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Assessment of Surgical Approach and Overall Survival in Young Women With Breast Cancer

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ABSTRACT

Objective: Mastectomy rates are increasing in young patients despite few data supporting improved outcomes. We investigated the association between surgical approach and survival in young patients with breast cancer.

Materials and Methods: Retrospective review identified women ≤40 years old with operable, non-metastatic invasive breast cancer treated between 2010–2019. Cox proportional hazard analyses, stratified by hormone receptor and human epidermal growth factor receptor 2 (HER2) status, identified factors associated with increased risk of recurrence and death.

Results: Of 588 patients, 65% underwent mastectomy and 35% breast conserving surgery (BCS). Median follow-up was 5.9 years. Overall recurrence and mortality rates were 15% and 12%, respectively. On multivariable analysis, black race [hazard ratio (HR), 2.14 (1.26–3.61), p = 0.005], lymphovascular space invasion (LVSI) [HR, 1.98 (1.17–3.36), p = 0.01], and extranodal extension [HR, 2.12 (1.09–4.12), p = 0.03] were associated with increased risk of death. Stage III disease [HR, 2.06 (1.05–4.03), p = 0.04] and LVSI [HR, 2.18 (1.43–3.32), p<0.001] were associated with increased risk of recurrence. Increasing age decreased the risk of death [HR, 0.94 (0.88–0.99), p = 0.02] and recurrence [HR, 0.95 (0.90–0.99), p = 0.02]. Mastectomy versus BCS did not impact recurrence [HR, 1.18 (0.73–1.92), p = 0.51] or overall survival (OS) [HR, 0.86 (0.46–1.58), p = 0.62] in the entire cohort. BCS was associated with increased risk of recurrence in the hormone receptor-/HER2+ subtype [HR, 9.06 (1.03–80.00), p = 0.047] but did not affect survival.

Conclusion: OS does not differ by surgery type in young patients with breast cancer. Future research should focus on racial disparities in breast cancer care.

Keywords: Breast cancer; lumpectomy; mastectomy; overall survival; young women

KEY POINTS

- Mastectomy rates are increasing in young patients with breast cancer despite no evidence of improved survival.
- We assessed surgical approach and survival in a large cohort of young patients with breast cancer.
- Overall survival did not differ based on mastectomy versus lumpectomy.

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Introduction

Breast cancer in women under 40 years of age is uncommon, with <5% of those at average-risk being affected (1). However, the incidence in this population has been increasing over time (1). Younger patients are burdened by highly proliferative and poorly differentiated tumors, which often translates to less favorable outcomes when compared to their older counterparts (1-5). Contemporary breast cancer management is driven by results of landmark trials that historically excluded young women, and this often results in the universal application of guidelines irrespective of age (4-7). However, recent data suggest that age itself may play a role in tumor heterogeneity, biology, and hormonal factors (4, 6-9).

Although there is a clear difference among age groups with respect to breast cancer recurrence (10), an abundance of literature supports the use of breast conserving surgery (BCS) with lumpectomy and adjuvant radiation in the appropriate setting. However, a reluctance to apply this therapy to young patients persists (11). Young patients frequently report being offered more "aggressive" treatment based upon their age alone. The consensus by the European School of Oncology and the European Society of Medical Oncology recommends that surgical management of young patients mirror that of older women, reporting no survival benefit to mastectomy, unless clinically indicated (12, 13). Despite lack of data supporting improved outcomes with more extensive surgery, there is a national trend towards mastectomy, and even contralateral prophylactic mastectomy in young women (14).

In this study, we evaluated a large cohort of patients with breast cancer aged 40 years or younger and treated with contemporary standard of care therapy at a single institution to determine whether surgical approach was an independent risk factor for outcomes. We also aimed to identify clinical, pathologic, and molecular features that may be utilized to predict recurrence-free survival (RFS) and overall survival (OS) in young women with breast cancer.

Materials and Methods

Patient Selection

Wake Forest University Health Sciences Institutional Review Board approval was obtained (approval number: IRB00083094, date: 09.05.2024). Patients 40 years or younger diagnosed with histologically confirmed, primary, non-metastatic, invasive breast carcinoma who underwent oncologic resection between 2010 and 2019 at the Levine Cancer Institute were identified. Patients with inflammatory or pregnancy-associated breast cancer were not excluded. Data pertaining to patient demographics, tumor characteristics, treatment details, and clinical outcomes were extracted from the prospectively maintained Sandra Levine Young Women's Database. Patients who presented with stage IV disease, were diagnosed with ductal or lobular carcinoma *in-situ*, and those with male sex assigned at birth were excluded from the analyses.

Primary and Secondary Endpoints

The primary objective of this study was to determine whether surgical approach with either BCS or mastectomy was an independent risk factor for OS in young women with breast cancer. Additionally, we aimed to identify clinical and pathologic variables that may help to predict both RFS and OS in young women with breast cancer. The standardized definitions for efficacy endpoints criteria were used to report these outcomes. RFS was defined as time from breast cancer diagnosis to first recurrence of breast cancer (ipsilateral breast, local-regional, or distant) or death from any cause. OS was defined as date of diagnosis to death from any cause. Survival and recurrence data were censored at the date of last follow-up.

