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Tumor Biology and Response to Chemotherapy Impact Breast Cancer-Specific Survival in Node-Positive Breast Cancer Patients Treated with Neoadjuvant Chemotherapy: Long-term Follow-up from ACOSOG Z1071 (Alliance)

Judy C. Boughey, M.D.¹, Karla V. Ballman, Ph.D.², Linda M. McCall, M.D.³, Elizabeth A. Mittendorf, M.D., Ph.D.⁴, W. Fraser Symmans, M.D.⁴, Thomas B. Julian, M.D.⁵, David Byrd, M.D.⁶, and Kelly K. Hunt, M.D.⁴

¹Mayo Clinic, Rochester, MN

²Alliance Statistics and Data Center, Weill Medical College of Cornell University, New York, NY

³Alliance Statistics and Data Center, Duke University, Durham, NC

⁴The University of Texas MD Anderson Cancer Center, Houston, TX

⁵NRG Oncology and The Allegheny Health Network, Pittsburgh, PA

⁶SWOG and University of Washington Medical Center, Seattle, WA

Abstract

Background—Women with node-positive breast cancer have high risk for recurrence. We evaluate the impact of approximated tumor subtype and response to chemotherapy on long-term outcomes in a node-positive cohort receiving neoadjuvant chemotherapy.

Methods—ACOSOG Z1071 enrolled cT0-4N1-2 breast cancer patients treated with neoadjuvant chemotherapy from 2009-2011. Factors impacting breast cancer-specific survival (BCSS) and overall survival (OS) were analyzed.

Results—Median follow-up of 701 eligible patients was 4.1 years (0.4–6.5). Ninety patients (12.8%) died from breast cancer. Approximated subtype and chemotherapy response were significantly associated with BCSS and OS ($p < 0.0001$). BCSS and OS was highest in patients who achieved pathologic complete response (pCR) ($p < 0.0001$ and $p < 0.0001$, respectively).

5-year BCSS was highest in HER2-positive disease (95.8%; 95%CI: 87.7–98.6), followed by hormone receptor (HR)-positive/HER2-negative (80.4%; 95%CI: 73.2–85.9) and lowest in triple-negative (TNBC) (74.8%; 95%CI: 66.6–81.2; $p < 0.0001$). Similar patterns were seen in OS.

In TNBC ($n = 174$), 5-year BCSS was higher in patients with pCR versus residual disease (89.8%; 95%CI: 78.8–95.3 versus 65.8%; 95%CI: 54.5–74.9; $p = 0.0013$). In HR-positive/HER2-negative ($n = 318$) disease, BCSS was 100% in patients with pCR and 78.3% (95%CI: 70.4–84.3) in those

Correspondence: Kelly K. Hunt, MD, Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1400 Pressler Street, Unit 1434, Houston, TX 77030, Phone: (713) 792-7216, khunt@mdanderson.org.

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with residual disease ($p=0.018$). In HER2-positive disease ($n=204$) there was no difference between pCR and residual disease (96.0%; 95% CI: 83.6–99.1 versus 95.8%; 95% CI: 81.4–99.1; $p=0.77$).

Conclusion—In node-positive breast cancer patients treated with neoadjuvant chemotherapy, BCSS and OS were associated with approximated subtype and chemotherapy response and were lowest in TNBC patients with residual disease. 5-year BCSS was >95% in HER2-positive disease independent of chemotherapy response.

Keywords

Breast cancer-specific survival; Overall survival; Node-positive breast cancer; Neoadjuvant chemotherapy

Introduction

Nodal staging in breast cancer remains important because it provides prognostic information and stratifies patients into higher and lower risk groups with respect to recurrence and mortality due to breast cancer. In patients with biopsy confirmed node-positive disease at initial presentation, the use of chemotherapy prior to surgical intervention (neoadjuvant chemotherapy) is often considered. Delivery of chemotherapy to patients in the neoadjuvant setting is associated with several advantages; increased rates of breast-conserving surgery, downstaging of disease in the regional nodal basins and the opportunity to assess response to therapy [1–6]. Eradication of disease from the breast and the lymph nodes, pathologic complete response (pCR), has been shown to be associated with improved survival when compared to the presence of residual disease after chemotherapy [7].

