Status	HER-2 +	16	47.4
	HER-2 –	18	52.6
	Unknown	127	
Surgery	Lumpectomy/partial mastectomy	32	20.13
	Mastectomy/MRM	127	79.87
	Neoadjuvant Chemo	23	20
	Adjuvant Chemo	92	80
	Unknown	31	
	Anthracycline	64	87.7
	No Anthracycline	9	12.3
	Unknown	58	
	Taxane	49	68.1
	No Taxane	23	31.9
	Unknown	57	
Radiation	Yes	95	59.01
	No	66	40.99
Hormonal Therapy	Tamoxifen	26	55.3
	Aromatase Inhibitor	21	44.7
	Unknown	20	
Chemotherapy	Neoadjuvant Chemotherapy	27	16.8
	Adjuvant Chemotherapy	100	62.1
	None	34	21.1
Cause of Death	Breast Cancer	79	82.2
	Other	17	17.8
	Alive	65	

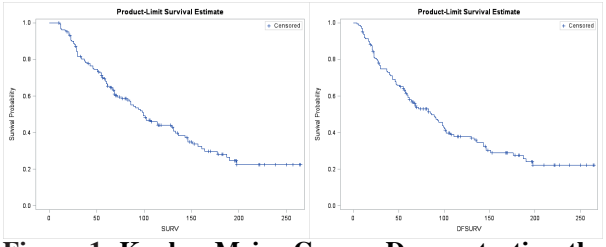
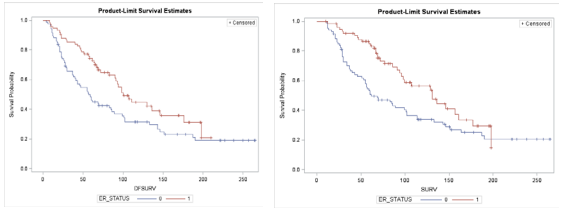


Figure 1. Kaplan Meier Curves Demonstrating the Disease-free and Overall Survival for a Population of n=161 Breast Cancer Patients, with ≥10 Lymph Nodes at Diagnosis, Diagnosed at Mount Sinai Comprehensive Cancer Center (1990-2007)

Table 2. Median, Five and Ten-Year Disease-Free Survival Rates for Studied Factors in the Breast Cancer Study with ≥10 Lymph Nodes at Diagnosis-Mount Sinai Comprehensive Cancer Center (1990-2012)

Category	Median DFS	5 year DFS (%)	10 year DFS*	p-value**
Overall	86 (62, 101)	59.3	37.9	
Race				
White	72 (59, 98)	56.7	34.4	0.036
Black	198 (83, -)	76.4	63	
Ethnicity				0.69
Hispanic	111 (57, 146)	61.9	45.5	
Non-Hispanic	86 (59, 100)	58.5	36.1	
Age Range				0.13
21-45	187 (85, -)	80.1	58.2	
46-55	72 (43, 198)	62.1	41.9	
56-70	83 (47, 111)	55.6	36.6	
70+	60 (30, 89)	49.5	23.5	
Year of Diagnosis				
1990-1999	69 (47, 94)	53.8	34.2	0.09
2000-2007	98 (83, -)	67.2	42.9	
Pathologic Subtype				
Invasive Ductal	90 (62, 143)	61.8	42.5	0.37
Lobular	98 (58, 146)	65.6	42.9	
Mixed	69 (40, 136)	57.8	34.5	
Other carcinomas	50 (29, 102)	38.9	16.6	
Size at Diagnosis				0.59
0-2cm.	146 (57, -)	65.9	51.4	
2-5cm.	86 (62, 102)	61.6	32.9	
>5cm.	80.5 (27, 146)	53.8	42.3	
Positive Nodes				0.07
15-Oct	98 (72, 130)	65.8	40.7	
>15	62 (43, 89)	50.4	34.2	
ER status				0.0019
Positive	100 (90, 146)	72.8	44.6	
Negative	57 (40, 86)	46.1	31.4	
HER-2 Status				0.58
HER2 +	83 (23, -)	56.2	33.7	
HER2 –	89 (62, 102)	59.7	38.2	
Surgery				0.81
Lumpectomy/partial mast	93 (30, -)	56.2	42.2	
Mastectomy/MRM	85 (62, 100)	59.5	35.9	
Chemotherapy				0.607
Neoadjuvant CT	62 (46, 176)	50.1	40.2	
No neoadjuvant	94 (64, 107)	62.1	39.2	
Anthracycline	98 (64, -)	68.1	46.4	0.051
No Anthracycline	70 (47, 99)	53.4	33	
Taxane	98 (55, -)	59.9	39.9	0.96
No Taxane	85 (60, 101)	59	37.4	
Radiation				0.64
Yes	90 (60, 100)	60.7	33.2	
No	83 (46, 136)	57.1	43.1	
Hormonal Therapy				0.48
Tamoxifen	100 (58, -)	64.8	40.5	
Aromatase Inhibitor	91 (90, -)	80.4	48.2	
Hormonal Therapy				0.023
Tamoxifen+ Aromatase Inhibitor	100 (90, -)	71.1	44	
Nothing	69 (55, 98)	48.4	35.2	