Statistical Analysis

Patients were stratified into four molecular subtypes based upon hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status: HR+/HER2-, HR+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC). Baseline demographics and clinical characteristics were summarized for all subjects and for each surgery type, with frequencies or medians and interquartile ranges (IQR), as appropriate. Comparisons of categorical variables between surgery types were conducted using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the independent samples t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data.

Pathologic stage was not included in the analyses as some patients received chemotherapy in the neoadjuvant setting. Pathologic stage data are provided in Supplemental Table 1. Univariable and multivariable proportional hazards regression analyses were used to study the effect of surgery type on RFS and OS. In multivariable proportional hazards regression analysis, the following covariates were adjusted in the model: age at diagnosis, race, body mass index (BMI), clinical stage, the presence of lymphovascular space invasion (LVSI), the presence of extranodal extension (ENE), use of hormonal therapy, use of chemotherapy, and use of radiation therapy. Multivariable proportional hazards regression was performed for the entire cohort, and then for each molecular subtype separately. Both the hazard ratio and overall *p*-values are presented in the tables. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the difference between two categories while the overall *p*-value assesses difference across all

categories together. When a specific category is compared to the reference category, the hazard ratio *p*-value is referenced in the text. All statistical tests were two-sided with a significance level of $\alpha = 0.05$.

Results

Patient Population

Of 885 patients assessed for eligibility, 588 were included in the analysis (Figure 1). Demographic and clinical characteristics are shown in Table 1. Patients were 66% white, 26% black, and 8% other race with a median age at diagnosis of 37 years (IQR, 34–39). The median follow-up time was 5.9 years. The proportion of women within each molecular subtype was 53% (*n* = 314) HR+/HER2-, 21% (*n* = 122) HR+/HER2+, 7% (*n* = 39) HR-/HER2+, and 19% (*n* = 113) TNBC. Patients with *BRCA1* and *BRCA2* mutations represented 7.7% (*n* = 45) and 4.8% (*n* = 28) of the cohort, respectively. A higher percentage of patients underwent mastectomy (64.6%; *n* = 380) compared with lumpectomy (35.4%; *n* = 208), a trend that persisted among the four molecular subtypes. A higher percentage of patients who underwent lumpectomy received radiation therapy (99.5%; n = 207) compared to those who underwent mastectomy (47.9%; *n* = 182) (*p*<0.0001). Chemotherapy was administered in 81.3% (*n* = 478) of patients, with 53.4% (*n* = 314) in a neoadjuvant setting and 27.9% (*n* = 164) in an adjuvant setting. Surgical approach was not statistically different *p* = 0.47 between neoadjuvant and adjuvant chemotherapy settings (neoadjuvant, 65.6% mastectomy; adjuvant, 68.9% mastectomy). The majority of patients had either stage I or II tumors on surgical pathology (34.5% and 52.6%, respectively). With a median follow-up time of 5.9 years (IQR 3.8–8.8), 15.1% (*n* = 89) of patients in the entire cohort experienced a recurrence, with distant metastatic disease (67.4%; *n* = 60) being more common than a local (22.5%; *n* = 20) or regional event (10.1%; *n* = 9).

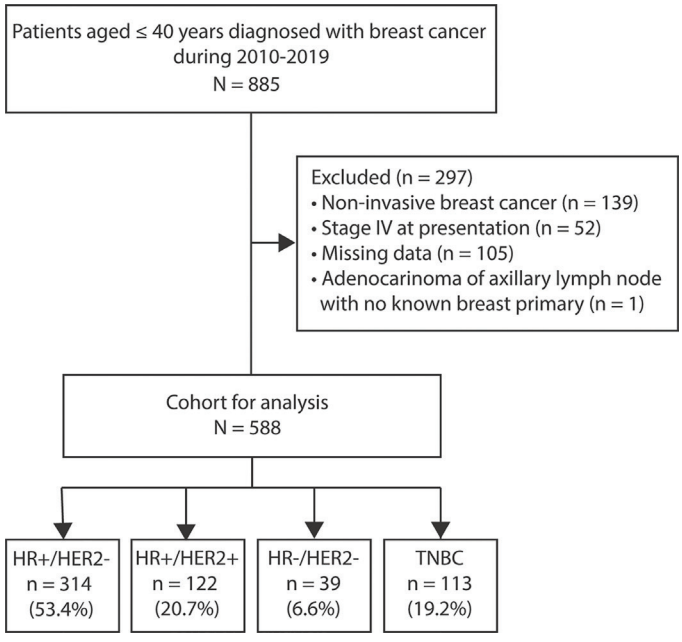

Figure 1. Flow chart of the study cohort

HR: Hormone receptor; TNBC: Triple negative breast cancer

The patients with TNBC and HR-/HER2+ subtypes presented with higher grade tumors compared with the remainder of patients, had a higher rate of recurrence, and worse long-term survival (Supplemental Table 2). The overall mortality rate across all molecular subtypes was 12.1% (*n* = 71). The best survival outcomes were observed among those with HR+ disease, 89.5% for the HR+/HER2- subtype and 89.3% for HR+/HER2+ subtype.