Invasive breast cancers are routinely classified into approximated subtypes based on the status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) on immunohistochemistry studies of the primary tumor. Tumors overexpressing HER2 are known to be biologically more aggressive; however, currently available HER2-targeted therapies are highly effective and have been shown to improve outcomes when patients receive HER2-targeted therapy with chemotherapy. In hormone receptor (HR) positive disease (ER positive and/or PR positive), endocrine therapy is an important component of systemic treatment and is usually given in the adjuvant setting. For triple-negative breast cancer (TNBC), defined as ER negative, PR negative, and HER2 negative, chemotherapy is the only current systemic therapy option. Studies evaluating administration of chemotherapy in the neoadjuvant setting have shown that response rates to chemotherapy vary by tumor subtype [8–11] and that pCR is associated with prognosis [7, 12, 13].

In this study, we report the five-year breast cancer-specific survival (BCSS) and overall survival (OS) rates in women with node-positive breast cancer who were treated with neoadjuvant chemotherapy and enrolled on the American College of Surgeons Oncology Group (ACOSOG) Z1071 trial. We also examine the impact of approximated subtype on response to chemotherapy and survival.

Methods

ACOSOG Z1071 was a prospective clinical trial that enrolled 756 patients with clinical cT1-3, N1-2 breast cancer treated with neoadjuvant chemotherapy across 136 institutions from 2009–2011. The primary endpoint of the trial, false negative rate of sentinel lymph node surgery, was previously reported [14]. All patients underwent axillary dissection. Data regarding clinical stage at presentation, ER, PR, and HER2 status, chemotherapy delivered, surgical procedure, pathologic stage, and use of adjuvant treatment, were collected prospectively on the case report forms at the treating institution and reported to the ACOSOG (Alliance) Statistics and Data Center. Breast cancer approximated subtype was defined by hormone receptor (HR) status from combined ER and PR status and HER2 status as follows: HR positive, HER2-negative (ER positive and/or PR positive, and HER2-negative); HER2-positive (HER2 3+ by immunohistochemistry or amplified by FISH or ISH); and triple negative (ER <1%, PR <1% and HER2-negative). Pathologic complete response was defined as no residual invasive disease in the breast or axillary lymph nodes.

The extent of disease in the surgical specimen was evaluated by the pathologist at the local site and residual disease was staged using the yp-stage designation of the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. Additionally, reporting on the residual cancer burden (RCB) was requested on the case report forms and, where available, analysis of the RCB class was performed. Calculation of RCB provides a standardized procedure for pathologic evaluation of post-neoadjuvant specimens. Educational materials with detailed instructions and an online calculator to determine RCB are posted on a publically available website [15, 16]. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines.

Statistical Considerations

Pathologic response rates were summarized with binomial estimates and 95% confidence intervals (CIs). Comparisons of categorical baseline variables were made among groups with a chi-square test and with a t-test or ANOVA as appropriate for continuous variables. BCSS and OS were measured from the time of surgery and estimated with a Kaplan-Meier estimator. BCSS events were defined as deaths due to breast cancer. Patients were censored if they died from another cause or if they were alive at the time of analysis. Overall survival events were defined as death due to any cause and patients who were alive at the time of analysis were censored. Univariable and multivariable Cox models were used to generate hazard ratios with 95% confidence intervals (CIs). The multivariable model was adjusted for known prognostic variables. Statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chair following Alliance policies. The database used for these analyses was locked October 5, 2016. The trial was registered on clinicaltrials.gov with trial identifier NCT00881361.

Results

Of 756 women enrolled on the ACOSOG Z1071 trial, 701 patients met eligibility criteria. Median follow-up was 4.1 years (range 0.4–6.5). Patient and tumor characteristics are

summarized in Table 1. As reported previously, [17] pCR rate varied by approximated tumor subtype, being highest in HER2-positive disease and lowest in HR-positive/HER2-negative disease. All 204 patients with HER2-positive disease were treated with a regimen that included chemotherapy and HER2-targeted therapy. Among the 442 patients with HR-positive disease (regardless of HER2 status), 369 (92.5%) received endocrine therapy in the adjuvant setting.