*Estimated overall survival; **logrank or generalized Wilcoxon test



Generalized Wilcoxon, p=0.0019 Generalized Wilcoxon test, p=0.0002

Figure 2. Kaplan Meier Curves Demonstrating the Disease-free and Overall Survival Based on Age at Diagnosis and ER Status

Table 3. Median, Five and Ten-year Overall Survival Rates for Studied Factors in the Breast Cancer Study with ≥10 Lymph Nodes at Diagnosis-Mount Sinai Comprehensive Cancer Center (1990-2012)

Category	Median Overall Survival	5 year OS (%)	10 year OS*	p-value**
Overall	99 (83, 131)	66.6	43.9	
Race				
White	96 (70, 129)	65.3	41.7	0.15
Black	198 (83, -)	75.8	61.2	
Ethnicity				
Hispanic	143 (67, 187)	75.4	58.6	0.134
Non-Hispanic	94 (69, 114)	63.8	40	
Age Range				0.06
21-45	187 (85, -)	82.8	58.4	
46-55	99 (65, -)	70.8	45.2	
56-70	129 (67, 157)	65	51.1	
70+	70 (51, 96)	55.1	22.5	
Year of Diagnosis				
1990-1999	86 (62, 129)	61.9	40.7	0.13
2000-2007	114 (91, -)	73.3	46.5	
Pathologic Subtype				
Invasive Ductal	107 (69, 161)	67.9	47.4	0.35
Lobular	114 (86, 146)	75	46.7	
Mixed	72 (43, -)	63.1	38.3	
Other carcinomas	80 (30, 129)	50	31.2	
Size at Diagnosis				0.24
0-2cm.	157 (85, -)	74.7	63.2	
2-5cm.	96 (70, 131)	69.3	40.9	
>5cm.	98 (43, 146)	60.9	38.9	
Positive Nodes				0.13
10 to 15	107 (91, 136)	73.3	47.9	
>15	85 (55, 164)	60.7	38.6	
ER status				0.0002
Positive	131 (96, 161)	84.8	56.4	
Negative	62 (53, 101)	50.8	33.6	
HER-2 Status				0.92
HER2 +	91 (29, 164)	68.2	36.5	
HER2 –	99 (72, 131)	66.4	44.4	
Surgery				0.88
Lumpectomy/partial mast	107 (55, -)	64.9	46.6	
Mastectomy/MRM	96 (77, 131)	66.5	42.3	
Chemotherapy				0.073
Anthracycline	114 (83, -)	72.5	49.9	
No Anthracycline	89 (61, 129)	61.5	40.1	
Chemotherapy				
Taxane	107 (69, -)	67.4	44.4	0.65
No Taxane	96 (70, 131)	66.2	43.4	
Treatment				0.11
Neoadjuvant CT	60 (46, 177)	48.3	40.3	
No neoadjuvant	107 (89, 161)	71.1	47.9	
Radiation				0.72
Yes	98 (72, 131)	67.1	41.8	
No	102 (62, 146)	65.7	46.2	
Hormonal Therapy				0.87
Tamoxifen	131 (77, -)	80.2	58.2	
Aromatase Inhibitor	96 (91, -)	79.1	47.5	
Hormonal Therapy				0.0312
Tamoxifen+ Aromatase Inhibitor	131 (96, -)	79.8	54.9	
Nothing	86 (65, 114)	61.7	39.8	

*Estimated overall survival; **logrank or generalized Wilcoxon test

the 96 patients who died, 82% of them died from breast cancer.