Survival Analysis of Entire Patient Population

Univariate analysis indicated that among the entire cohort, younger age at diagnosis was associated with increased risk of recurrence and death (Table 2). For RFS, each additional year of age was associated with a 6% reduction in the risk of recurrence or death [hazard ratio, 0.94 (0.90–0.98), *p* = 0.005]. For OS, each additional year of age was associated with a 7% reduction in the risk of death [hazard ratio, 0.93 (0.88–0.98), *p* = 0.007]. Increasing stage, the presence of LVSI, and the presence of ENE were associated with an increased risk of both recurrence and death. There was a significant difference in OS between races (overall *p* = 0.002), with black race associated with an increased risk of death compared to white race [hazard ratio, 2.33 (1.43–3.82), hazard ratio *p*<0.001]. There was no significant association between surgical approach and RFS [Figure 2A; hazard ratio, 0.92 (0.62–1.38), *p* = 0.70] or OS [Figure 2B; hazard ratio, 0.72 (0.43–1.22), *p* = 0.22] in this cohort of young women with breast cancer.

To account for imbalances between treatment groups, multivariable analysis was conducted with adjustment for potential confounders included in the model. On multivariable analysis of the entire cohort, race remained significantly associated with an increased risk of death (overall *p* = 0.01), with women of black race at two times higher risk of death compared to women of white race [hazard ratio, 2.114 (1.26–3.61), hazard ratio *p* = 0.005] (Table 3). Increasing age at diagnosis decreased the risk of death [hazard ratio, 0.94 (0.88–0.99), *p* = 0.02]. The presence of LVSI [hazard ratio, 1.98 (1.17–3.36), hazard ratio *p* = 0.01], and the presence of ENE [hazard ratio, 2.12 (1.09–4.12), *p* = 0.03] were associated with increased risk of death. Increasing age decreased the risk of recurrence [hazard ratio, 0.95 (0.90–0.99), *p* = 0.02]. Stage III disease [hazard ratio, 2.06 (1.05–4.03), hazard ratio *p* = 0.04] and the presence of LVSI [hazard ratio, 2.18 (1.43–3.32), hazard ratio *p*<0.001] increased risk of recurrence.

Table 1. Demographic and clinical characteristics by surgical approach				
Characteristic	**Total (*n* = 588)**	**Lumpectomy (*n* = 208)**	**Mastectomy (*n* = 380)**	***p*-value**
Age at diagnosis, years				0.20
Median (IQR)	37 (34–39)	38 (34–40)	37 (34–39)	
Follow-up time (OS), months				0.69
Median (IQR)	73 (45–105)	71 (43–105)	74 (48–105)	
Minimum	6	9	6	
Maximum	148	139	148	
Follow-up time (RFS), months				0.83
Median (IQR)	71 (45–105)	71 (43–103)	71 (46-105)	
Minimum	6	9	6	
Maximum	148	139	148	
BMI, kg/m^2				0.05
Mean ± SD	28.6±7.5	29.5±8.2	28.0±7.0	
Race				**0.001**
Black	153 (26.0%)	72 (34.6%)	81 (21.3%)	
White	388 (66.0%)	125 (60.1%)	263 (69.2%)	
Other	47 (8.0%)	11 (5.3%)	36 (9.5%)	
Hormone status				0.60
HR+/HER2-	314 (53.4%)	104 (50.0%)	210 (55.3%)	
HR+/HER2+	122 (20.7%)	44 (21.2%)	78 (20.5%)	
HR-/HER2+	39 (6.6%)	15 (7.2%)	24 (6.3%)	
TNBC	113 (19.2%)	45 (21.6%)	68 (17.9%)	
Radiation therapy				**<0.0001**
No	199 (33.8%)	1 (0.5%)	198 (52.1%)	
Yes	389 (66.2%)	207 (99.5%)	182 (47.9%)	
Chemotherapy				**0.03**
No	110 (18.7%)	49 (23.6%)	61 (16.1%)	
Yes	478 (81.3%)	159 (76.4%)	319 (83.9%)	
Chemotherapy timing				0.06
Neoadjuvant	314 (53.4%)	108 (51.9%)	206 (54.2%)	
Adjuvant	164 (27.9%)	51 (24.5%)	113 (29.7%)	
No chemotherapy	110 (18.7%)	49 (23.6%)	61 (16.1%)	
Hormone therapy				0.47
No	64 (10.9%)	22 (10.6%)	42 (11.1%)	
Yes	372 (63.3%)	126 (60.6%)	246 (64.7%)	
Not applicable	152 (25.9%)	60 (28.8%)	92 (24.2%)	
Stage group				**0.004**
I	203 (34.5%)	78 (37.5%)	125 (32.9%)	
II	309 (52.6%)	116 (55.8%)	193 (50.8%)	
III	76 (12.9%)	14 (6.7%)	62 (16.3%)	
T classification				0.09
cT0	1 (0.2%)[a]	0 (0.0%)[a]	1 (0.3%)[a]	