At the time of analysis, 107 patients had died, 90 of breast cancer and 17 from other causes. The five-year BCSS was 83.4% (95% CI: 79.2 to 86.8) and five-year OS was 80.5% (95% CI: 76.1 to 84.2). Univariable and multivariable analyses showing factors impacting BCSS and OS are shown in table 2. On univariable analysis, approximated tumor subtype was associated with BCSS and OS ($p<0.0001$); patients with HER2-positive disease had the best BCSS and OS followed by those with HR-positive, HER2-negative disease. The worst BCSS and OS were observed in TNBC patients. Response in the breast and the nodes to neoadjuvant chemotherapy was strongly associated with BCSS ($p<0.0001$) and OS ($p<0.0001$); increasing pathologic tumor category at surgery and increasing pathologic nodal category at surgery were both strongly associated with reduced BCSS and OS. Clinical tumor category at presentation, use of adjuvant radiation, and type of primary tumor surgery were not statistically significantly associated with BCSS or OS. On multivariable analysis, which included clinical tumor category, approximated tumor subtype, pathologic tumor category, pathologic nodal category, surgical procedure, and use of adjuvant radiation in the model, the statistically significant factors for BCSS and OS were approximated tumor subtype and pathologic nodal category and for OS pathologic tumor category was also significant.

Approximated tumor subtype

We further evaluated the association of BCSS and OS with approximated tumor subtype. BCSS was best in patients with HER2-positive tumors, with a five-year BCSS of 95.8% (95% CI: 87.7 to 98.6), followed by patients with HR-positive/HER2-negative disease who had five-year BCSS of 80.4% (95% CI: 73.2 to 85.9). Patients with TNBC had a five-year BCSS of 74.8% (95% CI: 66.6 to 81.2). The observed differences in BCSS among the approximated subtypes were statistically significant ($p<0.0001$).

Similarly, statistically significant differences were observed in OS ($p<0.0001$), with the highest five-year OS observed in patients with HER2-positive tumors at 93.5% (95% CI: 86.2 to 97.0), followed by HR-positive/HER2-negative disease with five-year OS of 76.6% (95% CI: 69.0 to 82.6). The lowest five-year OS was observed in patients with triple negative disease at 73.1% (95% CI: 64.9 to 79.6).

Dividing the patients with HER2-positive tumors into HER2-positive/HR-positive and HER2-positive/HR-negative, the rate of pCR was significantly higher in HER2-positive/HR-negative disease at 53.6% compared with HER2-positive/HR-positive disease where the pCR rate was 39.2% ($p=0.042$), however, there was no difference in 5-year OS between HER2-positive/HR-negative at 95.6% (95% CI: 81.7 to 99.0) and HER2-positive/HR-positive at 92.1% (95% CI: 80.7 to 96.9, $p=0.56$). Similarly, there was no difference in 5-

year BCSS between HER2-positive/HR-negative at 95.6% (95% CI: 81.7 to 99.0) and HER2-positive/HR-positive at 95.8% (95% CI: 80.8 to 99.1, $p=0.68$).

Pathologic response

BCSS and OS were highest in patients with pCR compared to those with residual disease (Figure 1A; $p<0.0001$ and $p<0.0001$, respectively). The five-year BCSS was best in patients who experienced a pCR (94.7%; 95% CI: 89.2 to 97.4), followed by patients with residual disease in the breast only (eradication of nodal disease) (93.7%; 95% CI: 85.3 to 97.3) and those with residual disease in the lymph nodes only (eradication of disease in the breast) (92.2%; 95% CI: 70.5 to 98.1). The worst BCSS was observed in patients with residual disease in both the breast and lymph nodes (74.8%; 95% CI: 68.0 to 80.3).

In the subset of 532 patients where the RCB class was available, RCB class was associated with BCSS and OS (both $p<0.0001$, Figure 1B). RCB-III had significantly poorer survival compared with RCB 0/I/II; for OS, the hazard ratio for RCB-III (vs 0/I/II) was 5.22 (3.32, 8.21), $p<0.0001$ and for BCSS, the hazard ratio for RCB-III (vs 0/I/II) was 4.95 (3.03, 8.07), $p<0.0001$.

Impact of pathologic response by approximated subtype

As previously reported, pCR rates varied by approximated tumor subtype. Patients with HER2-positive disease had the highest pCR rate (45.1%), followed by TNBC (42.0%). HR-positive/HER2-negative disease had the lowest pCR rate (11.5%), $p<0.0001$.