With a median and mean follow-up of 70 and 89.9 months, respectively, the estimated median disease-free and overall survival was 86 and 99 months, respectively (Table 2-4). The five-year DFS was 59.3% and the ten-year DFS was 37.9% (Figure 1), whereas the five- and ten-year OS was 66.6% and 43.9%, respectively. There were no

Table 4. Univariate Cox-Proportional Hazards Analysis for Breast Cancer Patients, with ≥10 Lymph Nodes, Diagnosed at Mount Sinai Comprehensive Cancer Center (1990-2012).

Variable		DFS Hazard Ratio (95% Confidence Limits)	p-value	OS Hazard Ratio (95% Confidence Limits)	p-value
Race	White	5.07 (1.57, 31.04)	0.0243	1.84 (0.87, 4.75)	0.14
	Black (reference)	1		1	
Ethnicity	Non-Hispanic	0.79 (0.44, 1.49)	0.448	1.60 (0.93, 2.98)	0.1
	Hispanic (reference)	1		1	
Age Range	21-45	0.37 (0.13, 0.92)	0.042	0.45 (0.18, 0.99)	0.059
	46-55	0.42 (0.16, 0.97)	0.05	0.79 (0.41, 1.52)	0.48
	56-70	0.72 (0.38, 1.41)	0.32	0.79 (0.45, 1.43)	0.43
	>70 (reference)	1		1	
Year of Diagnosis	1990-1999 (reference)	1		1	
	2000-2007	0.67 (0.37, 1.21)	0.19	0.75 (0.44, 1.22)	0.25
Pathologic Subtype	Invasive Ductal	0.65 (0.31, 1.54)	0.29	0.65 (0.34, 1.35)	0.22
	Lobular	0.45 (0.16, 1.27)	0.13	0.75 (0.36, 1.65)	0.46
	Mixed	0.73 (0.24, 2.10)	0.56	0.90 (0.37, 2.16)	0.82
	Other (reference)	1		1	
Size at Diagnosis	0-2cm.(reference)	1		1	
	2-5cm.	1.64 (0.79, 3.86)	0.21	1.46 (0.82, 2.77)	0.21
	>5cm.	2.15 (0.84, 5.66)	0.1	1.39 (0.64, 2.99)	0.38
Positive Nodes	10-15 (reference)	1		1	
	>15	1.40 (0.81, 2.41)	0.219	1.207 (0.77, 1.88)	0.406
ER status	Positive	0.69 (0.39, 1.21)	0.199	0.66 (0.42, 1.04)	0.077
	Negative (reference)	1		1	
HER-2 Status	HER2 +	1.32 (0.54, 2.76)	0.49	0.96 (0.40, 1.95)	0.93
	HER2 – (reference)	1		1	
Surgery	Lumpectomy/ partial mastectomy (reference)	1		1	
	Mastectomy/MRM	1.26 (0.64, 2.76)	0.402	0.95 (0.56, 1.70)	0.86
Chemotherapy	Anthracycline	0.54 (0.29, 0.97)	0.046	0.805 (0.49, 1.28)	0.37
	No Anthracycline (reference)	1		1	
	Taxane	0.94 (0.51, 1.69)	0.85	1.08 (0.64, 1.76)	0.75
	No Taxane (reference)	1		1	
	Neoadjuv Chemo	1.41 (0.64, 2.82)	0.35	1.20 (0.50, 2.55)	0.65
	Adjuv Chemo (reference)	1		1	
Radiation	Yes	0.93 (0.53, 1.67)	0.81	0.88 (0.56, 1.38)	0.59
	No (reference)	1		1	
Hormonal Therapy	Tamoxifen	1.40 (0.55, 4.02)	0.49	0.82 (0.28, 2.52)	0.72
	Aromatase Inhibitor	1		1	
	Tamoxifen+ Aromatase Inhibitors	0.61 (0.37, 0.97)	0.047	0.60 (0.35, 0.98)	0.055
	Nothing	1		1	