Table 1. Continued

Characteristic	Total ($n = 588$)	Lumpectomy ($n = 208$)	Mastectomy ($n = 380$)	*p*-value
cT1	202 (34.4%)	77 (37.0%)	125 (32.9%)	
cT2	279 (47.4%)	105 (50.5%)	174 (45.8%)	
cT3	103 (17.5%)	26 (12.5%)	77 (20.3%)	
cT4	3 (0.5%)	0 (0.0%)	3 (0.8%)	
N classification				**0.02**
cN0	412 (70.1%)	160 (76.9%)	252 (66.3%)	
cN1	155 (26.4%)	46 (22.1%)	109 (28.7%)	
cN2	12 (2.0%)	1 (0.5%)	11 (2.9%)	
cN3	9 (1.5%)	1 (0.5%)	8 (2.1%)	
Grade				0.66
1	52 (8.8%)	19 (9.1%)	33 (8.7%)	
2	243 (41.3%)	79 (38.0%)	164 (43.2%)	
3	281 (47.8%)	105 (50.5%)	176 (46.3%)	
Unknown	12 (2.0%)	5 (2.4%)	7 (1.8%)	
Lymphovascular invasion				**0.002**
No	385 (65.5%)	156 (75.0%)	229 (60.3%)	
Yes	148 (25.2%)	39 (18.8%)	109 (28.7%)	
Indeterminate	55 (9.4%)	13 (6.3%)	42 (11.1%)	
Extranodal extension				**0.02**
No	528 (89.8%)	195 (93.8%)	333 (87.6%)	
Yes	60 (10.2%)	13 (6.3%)	47 (12.4%)	
Status				0.18
Alive	517 (87.9%)	188 (90.4%)	329 (86.6%)	
Deceased	71 (12.1%)	20 (9.6%)	51 (13.4%)	
Recurrence				0.91
No	499 (84.9%)	177 (85.1%)	322 (84.7%)	
Yes	89 (15.1%)	31 (14.9%)	58 (15.3%)	
Recurrence site $n = 89$				0.27
Local	20 (22.5%)	10 (32.3%)	10 (17.2%)	
Regional	9 (10.1%)	3 (9.7%)	6 (10.3%)	
Distant	60 (67.4%)	18 (58.1%)	42 (72.4%)	

BMI: Body mass index; HR: Hormone receptor; SD: Standard deviation; TNBC: Triple negative breast cancer; OS: Overall survival; IQR: Interquartile range; HER2: Human epidermal growth factor receptor 2; RFS: Recurrence-free survival. Bold indicates $p<0.05$. [a]: cT0N1

The hormone therapy not applicable category is equivalent to the combination of HR-/HER2+ and TNBC subgroups. As a result, the model was not able to estimate the effect of TNBC when hormone therapy was included (Table 3). We also ran an alternative model (result not shown), where the categories of hormone therapy and hormone status were combined to resolve the collinearity issue. Neither of the two models found significant effect from hormone treatment or hormone status or the combination of the two. The administration of chemotherapy in any setting was not associated with RFS or OS in multivariable analysis.

Table 2. Univariable recurrence-free survival and overall survival analysis for all subjects

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Age at diagnosis, 1-yr increase	588	0.94 (0.90–0.98)	**0.005**	**0.005**	0.93 (0.88–0.98)	**0.007**	**0.007**
BMI, kg/m^2							
<25	232	ref		0.38	ref		0.18
≥25	356	1.19 (0.81–1.77)	0.38		1.41 (0.86–2.31)	0.18	
Race							
White	388	ref		0.06	ref		**0.002**
Black	153	1.60 (1.06–2.40)	**0.03**		2.33 (1.43–3.82)	**<0.001**	
Other	47	1.56 (0.80–3.05)	0.19		2.10 (0.93–4.75)	0.08	
Surgical approach							
Mastectomy	380	ref		0.70	ref		0.22
Lumpectomy	208	0.92 (0.62–1.38)	0.70		0.72 (0.43–1.22)	0.22	
Radiation therapy							
Yes	389	ref		0.74	ref		0.96
No	199	0.93 (0.62–1.40)	0.74		1.01 (0.62–1.65)	0.96	
Chemotherapy							
No	110	ref		0.07	ref		0.24
Yes	478	1.72 (0.96–3.07)	0.07		1.52 (0.76–3.07)	0.24	
Hormone therapy							
No	64	ref		0.16	ref		**0.046**
Yes	372	0.79 (0.43–1.47)	0.47		0.63 (0.30–1.31)	0.22	
Not applicable	152	1.19 (0.62–2.30)	0.60		1.18 (0.55–2.53)	0.67	
Stage group							
I	203	ref		**0.001**	ref		**0.008**
II	309	1.85 (1.14–2.98)	**0.01**		1.92 (1.05–3.53)	**0.04**	
III	76	2.94 (1.64–5.28)	**<0.001**		3.11 (1.52–6.37)	**0.002**	
T classification							
cT1	202	ref		**<0.001**	ref		**<0.001**
cT0[a]	1	8.98 (1.21–66.68)	**0.03**		13.20 (1.72–101.2)	**0.01**	
cT2	279	1.63 (0.99–2.68)	0.05		1.89 (0.99–3.61)	0.06	
cT3	103	3.68 (2.17–6.23)	**<0.001**		4.31 (2.20–8.43)	**<0.001**	
cT4	3	2.13 (0.29–15.81)	0.46		3.33 (0.43–25.63)	0.25	
N classification							
cN0	412	ref		0.22	ref		0.40
cN1	155	1.38 (0.91-2.08)	0.13		1.20 (0.71–2.03)	0.50	
cN2	12	1.69 (0.53–5.37)	0.374		2.11 (0.66–6.80)	0.21	
cN3	9	2.40 (0.75–7.61)	0.14		2.31 (0.56–9.51)	0.25	
Grade							
1	52	ref		0.29	ref		0.11
2	243	1.49 (0.63–3.53)	0.36		1.90 (0.57–6.34)	0.30	
3	281	1.98 (0.85–4.57)	0.11		3.04 (0.94–9.82)	0.06	