Comparing all patients who achieved a pCR, five-year BCSS was high, with rates of 100% for HR-positive/HER2-negative disease and 96.0% (95% CI: 83.6 to 99.1) for HER2-positive, however was lower at 89.8% (95% CI: 78.8 to 95.3) for TNBC ($p=0.018$). There was no statistically significant difference in OS between the approximated subtypes in patients with a pCR ($p=0.086$, table 3). In patients with residual disease after chemotherapy, five-year BCSS was significantly higher in patients with HER2-positive disease at 95.8% (95% CI: 81.4 to 99.1) compared to patients with HR-positive/HER2-negative disease at 78.3% (95% CI: 70.4 to 84.3) and those with TNBC at 65.8% (95% CI: 54.5 to 74.9). These differences were statistically significant, ($p<0.0001$). Similar patterns of OS by approximated tumor subtype was seen in patients with residual disease ($p<0.0001$).

An evaluation of the impact of pCR on BCSS by approximated tumor subtype yielded a significant difference in patients with TNBC ($n=174$) between those with a pCR, with a five-year BCSS of 89.8% (95% CI: 78.8 to 95.3) compared to those with residual disease, with five-year BCSS of 65.8% (95% CI: 54.5 to 74.9), $p=0.0013$ (Figure 2). In the 204 patients with HER2-positive disease, there was no statistically significant difference in BCSS between those patients that achieved a pCR, with 96.0% (95% CI: 83.6 to 99.1) five-year BCSS; compared to those with residual disease, with 95.8% (95% CI: 81.4 to 99.1) five-year BCSS, $p=0.77$. In the 323 patients with HR-positive/HER2-negative breast cancer, the proportion of patients achieving a pCR was low (11.5%), and there were no BCSS events seen in the patients with a pCR. The five-year BCSS rate of patients with residual disease was 78.3% (95% CI: 70.4 to 84.3). In patients with HR-positive/HER2-negative disease, the five-year OS rates were 97.1% (95% CI 80.9 to 99.6) in patients with a pCR and 74.4%

(95% CI 66.2 to 80.9) in patients with residual disease ($p=0.033$). BCSS and OS by RCB class for each approximated tumor subtype is shown in Figure 3. As RCB class increases, BCSS and OS decrease in HR-positive/HER2-negative and TNBC.

Discussion

In this prospective clinical trial of biopsy-proven node-positive breast cancer patients treated with neoadjuvant chemotherapy, we have confirmed that BCSS and OS were associated with approximated tumor subtype and response to chemotherapy. The highest five-year survival rates were seen in the patients with HR-positive/HER2-negative disease who achieved a pCR, although this was a small group of patients and HR-positive tumors are known to have a longer time to relapse. Five-year BCSS was >95% in patients with HER2-positive disease treated with HER2-targeted therapy, regardless of extent of residual disease after neoadjuvant chemotherapy. The poorest survival was seen in TNBC patients with residual disease. Pathologic complete response was a strong indicator of outcome in TNBC and HR-positive/HER2-negative disease.

Assessment of pCR is valuable information for estimating survival as patients with pCR have improved survival compared with those patients with residual disease. This finding has been consistent across studies that have documented that disease response correlates with survival. [7, 13, 18–20] Previous studies, however, have shown that dichotomous distinction of pCR and residual disease is a suboptimal prognostic surrogate. Evaluation of location of residual disease showed that residual disease in the nodes was associated with a worse prognosis compared with residual disease in the breast alone. The greatest difference was seen between those with residual disease in either the breast or nodes only compared to those patients with residual disease in both the breast and nodes. Estimation of extent of disease by Residual Cancer Burden has been proposed as an informative method for assessment of extent of residual disease after neoadjuvant chemotherapy, since RCB class has been shown to correlate with survival. [15, 21–23] As demonstrated in our data, and in keeping with previous reports, the RCB class provides additional discrimination, in particular to identify those patients with the poorest outcome, as identified by RCB class III. RCB-III is a group of patients at significantly higher risk of relapse and identifies a patient group which may benefit from further systemic therapy and an area to focus additional research. The impact of additional systemic therapy in patients with high volume residual disease remains an area under investigation and data from prospective trials are needed to address this question. One prospective randomized study in patients with HER2-negative breast cancer with residual disease after neoadjuvant chemotherapy showed that adjuvant capecitabine resulted in a better recurrence-free survival. [24] The survival curves for RCB-I and II did not demonstrate significant separation in the Z1071 cohort. It may be that longer follow-up is needed in order to demonstrate differences between these RCB classes.