Table 5. Prognostic Factors in the Final Cox-Proportional Hazards Model for Breast Cancer Patients, with ≥10 Lymph Nodes at Diagnosis, Diagnosed at Mount Sinai Comprehensive Cancer Center (1990-2007)*

Parameter		Hazard ratio	Confidence Interval	p value
Race**	White	2.14	(1.05, 4.94)	0.0503
	Black (reference)	1		
Age Groups**	21-45	0.385	(0.183, 0.754)	0.0076
	46-55	0.866	(0.468, 1.572)	0.639
	56-70	0.795	(0.494, 1.296)	0.349
	70+ (reference)	1		
ER status**	Positive	0.56	(0.37, 0.85)	0.0073
	Negative (reference)	1		
Age Groups***	21-45	0.393	(0.164, 0.889)	0.028
	46-55	0.923	(0.449, 1.913)	0.826
	56-70	0.743	(0.393, 1.458)	0.371
	70+ (reference)	1		
ER status***	Positive	0.448	(0.258, 0.758)	0.0034
	Negative (reference)	1		
Treatment***	Neoadjuvant	1.77	(0.95, 3.129)	0.056
	No-neoadjuv	1		

*All significant covariates at 0.25 level in the univariate analysis were used for the modeling of both, disease-free and overall survival (from Table 4). In both cases an alpha level of 0.10 should be considered for significance in the final model, since the sample size is small; **Time: DFS; ***Time: OS

significant differences in DFS or OS based on ethnicity, age range, diagnosis timeframe, pathologic subtype, HER2 status, 10-15 *vs* >15 positive lymph nodes, type of surgery, radiation, or taxane chemotherapy. The use of hormonal therapy only improved DFS and OS in univariate analysis (p=0.023, p=0.03, respectively). There was a trend toward improved DFS and OS with anthracycline use (p=0.051, p=0.073), but this did not persist in the multivariate analysis. In multivariate analysis, patient's aged 21-45 had a significant improvement in DFS and OS (p=0.0076, p=0.028; Table 5. In our population, there was a significant improvement in DFS and OS in patients with ER positive tumors (p=0.0019, p=0.0002; Figure 2), which remained statistically significant in multivariate analysis (p=0.0073, p=0.0034. Although there were no differences in DFS or OS based on race in the univariate analysis, the multivariate model revealed that black patients has significantly improved DFS (p=0.05). Although there were no differences in DFS or OS based on mode of chemotherapy in the univariate analysis, the multivariate model revealed that patients receiving neoadjuvant chemotherapy had a trend toward significantly worse OS (p=0.056).

Table 6. Comparison of DFS and OS from Studies with Breast Cancer Patients, with ≥10 Lymph Nodes at Diagnosis

Study	Dates	Patients	5-year DFS (%)	10-year DFS (%) **	5-year OS (%)	10 year OS (%) **
Buzdar et al (1991)46	1974-1986	283, multi-institutional	41	30		
Walker et al (1995)45	1969-1991	141, single institution	-	-	38	29
Schmoor et al (2001)44	1984-1989	141, multi-institutional	22*	14*	39	19
Montero et al (2005)8	1954-1998	882, multi-institutional	Adjuvant: 39 No Adjuvant: 30	Adjuvant: 30 No Adjuvant: 20	Adjuvant: 53 No Adjuvant: 38	Adjuvant: 35 No Adjuvant: 20
Lee et al (2011)42	1986-2006	304, single institution	42.9	-	57.8	-
Basaran et al (2011)43	1998-2008	73, single institution	66	-	81	-
Koca et al (2013)34	2002-2012	218 , single institution	46.2	-	69.8	-
Our study	1990-2007	161, single institution	59.3	37.9	66.6	43.9