Table 2. Continued

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Unknown	12	1.49 (0.30–7.38)	0.66		3.17 (0.53–19.01)	0.21	
Hormone status							
HR+/HER2-	314	ref		0.12	ref		0.17
HR+/HER2+	122	1.04 (0.63–1.72)	0.88		0.96 (0.50–1.82)	0.90	
HR-/HER2+	39	2.12 (1.13–3.97)	**0.02**		1.53 (0.64–3.67)	0.34	
TNBC	113	1.25 (0.76–2.06)	0.38		1.77 (1.01–3.12)	**0.047**	
LVSI							
No	385	ref		**<0.001**	ref		**0.002**
Yes	148	2.42 (1.64–3.59)	**<0.001**		2.28 (1.41–3.69)	**<0.001**	
Indeterminate	55	1.21 (0.58–2.55)	0.61		0.92 (0.33–2.59)	0.87	
Extranodal extension							
No	528	ref		**<0.001**	ref		**<0.001**
Yes	60	2.64 (1.67–4.19)	**<0.001**		2.83 (1.62–4.96)	**<0.001**	

BMI: Body mass index; HR: Hormone receptor; HER2: Human epidermal growth factor receptor 2; CI: Confidence interval; LVSI: Lymphovascular space invasion; TNBC: Triple negative breast cancer; ref: Reference. Bold indicates $p<0.05$. [a]: cT0N1. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

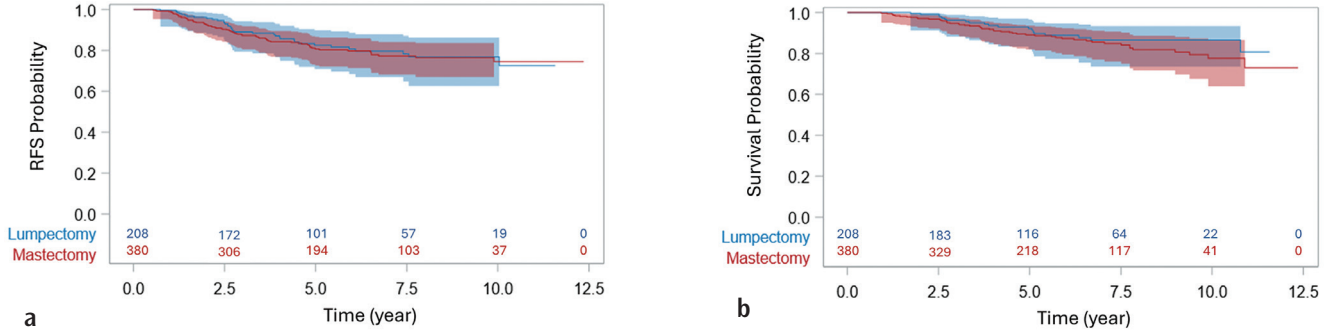

Figure 2. Kaplan-Meier curves for RFS (A) and OS (B) by surgical approach. In both plots, Kaplan-Meier curves, 95% confidence intervals (shaded bands), and the number of patients at risk at each time interval are provided for lumpectomy (blue) and mastectomy (red). Surgical approach was not significantly associated with RFS ($p = 0.95$) or OS ($p = 0.22$)

RFS: Recurrence-free survival; OS: Overall survival

Outcomes by Molecular Subtype

Using multivariable analysis, increasing age [hazard ratio, 1.40 (1.02–1.92), $p = 0.04$], higher BMI [hazard ratio, 8.45 (1.14–62.76), $p = 0.04$], stage III disease [hazard ratio, 129.94 (2.84–5583), hazard ratio $p = 0.01$], and lumpectomy [hazard ratio, 9.06 (1.03–80.0), $p = 0.047$] increased the risk of any recurrence in patients with the HR-/HER2+ subtype (Supplemental Table 3). Black race as compared to white race increased the risk of any recurrence [hazard ratio, 3.36 (1.16–9.71), hazard ratio $p = 0.03$] in patients with TNBC. Patients in the HR+/HER2- subgroup with LVSI had an increased risk of recurrence (overall $p = 0.02$) as compared to patients without LVSI.

In the HR+/HER2- subgroup, increasing age was significantly associated with a decreased risk of death [hazard ratio, 0.90 (0.82–0.98), hazard ratio $p = 0.01$] (Table 4). Black race as compared to white race increased the risk of death in the TNBC [hazard ratio, 4.20 (1.27–13.90), hazard ratio $p = 0.02$] subgroup. In this stratified analysis according to molecular subtype, despite controlling for other demographic and tumor characteristics, there was no difference in OS based upon surgical approach in any of the molecular subtypes.