TNBC is known to be an aggressive subtype of breast cancer, with poor outcomes compared to other tumor subtypes. [25] This is likely due to the heterogeneity of the disease and the lack of availability of targeted therapy for this subtype. Consistent with other studies, we found that patients with TNBC that achieved a pCR had a significantly better BCSS and OS compared with those with residual disease. [26] In fact, patients with TNBC who

experienced a pCR had 5-year BCSS and OS in keeping with the other tumor subtypes. It is reassuring that such patients with “chemosensitive” TNBC, have an excellent outcome, such that additional systemic therapy may not be necessary. This highlights one of the advantages of delivery of chemotherapy in the neoadjuvant setting, as it provides outcome information to the treating physicians and patients early in the course of treatment and can be an opportunity to tailor treatment recommendations based on response. Patients with chemotherapy-resistant TNBC are at the highest risk of recurrence and death due to breast cancer and therefore multiple studies are evaluating the role of additional systemic therapy in these patients. One such study is SWOG 1418 which is randomizing patients with TNBC who have residual disease after neoadjuvant chemotherapy to pembrolizumab versus no additional therapy. [27]

HER2-positive breast cancer is a biologically aggressive subtype of breast cancer and early studies demonstrated poor survival in these patients. However, as understanding of HER2-positive disease advanced and HER2-targeted therapies are now routinely administered, the survival rates have dramatically improved. Studies have shown that the use of HER2-targeted therapy, in addition to chemotherapy, in the neoadjuvant setting resulted in high rates of pathologic complete response [8, 9, 28–33]. During the time that the ACOSOG Z1071 trial was conducted, patients with HER2-positive disease treated in the neoadjuvant setting routinely received chemotherapy and trastuzumab. Currently, treatment for HER2-positive breast cancer in the neoadjuvant setting can include more than one HER2-targeted agent in addition to chemotherapy (trastuzumab and pertuzumab) and results in even higher pCR rates. [10, 12, 31, 34].

The pCR rate observed in patients with HER2-positive disease in Z1071 was 45%. Interestingly, the five-year OS and BCSS were not impacted by the presence of residual disease in this cohort of patients. A prior small study that included 53 patients with HER2-positive disease demonstrated favorable locoregional recurrence rates regardless of response to neoadjuvant chemotherapy. [26] The findings from this study and the current study are in contrast to multiple previous studies which have shown that in patients with HER2-positive disease pCR is associated with improved survival compared to those with residual disease. [7, 11, 13, 33, 35] A meta-analysis of studies by Cortazar et al. which included 1989 patients with HER2-positive disease showed a significant difference in event-free survival between the 586 patients who achieved a pCR and the 1403 patients with residual disease. [7] The finding that there was no difference in survival outcomes in Z1071 in the HER2-positive patients with or without pCR may be due to the relatively small sample size and the relatively short follow-up time. With the addition of pertuzumab, and possibly other HER2-targeted agents in the future, outcomes for patients with HER2-positive disease may continue to improve. Current clinical trials are addressing the role of HER2-targeted therapies without chemotherapy.

Hormone receptor-positive/HER2-negative breast cancer is considered a less aggressive subtype and breast cancer recurrences often occur much later in the course of the disease, with risk of recurrence remaining elevated beyond 10 years. [36] The presence of a target (estrogen receptor) for adjuvant systemic therapy along with the availability of endocrine therapy that is reasonably well tolerated has led to lower rates of breast cancer events in this

patient population. Rates of pCR in the patients with HR-positive/HER2-negative disease were low at 11.5%. This is consistent with other studies that have previously shown lower pCR rates in HR-positive disease. [7, 13, 37] Additionally, the number of breast cancer recurrences or deaths in the patients who achieved a pCR was so small that statistical comparison of the impact of pCR on outcome was limited. Since these patients are treated with adjuvant endocrine therapy for 5 years and in some instances 10 years after surgery, they remain at risk for future breast cancer events for over 10 years. [36] One limitation of the Z1071 trial is that luminal A tumors could not be distinguished from luminal B tumors based on the available information.