*Event-free survival; ** Estimated

Discussion

Numerous studies have shown that even after accounting for health access disparities, young African American women tend to have worse outcomes in breast cancer (Balakrishnan and Rao, 2002; Palmer et al., 2003). Our study demonstrated a paradoxical effect and showed that black patients had improved DFS in this N3 population even when accounting for all other variables in the multivariate model. There are several possible explanations for this unusual finding. First of all, the number of black patients in our study was small (n=23), and thus it is likely that a few long-term survivors skewed the survival results for the entire group. Upon sub-group analysis based on race, a greater percentage of black patients were younger (21-45: 26.1% *vs* 18.5%), diagnosed in the later time frame (2000-2007: 69.6% *vs* 37.0%), had fewer involved nodes (>15: 30.4% *vs* 44.9%), and received an anthracycline as part of neo-adjuvant/ adjuvant chemotherapy (92.3% *vs* 86.2%). Taxanes were more commonly used in white patients (70.6% *vs* 57.1%). All of the other clinical variables and treatment regimens were similar among the cohorts. This subgroup analysis suggests the black patients in our cohort had more favorable prognostic variables than their white counterparts. This hypothesis is supported by the fact that only 34.8% of black patients in our cohort relapsed compared to 60.9% and of white patients.

There has been conflicting data on the outcomes of Hispanic patients with breast cancer compared to non-Hispanics (Woodward et al., 2006; Banegas and Li, 2012; Anaya-Ruiz, 2014). Most studies have suggested that socioeconomic status and patient access to care are greater determinants of long-term survival than ethnicity alone (Livaudais et al., 2012). In our study, there was a paradoxical effect showing a trend toward an improved overall survival in Hispanics compared to Non-Hispanics, even when controlling for all other variables in the multivariate analysis. The Hispanic paradox has been well described (Turra and Elo, 2008; Blue and Fenelon, 2011).

We observed a significant improvement in DFS among patient aged 21-45, but not in OS. This observed difference was likely secondary to the selection of fit, healthy patients who were able to complete multi-modality therapy compared with those older patients who had associated comorbidities, were unable to tolerate standard treatment, and were likely to die due to secondary causes. However, the magnitude of this effect was likely tempered, and failed to reach significance on multivariate analysis, by the fact that younger patients often have tumors that have inherently more aggressive biology (Anders et al., 2008) and have associated poor prognostic factors (Fan et al., 2006, Keramatinia et al., 2014).

In our study, ER tumor status was found to be significant for both DFS and OS in the multivariate analysis. This finding supports the fact that ER positive tumors have less aggressive biology, are more likely to metastasize later, and are more likely to metastasize to bone as opposed to visceral organs. These findings support previous studies suggesting different inherent genetic profiles between ER positive and ER negative tumors (Carey et al., 2006; Hu et al., 2006; Parker et al., 2009; Voduc et al., 2010; Livi et al., 2012). Although we only had data for a small minority of patients, our cohort had high rates of HER2 positive disease (47%) compared with the 25-30% incidence seen in the general breast cancer population. This finding is not surprising given the fact that HER2 positive tumors are known to be more locally aggressive (essentially all of our patients) and have a greater potential to metastasize early (Koca et al., 2013).

Not surprisingly, there was no difference in DFS or OS based on histopathologic subtype. Interestingly, the size of the initial tumor had no significant effect on DFS or OS. This finding is in contrast to numerous large studies and TNM staging, which dictate that larger primary tumors have a higher recurrence rate and a worse overall survival (Akhsan and Aryandono, 2010; Rezaianzadeh et al., 2012). Our study suggests that tumor size may not be of great importance in this select group of high-risk patients. Within our cohort, there was no difference in survival based on number of involved lymph nodes at diagnosis (10-15 versus >15). This finding suggests that 10 involved axillary lymph nodes remains a critical threshold at which more involved nodes may not confer a worse prognosis. These findings are consistent with current TNM breast cancer staging, which designates ten involved axillary lymph nodes as the highest nodal stage (pN3a), beyond which prognosis remains unchanged. Meanwhile, several studies have shown alternative and possibly improved prognostication with use of lymph node ratio (LNR), or the number of positive axillary lymph nodes to the number of total nodes removed (Vinh-Hung et al., 2004; Danko et al., 2010). Vinh-Hung et al proposed a new node staging system in which patients were divided based on risk (low: ≤0.2; moderate: >0.2, ≤0.65; high: >0.65; Vinh-Hung et al., 2004). To date, this proposed staging system has not been studied in large randomized studies.