Table 3. Multivariable recurrence-free survival and overall survival analysis for all subjects

Variable	n	Recurrence-free survival			Overall survival		
		Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Age at diagnosis, 1-yr increase	588	0.95 (0.90–0.99)	**0.02**	**0.02**	0.94 (0.88–0.99)	**0.02**	**0.02**
BMI, kg/m^2							
<25	232	ref		0.87	ref		0.69
≥25	356	1.04 (0.68–1.57)	0.87		1.12 (0.65–1.91)	0.69	
Race							
White	388	ref		0.19	ref		**0.01**
Black	153	1.46 (0.95–2.25)	0.08		2.14 (1.26–3.61)	**0.005**	
Other	47	1.40 (0.69–2.83)	0.35		1.87 (0.80–4.39)	0.15	
Surgical approach							
Mastectomy	380	ref		0.51	ref		0.62
Lumpectomy	208	1.18 (0.72–1.92)	0.51		0.86 (0.46–1.58)	0.62	
Radiation therapy							
Yes	352	ref		0.15	ref		0.23
No	236	1.46 (0.87–2.44)	0.15		1.47 (0.79–2.77)	0.23	
Chemotherapy							
No	110	ref		0.91	ref		0.82
Yes	478	1.04 (0.53–2.02)	0.91		0.91 (0.40–2.08)	0.82	
Hormone therapy							
No	64	ref		0.39	ref		0.17
Yes	372	0.76 (0.40–1.43)	0.39		0.58 (0.27–1.26)	0.17	
Not applicable	152	1.02 (0.48–2.20)	0.95		1.21 (0.49–2.95)	0.68	
Stage group							
I	203	ref		0.10	ref		0.34
II	309	1.58 (0.94–2.65)	0.09		1.49 (0.77–2.89)	0.24	
III	76	2.06 (1.05–4.03)	**0.04**		1.86 (0.80–4.30)	0.15	
Hormone status							
HR+/HER2-	314	ref		0.34	ref		0.85
HR+/HER2+	122	0.90 (0.53–1.52)	0.68		0.82 (0.41–1.64)	0.58	
HR-/HER2+	39	1.69 (0.82–3.51)	0.16		0.94 (0.36–2.44)	0.90	
TNBC	113	NA	NA		NA	NA	
LVSI							
No	385	ref		**0.001**	ref		0.03
Yes	148	2.18 (1.43–3.32)	**<.001**		1.98 (1.17–3.36)	**0.01**	
Indeterminate	55	1.24 (0.58–2.65)	0.59		0.91 (0.32–2.63)	0.86	
Extranodal extension							
No	528	ref		**0.006**	ref		**0.03**
Yes	60	2.14 (1.25–3.66)	**0.006**		2.12 (1.09–4.12)	**0.03**	

BMI: Body mass index; HR: Hormone receptor; CI: Confidence interval; LVSI: Lymphovascular space invasion; HER2: Human epidermal growth factor receptor 2; TNBC: Triple negative breast cancer; ref: Reference; NA: Not applicable. Bold indicates $p<0.05$. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

Table 4. Multivariable overall survival analysis stratified by molecular subtype

	HR+/HER2- (*n* = 314)			HR+/HER2+ (*n* = 122)			HR-/HER2+ (*n* = 39)			TNBC (*n* = 113)		
Characteristic	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**	**Hazard ratio (95% CI)**	**Hazard ratio *p*-value**	**Overall *p*-value**
Age at diagnosis, 1-yr increase	0.90 (0.82–0.98)	**0.01**	**0.01**	0.96 (0.83–1.12)	0.62	0.62	1.10 (0.78–1.56)	0.57	0.57	0.93 (0.81–1.06)	0.29	0.29
BMI, kg/m^2												
<25	ref		0.42	ref		0.43	ref		0.78	ref		0.69
≥25	1.40 (0.62–3.20)	0.42		1.75 (0.44–7.03)	0.43		1.39 (0.14–13.49)	0.78		0.79 (0.25–2.52)	0.69	
Race												
White	ref		0.14	ref		0.31	ref		0.10	ref		0.05
Black	0.84 (0.34–2.09)	0.71		3.44 (0.69–17.22)	0.13		16.63 (0.97–286)	0.05		4.20 (1.27–13.90)	**0.02**	
Other	2.64 (0.93–7.48)	0.07		2.42 (0.08–71.92)	0.61		0.90 (0.03–27.33)	0.95		3.10 (0.60–16.18)	0.18	
Surgical approach												
Mastectomy	ref		0.47	ref		0.57	ref		0.81	ref		0.65
Lumpectomy	0.70 (0.27–1.84)	0.47		0.60 (0.10–3.49)	0.57		0.68 (0.03–15.30)	0.81		0.75 (0.21–2.62)	0.65	
Radiation therapy												
Yes	ref		0.33	ref		0.78	ref		0.93	ref		0.95
No	1.56 (0.64–3.77)	0.33		0.76 (0.12–4.97)	0.78		1.16 (0.04–37.10)	0.93		1.05 (0.27–4.10)	0.95	
Chemotherapy												
No	ref		0.68	ref		0.08	ref		0.39	ref		0.37
Yes	0.80 (0.29–2.25)	0.68		0.12 (0.01–1.31)	0.08		0.05 (0.00–53.52)	0.39		0.37 (0.04–3.32)	0.37	
Hormone therapy												
No	ref		0.15	ref		0.16	NA	NA	NA	NA	NA	NA
Yes	0.49 (0.19–1.30)	0.15		0.27 (0.04–1.69)	0.16		NA	NA		NA	NA	