In HR-positive/HER2-negative disease, alternative strategies for treatment are being explored and utilized in the clinical practice, in particular the use of neoadjuvant endocrine therapy to assess the endocrine responsiveness of the tumor. Patients with an excellent response to neoadjuvant endocrine therapy may be candidates to avoid chemotherapy.[38] Additionally, prognostic indicators such as the 21-gene recurrence score are being used in patients with ER-positive disease, both in node-negative and in some cases in node-positive patients, to evaluate the potential benefit from chemotherapy. In node-positive patients with ER-positive disease, use of the 21-gene recurrence score assay is based mainly on retrospective data. Data from the prospective trial (RxPONDER trial) is awaited. [39] In one retrospective study, use of the 21-gene recurrence score in node-positive disease was shown to decrease the rate of recommendation for adjuvant chemotherapy from 81% to 50%. [40] The West German Plan B prospective trial showed excellent 3-year survival of patients with a recurrence score ≥ 11 treated without chemotherapy and included patients with node-positive disease. [41]

One of the major limitations of this study is that the patients enrolled in Z1071 were a heterogeneous cohort and were not selected based on tumor subtype. There was no standardized chemotherapy regimen recommended and although RCB reporting was recommended in the protocol it was not completed in a significant proportion (24%) of patients. The follow-up time is relatively short with an average follow-up of four years at the time of this report and additional follow-up is awaited. Additionally, the tumor subtyping is based on approximated subtype using receptor status reported from the local pathology laboratory and not based on central pathology review or molecular analysis of the individual tumors. A large proportion of patients enrolled had HR-positive/HER2-negative disease and practice patterns have shifted toward more use of endocrine therapy in these patients and less chemotherapy. Since HR-positive/HER2-negative tumors have lower pCR rates and longer time to recurrence, the high proportion of these patients in the study limits the interpretation of impact of RCB. We did observe higher rates of RCB-III than previously reported, raising the possibility of over-estimation; however this may be attributable to the fact that all patients enrolled in Z1071 were clinically node-positive at time of diagnosis.

In summary, neoadjuvant chemotherapy is effective at achieving pCR in a substantial proportion of patients with HER2-positive and TNBC. For HER2-positive disease treated with chemotherapy and HER2-targeted therapy, 5-year BCSS and OS are excellent, regardless of response to therapy. For patients with chemotherapy-resistant TNBC, with

residual disease after neoadjuvant chemotherapy, alternative strategies should and are being explored to improve patient outcome.

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Figure 1. Breast Cancer-Specific Survival and Overall Survival by: A) Pathologic complete response (pCR) versus any residual disease, and B) Residual Cancer Burden Class (n=532).

Figure 2. Breast Cancer-Specific Survival and Overall Survival comparing patients with a pathologic complete response (pCR) to those with residual disease in triple-negative breast cancer, HER2-positive breast cancer, and Hormone Receptor (HR)-positive/HER2-negative breast cancer.

Figure 3.
Breast Cancer-Specific Survival and Overall Survival by Residual Cancer Burden class (n=532) in triple-negative breast cancer, HER2-positive breast cancer, and Hormone Receptor (HR)-positive/HER2-negative breast cancer.

Table 1

Patient and tumor characteristics overall and by approximated tumor subtype of the eligible patients on ACOSOG Z1071 (Alliance)