Our study produced long-term DFS (5-year: 59.3%;

10-year: 37.9%) and OS (5-year: 66.6%; 10-year: 43.9%) similar to other cohorts analyzed over the past decade, which produced a 5-year DFS ranging from 42.9-66% and a 5-year OS ranging from 57-81% (Table 5, Schmoor et al., 2001; Basaran et al., 2011; Lee et al., 2011). This is in stark contrast to earlier cohorts that saw 5- and 10-year OS survival rates of 39% and 24%, respectively (Buzdar et al., 1992; Walker et al., 1995). Despite this apparent improvement, there was no statistical difference in DFS or OS between the two timeframes. There are several explanations for this seemingly surprising finding. Our study only had a median follow-up of 70 months. Therefore, it is likely that there was not enough follow-up for the patients diagnosed in the later cohort to show a significant improvement in survival. We suspect, with 10 years of follow-up, the difference between the two groups would be readily apparent, especially among patients with ER negative tumors, who are known to recur earlier. The use of anthracyclines as part of standard adjuvant chemotherapy dates back to the late 1980's-early 1990's (Ambrosini et al., 1988). Therefore, most of the patients, for whom we had data, received this type of chemotherapy (87.7%). However, taxanes, currently part of the standard of care, did not appear in widespread practice until the early 2000's and thus fewer patients received this class of chemotherapy (68%; Nabholtz et al., 2001). Tamoxifen (55% of ER positive patients in our study) had been used in widespread clinical practice since the late 1980s, but aromatase inhibitors (47% of ER positive patients in our study), another hormonal therapy used in hormone receptor positive patients, was not used in widespread clinically practice until the late 1990's (Buzdar et al., 1996). Her-2 testing and trastuzumab became part of the standard of care in the early 2000s, and although we don't have all of the Her-2 data on our population sample, we suspect many of the patients diagnosed in the later timeframe, who were Her-2 positive, did in fact receive this therapy (Mieog et al., 2007).

As previously mentioned, there was a lack of improvement in DFS or OS in the final multivariate model, with the use of an adjuvant anthracycline, with or without the use of a taxane. Although ER positive patients had a significantly improved survival, patients who received hormonal therapy did not have significantly improved DFS or OS in our final multivariate model. This finding, likely accounting for the lack of improvement in survival endpoints between the time frame cohorts, suggests that chemotherapy and hormonal therapy may only improve long-term survival in a select subset of very high-risk patients. There was no significant improvement in DFS or OS in patients who were HER2 positive. For reasons that are unclear, there was a low rate of adjuvant radiation among the patients in our cohort (59%), but surprisingly, there was no difference in DFS or OS in those patients who received this therapy. This finding suggests that adjuvant radiation may only improve local disease control in a subset of patients and is in contrast to studies showing that those patients who do not receive radiation have high local-regional recurrence (LRR). Not surprisingly, patients receiving neoadjuvant chemotherapy had a worse overall survival. This finding is likely due to a selection bias, as patients who received neoadjuvant chemotherapy had larger, more aggressive tumors than those patients who received adjuvant chemotherapy (Duman et al., 2012; Prajoko and Aryandono, 2014). Type of surgery performed was not found to have a significant impact on overall survival, which is in contrast to previous studies (Zeichner et al., 2014).

One of the main limitations with our study was our inability to make a definitive statement regarding the impact of HER2 status and trastuzumab therapy on long term-outcomes. Although there was no significant difference seen among patients based on HER2 status, we only had this information for less than 25% of our cohort. In this single institution study of patients with greater than 10 positive axillary nodes, black patients had a significantly improved DFS compared with white patients. Young age and ER tumor positivity was associated with improved outcomes. Using multivariate analysis, there were no other variables associated with statistically significant improvements in DFS or OS including date of diagnosis. Further work is needed to improve breast cancer survival in this subgroup of patients.

References

Akhsan A, Aryandono T (2010). Prognostic factors of locally advanced breast cancer patients receiving neoadjuvant and adjuvant chemotherapy. *Asian Pac J Cancer Prev*. **11**, 759-61.

Ambrosini G, Balli M, Garusi G, et al (1988). Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial. Italian Multicentre Breast Study with Epirubicin. *J Clin Oncol*, **6**, 976-82.