Table 4. Continued

Characteristic	HR+/HER2- (*n* = 314)			HR+/HER2+ (*n* = 122)			HR-/HER2+ (*n* = 39)			TNBC (*n* = 113)		
	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value	Hazard ratio (95% CI)	Hazard ratio *p*-value	Overall *p*-value
Stage group												
I	ref		0.15	ref		0.89	ref		0.44	ref		0.94
II	1.86 (0.71–4.89)	0.21		1.23 (0.21–7.23)	0.82		8.90 (0.11–758)	0.34		0.83 (0.21–3.37)	0.80	
III	3.58 (1.00–12.83)	0.05		0.84 (0.11–6.45)	0.86		25.52 (0.18–3620)	0.20		0.99 (0.17–5.71)	0.99	
LVSI												
No	ref		0.26	ref		0.70	ref		0.99	ref		0.25
Yes	1.77 (0.84–3.73)	0.14		1.80 (0.36–9.01)	0.47		1.08 (0.05–24.97)	0.96		2.99 (0.83–10.76)	0.09	
Indeterminate	0.72 (0.12–4.17)	0.71		2.52 (0.21–30.92)	0.47		0.98 (0.01–76.78)	0.99		1.36 (0.28–6.60)	0.70	
ENE												
No	ref		0.16	ref		0.20	ref		0.73	ref		0.68
Yes	1.92 (0.77–4.83)	0.16		3.43 (0.52–22.81)	0.20		0.45 (0.01–43.23)	0.73		0.62 (0.06–6.27)	0.68	

BMI: Body mass index; HR: Hormone receptor; ENE: Extranodal extension; CI: Confidence interval; HER2: Human epidermal growth factor receptor 2; TNBC: Triple negative breast cancer; LVSI: Lymphovascular space invasion; ref: Reference; NA: Not applicable. Bold indicates $p<0.05$. For categorical variables with more than two categories, the hazard ratio *p*-value assesses the statistical significance of the comparison between a specific category and the reference category, while the overall *p*-value assesses whether there is a difference across all categories combined. For continuous or binary variables, the hazard ratio *p*-value and overall *p*-value are identical because there is only one comparison

Discussion and Conclusion

After the published results of landmark trials demonstrated oncologic equivalence between BCS and mastectomy, BCS became the treatment of choice for patients with early-stage breast cancer (15). However, women under 40 years of age were underrepresented in these trials, fueling the ongoing debate of whether BCS is safe in young patients. Randomized trials to determine whether surgical approach impacts survival in women ≤40 years are unlikely to surface given currently available information. Several observational studies have investigated whether surgical approach might impact OS in young patients with early-stage breast cancer; however, many of these included patients treated over a decade ago. Systemic therapy for breast cancer has rapidly developed in recent years, especially with respect to treatment of specific molecular subtypes, and updated data are required to make relevant clinical decisions (10, 12). Our retrospective study contributes to the literature by analyzing a large cohort of almost 600 young women with breast cancer who have been treated with modern-day systemic and local therapies. This research utilized data from the Sandra Levine Young Women's Program, a prospectively collected database, which is updated regularly to minimize missing data variables. After 5.9 years of follow-up, our analysis indicates that mastectomy does not offer improved OS compared with BCS in young women with breast cancer. Despite lack of improved survival, our patient population was more likely to undergo mastectomy. Currently, about 60% of women of all ages with early-stage breast cancer undergo BCS (16, 17); however, despite no survival benefit, a national trend towards mastectomy in young patients persists. Our patient population echoed this finding, with 65% of patients undergoing mastectomy and only 35% choosing lumpectomy. This trend towards mastectomy was consistent among all molecular subtypes.

Young patients with breast cancer are plagued with notoriously poor outcomes and are up to 1.5 times more likely to die from their cancer (18) and experience a local recurrence (2, 19-21). Breast cancer in young women is characterized by highly proliferative molecular subtypes (2, 21). While HR+/HER2- (53.4%) disease was most common in our analysis, we did see a preponderance of HR+/HER2+ (20.7%) and TNBC (19.2%), molecular profiles that are consistent with breast cancer in young women (13). In addition, the HER2+ and TNBC tumors were more likely to demonstrate poorly differentiated pathology. Patients with TNBC also had the highest

mortality rate (16.8%) of all molecular subtypes, compared with the 12.1% mortality rate of the entire cohort. Furthermore, in our entire cohort of young women, black race was associated with an increased risk of death, emphasizing the importance of addressing racial disparities in future studies (22). Biological factors, lower socioeconomic status, and limited access to care may contribute to the poorer OS observed among young black women in our study. The difference in survival by race is consistent with a recent National Cancer Database analysis, which found that black women under forty had higher odds of death (odds ratio 1.50; 95% confidence interval: 1.46–1.55, $p<0.0001$) compared to their non-black peers after adjusting for age, tumor characteristics, and treatment (23).