Anaya-Ruiz M, Vallejo-Ruiz V, Flores-Mendoza L, Perez-Santos M (2014). Female breast cancer incidence and mortality in Mexico, 2000-2010. *Asian Pac J Cancer Prev*, **15**, 1477-9.

Anders CK, Hsu DS, Broadwater G, et al (2008). Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*, **26**, 3324-30.

Balakrishnan N, Rao CR (2002). Race, socioeconomic status, and breast cancer treatment and survival. Elsevier Science B.V.

Banegas MP, Li CI (2012). Breast cancer characteristics and outcomes among Hispanic Black and Hispanic White women. *Breast Cancer Res Treat*, **134**, 1297-304.

Basaran G, Devrim C, Caglar HB, et al (2011). Clinical outcome of breast cancer patients with N3a (≥10 positive lymph nodes) disease: has it changed over years? *Med Oncol*, **28**, 726-32.

Blue L, Fenelon A. (2011). Explaining low mortality among US immigrants relative to native-born Americans: the role of smoking. *Int J Epidemiol*, **40**, 786-93.

Buzdar AU, Kau SW, Hortobagyi GN, et al (1992). Clinical course of patients with breast cancer with ten or more positive nodes who were treated with doxorubicin-containing adjuvant therapy. *Cancer*, **69**, 448-52.

Buzdar A, Jonat W, Howell A, et al (1996). Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. *J Clin Oncol*, **14**, 2000-11.

Carey LA, Perou CM, Livasy CA, et al (2006). Race, breast

cancer subtypes, and survival in the Carolina Breast Cancer Study. *JAMA*, **295**, 2492.

Colleoni M, Rotmensz N, Peruzzotti G, et al (2005). Size of breast cancer metastases in axillary lymph nodes: clinical relevance ofminimal lymph node involvement. *J Clin Oncol*, **23**, 1379-89

Danko ME, Bennett KM, Zhai J, Marks JR, Olson JA Jr (2010) Improved staging in node-positive breast cancer patients using lymph node ratio: results in 1,788 patients with long-term follow-up. *J Am Coll Surg*, **210**, 797-805.

Duman BB, Afsar CU, GUnaldi M, et al (2012). Retrospective analysis of neoadjuvant chemotherapy for breast cancer in Turkish patients. *Asian Pac J Cancer Prev*, **13**, 4119-23.

Edge S, Byrd D, Compton C, et al (2010). American Joint Committee on Cancer. AJCC Cancer Staging Manual, 7th ed.

Fan C, Oh DS, Wessels L, et al (2006). Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med*, **355**, 560.

Giordano SH (2003). Update on locally advanced breast cancer. *Oncologist*, **8**, 521-30.

Han SJ, Guo QQ, Wang T, et al (2013). Prognostic significance of interactions between ER alpha and ER beta and lymph node status in breast cancer cases. *Asian Pac J Cancer Prev*, **14**, 6081-4.

Howlader N, Noone AM, Krapcho M, et al (2012).SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, SEER data submission, posted to the SEER web site, 2012.

Hu Z, Fan C, Oh DS, et al (2006) The molecular portraits of breast tumors are conserved across microarray platforms. *BMC Genomics*, **7**, 96.

Keramatinia A, Mousavi-Jarrahi SH, Hiteh M, Mosavi-Jarrahi A (2014). Trends in incidence of breast cancer among women under 40 in Asia. *Asian Pac J Cancer Prev*, **15**, 1387-90.

Koca E, Kuzan TY, Dizdar O, et al (2013). Outcomes of locally advanced breast cancer patients with ≥10 positive axillary lymph nodes. *Med Oncol*, **30**, 615.

Lee JS, Kim SI, Choi SY, et al (2011). Factors influencing the outcome of breast cancer patients with 10 or more metastasized axillary lymph nodes. *Int J Clin Oncol*, **16**, 473-81.

Livaudais JC, Hershman DL, Habel L, et al (2012). Racial/ethnic differences in initiation of adjuvant hormonal therapy among women with hormone receptor-positive breast cancer. *Breast Cancer Res Treat*, **131**, 607-17.

Livi L, Meattini I, Saieva C, et al (2012). Prognostic value of positive human epidermal growth factor receptor 2 status and negative hormone status in patients with T1a/T1b, lymph node-negative breast cancer. *Cancer*, **118**, 3236-43.

Mieog JS, van der Hage JA, van de Velde CJ. (2007). Preoperative chemotherapy for women with operable breast cancer. *Cochrane Database Syst Rev*.

Montero AJ, Rouzier R, Lluch A, et al (2005). The natural history of breast carcinoma in patients with > or=10 metastatic axillary lymph nodes before and after the advent of adjuvant therapy: a multiinstitutional retrospective study. *Cancer*, **104**, 229-35.

Nabholtz JM, Mackey JR, Smylie M, et al (2001). Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-linechemotherapy for metastatic breast cancer. *J Clin Oncol*, **19**, 314-21

Palmer JR, Wise LA, Horton NJ, Adams-Campbell LL, Rosenberg L (2003). Dual effect of parity on breast cancer risk in African-American women. *J Natl Cancer Inst*, **95**, 478.

Parker JS, Mullins M, Cheang MC, et al (2009). Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol*, **27**, 1160.

Prajoko YW(1), Aryandono T (2014). Expression of nuclear factor kappa B (NF-ϰB) as a predictor of poor pathologic response to chemotherapy in patients with locally advanced breast cancer. *Asian Pac J Cancer Prev*, **15**, 595-8.

Ragaz J, Jackson SM, Le N, et al (1997). Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. *N Engl J Med*, **337**, 956-62.

Rezaianzadeh A, Talei A, Rajaeefard A et al (2012). Vascular invasion as an independent prognostic factor in lymph node negative invasive breast cancer. *Asian Pac J Cancer Prev*, **13**, 5767-72

Ries LAG, Eisner MP and Kosary CL. (2001). SEER Cancer Statistics Review, 1973-1998, *National Cancer Institute*.

Robertson FM, Bondy M, Yang W, et al (2010). Inflammatory breast cancer: the disease, the biology, the treatment. *CA Cancer J Clin*, **60**, 351-75

Schmoor C, Sauerbrei W, Bastert G, Bojar H, Schumacher M (2001). Long-term prognosis of breast cancer patients with 10 or more positive lymph nodes treated with CMF. *Eur J Cancer*, **37**, 1123-31.

Suciu, GP, Lemeshow S, Moeschberger M (2004). Statistical Test of Equality of Survival Curves: Reconsidering the Options, Handbook of Statistics, Vol.23, Chapter 13. Eds.

Turra CM, Elo IT (2008). The Impact of Salmon Bias on the Hispanic Mortality Advantage: New Evidence from Social Security Data. *Popul Res Policy Rev*, **27**, 515-30.

VanderWalde A, Ye W, Frankel P, et al (2012). Long-term survival after high-dose chemotherapy followed by peripheral stem cell rescue for high-risk, locally advanced/inflammatory, and metastatic breast cancer. *Biol Blood Marrow Transplant*, **18**, 1273-80.

Vinh-Hung V, Verschraegen C, Promish DI, et al (2004) Ratios of involved nodes in early breast cancer. *Breast Cancer Res*, **6**, 680-8.

Voduc KD, Cheang MC, Tyldesley S, et al (2010). Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol*, **28**, 1684.

Woodward WA, Strom EA, Tucker SL, et al (2003) Changes in the 2003 American Joint Committee on Cancer staging for breast cancer dramatically affect stage-specific survival. *J Clin Oncol*, **21**, 3244-8

Woodward WA, Huang EH, McNeese MD, et al (2006).African-American race is associated with a poorer overall survival rate for breast cancer patients treated with mastectomy and doxorubicin-based chemotherapy. *Cancer*, **107**, 2662-8.

Woodward WA, Vinh-Hung V, Ueno NT, et al (2006) Prognostic value of nodal ratios in node-positive breast cancer. *J Clin Oncol*, **24**, 2910-6.

Zeichner SB, Zeichner SB, Ruiz AL, Markward NJ, Rodriguez E (2014). Improved long-term survival with contralateral prophylactic mastectomy among young women. *Asian Pac J Cancer Prev*, **15**, 1155-62.