Mastectomy is being replaced by a more conservative approach as the standard for local control of breast cancer (24-29), a paradigm shift that safely de-escalates surgery without compromising oncologic outcomes. More recently, multiple studies have questioned whether mastectomy continues to be a valid surgical option compared to BCS, which can be associated with not only improved esthetic outcomes, but also higher breast cancer-specific survival rates when compared to mastectomy alone (30-32). The Netherlands population-based cohort study demonstrated that BCS in conjunction with radiation resulted in improved 10-year OS when compared to mastectomy (31). Mastectomy is generally associated with an increased risk of complications including bleeding, infections and wound complications (33). Multiple studies support the benefits of BCS over more extensive surgery including improved patient satisfaction with cosmetic outcome (34), psychosocial well-being, body image, and quality of life (35). However, routine BCS in women younger than 40 is controversial, not only because of a lack of prospective data to support it in this high-risk population, but also because young age has been shown to be independently associated with local recurrence after breast conservation (10, 11, 36, 37). Nguyen et al. (11) recently compared the cumulative incidence of local recurrence in patients ≤40 years with breast cancer treated with lumpectomy and radiation versus mastectomy. Among 428 women with early-stage breast cancer, they found the lumpectomy group experienced a 2.5-fold increased risk of local recurrence. Furthermore, patients with isolated local recurrences after lumpectomy showed poor prognosis despite undergoing salvage therapies (11). Miles et al. (38) assessed patients treated from 1988 to 2011, which confirmed these findings (only 5.6% of the patients were <40 years old) and found that risk factors for local recurrence after BCS include node positivity, ER negativity, absence of adjuvant radiation therapy, and age <40 years. In our analysis, BCS increased the risk of local recurrence in patients with the HR-/HER2+ molecular subtype; however, it is important to note that only 7% of our patients were HR-/HER2+. A literature review revealed no studies with similar findings. The existing literature shows that the HR-/HER2+ subtype is seen in approximately 10% of women under the age of 40 (39). As previously noted, only 7% of our cohort was HR-/HER2+. Therefore, we recommend cautious interpretation of these results given the small sample size. Larger studies with longer follow-up are needed to confirm these findings.

Another interesting question is whether the timing of chemotherapy administration impacts young women. Several studies have found that the use of neoadjuvant chemotherapy (NAC) in the treatment of breast cancer has been increasing over time (40), despite trends towards a survival advantage for NAC in only specific cancer subtypes among young women (41). NAC offers the opportunity to de-escalate breast cancer surgery. The majority of patients in our study underwent chemotherapy; most commonly in a neoadjuvant approach. In addition, most of our patients who received NAC also underwent mastectomy, which implies that there were indications for neoadjuvant therapy other than to facilitate breast preservation. Previous studies have shown equivalent survival regardless of timing of chemotherapy (42, 43).

Study Limitations

This study has several limitations, including its retrospective design, patient exclusion due to missing data (archived medical records), and the 6-year duration of follow-up evaluation. In addition, our patient population may not be representative of all young women with breast cancer in the United States. Although the HR-/HER2+ molecular subtype was associated with an increased risk of local recurrence, the number of patients with HR-/HER2+ disease in our cohort was small, resulting in wide confidence intervals and unstable hazard ratio estimates. These findings should be interpreted with caution. Larger studies would be needed to confirm the findings in patients with HR-/HER2+ disease. We did not collect data pertaining to the surgical approach decision-making process. High-risk status, family history (e.g., *BRCA* mutation status), patient preference, genetic counseling, and cultural differences may all play a role in determining the surgical approach. Our cohort included 7.7% ($n = 45$) *BRCA1* carriers and 4.8% ($n = 28$) with *BRCA2* mutations. Although the number of patients with *BRCA* mutations was relatively small, *BRCA* status was not considered in the analyses, which is acknowledged as a limitation. Future studies of young patients with *BRCA* mutations could assess the influence of *BRCA* status on surgical choice and its effect on oncologic outcomes. Lastly, we did not include detailed information regarding specific chemotherapy protocols and radiation therapy fields for patients, which is a limitation of this study. However, chemotherapy administration was according to the standard of care following NCCN and ASCO guidelines. Radiation therapy

also followed standardized treatment per ASTRO guidelines.

In conclusion, our study reinforces the data demonstrating equivalent survival with breast conservation when compared to mastectomy in young women with breast cancer. Recurrence and mortality rates are associated with tumor subtypes and race, and not with surgical intervention. This information should be used to guide shared decision-making. Future research should focus on ethnic and racial disparities and whether this impacts breast cancer care in young patients.

Ethics

Ethics Committee Approval: Wake Forest University Health Sciences Institutional Review Board approval was obtained (approval number: IRB00083094, date: 09.05.2024).

Informed Consent: Waived informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.L.W., L.H-G.; Concept: L.H-G.; Design: R.L.W., L.H-G.; Data Collection or Processing: S.J.T., W.S., C.R.S.; Analysis or Interpretation: C.V.P., S.J.T., W.S., M.L.W., L.H-G.; Literature Search: C.V.P.; Writing: C.V.P., S.J.T., W.S., C.R.S., M.L.W., R.L.W., L.H-G.

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