Characteristic	All Patients (n = 701)	Triple-Negative (n = 174)	HER2-Positive (n = 204)	Hormone-Receptor-Positive, HER2-Negative (n = 323)	P Value
Patient age, years					0.22
<50	349 (50.2)	78 (45.1)	101 (49.8)	170 (53.3)	
50	346 (49.8)	95 (54.9)	102 (50.3)	149 (46.7)	
Unknown	6	1	1	4	
Clinical Tumor category at presentation					0.28
T0	9 (1.3)	3 (1.7)	4 (2.0)	2 (0.6)	
Tis	1 (0.1)	0	1 (0.5)	0	
T1	92 (13.1)	25 (14.4)	22 (10.8)	45 (14.0)	
T2	384 (54.9)	103 (59.2)	104 (51.0)	177 (55.0)	
T3	181 (25.9)	37 (21.3)	64 (31.4)	80 (24.8)	
T4	33 (4.7)	6 (3.4)	9 (4.4)	18 (5.6)	
Unknown	1	0	0	1	
Clinical Nodal category at presentation					0.57
N1	657 (94.4)	161 (93.1)	191 (94.1)	305 (95.3)	
N2	39 (5.6)	12 (6.9)	12 (5.9)	15 (4.7)	
Unknown	5	1	1	3	
Histologic Type					<0.0001
IDC	630 (89.9)	165 (94.8)	191 (93.6)	274 (84.8)	1
ILC	39 (5.6)	4 (2.4)	5 (2.4)	30 (9.3)	
IMC	26 (3.7)	3 (1.7)	4 (2.0)	19 (5.9)	
Other	6 (0.9)	2 (1.2)	4 (2.0)	0	
Pathologic Tumor category at surgery					<0.0001
T0/Tis	235 (33.8)	82 (47.6)	103 (51.0)	50 (15.5)	
T1	251 (36.1)	51 (29.6)	63 (31.2)	137 (42.6)	
T2	149 (21.4)	32 (18.6)	31 (15.4)	86 (26.7)	
T3	58 (8.3)	6 (3.5)	5 (2.5)	47 (14.6)	
T4	3 (0.4)	1 (0.6)	0	2 (0.6)	

Characteristic	All Patients (n = 701)	Triple-Negative (n = 174)	HER2-Positive (n = 204)	Hormone-Receptor-Positive, HER2-Negative (n = 323)	P Value
T3	5	2	2	1	
T4					
Unknown					
Pathologic Nodal category at surgery					<0.0001
N0	289 (41.3)	85 (48.8)	136 (66.7)	68 (21.1)	
N1	241 (34.4)	56 (32.2)	52 (25.5)	133 (41.3)	
N2	130 (18.6)	27 (15.5)	14 (6.9)	89 (27.6)	
N3	40 (5.7)	6 (3.4)	2 (1.0)	32 (9.9)	
Unknown	1	0	0	1	
pCR status					<0.0001
pCR both breast and axilla	195 (27.8)	66 (42.0)	92 (45.1)	37 (11.5)	
pCR breast only	40 (5.7)	16 (9.2)	11 (5.4)	13 (4.0)	
pCR axilla only	92 (13.1)	19 (10.9)	42 (20.6)	31 (9.6)	
no pCR	374 (53.4)	73 (42.0)	59 (28.9)	242 (74.9)	
Residual Cancer Burden class					<0.0001
0	195 (36.6)	66 (45.8)	92 (59.0)	37 (15.9)	
I	33 (6.2)	9 (6.2)	12 (7.7)	12 (5.2)	
II	146 (27.4)	32 (22.2)	29 (18.6)	85 (36.5)	
III	159 (29.8)	37 (25.7)	23 (14.7)	99 (42.5)	
Unknown	168	30	48	90	

Abbreviations: pCR = Pathologic complete response.

Evaluation of clinical and pathological variables on five-year breast cancer-specific survival and overall survival by univariable and multivariable analysis

Table 2

Variable	Breast Cancer-Specific Survival				Overall Survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Clinical Tumor category								
T0–T2	1.00 (ref)	0.093	1.00 (ref)	0.31	1.00 (ref)	0.045	1.00 (ref)	0.34
T3–T4	1.44 (0.94–2.22)		1.28 (0.79–2.09)		1.49 (1.00–2.21)		1.24 (0.79–1.96)	
Approximated Tumor biology								
HR-positive/HER2-negative	1.00 (ref)	<0.0001	1.00 (ref)		1.00 (ref)	<0.0001	1.00 (ref)	<0.0001
HER2 positive	0.13 (0.05–0.37)		0.25 (0.09–0.72)	<0.0001	0.28 (0.14–0.55)		0.56 (0.28–1.14)	
Triple negative	1.82 (1.19–2.80)		3.32 (2.07–5.32)		1.68 (1.12–2.52)		3.13 (1.99–4.92)	
Pathologic Tumor category								
T0/Tis	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
T1	2.96 (1.45–6.01)	<0.0001	2.40 (1.07–5.41)	0.069	2.56 (1.36–4.83)	<0.0001	2.16 (1.05–4.47)	0.044
T2	5.26 (2.59–10.67)		3.61 (1.52–8.57)		4.53 (2.41–8.52)		3.30 (1.52–7.16)	
T3	6.36 (2.78–14.51)		3.03 (1.04–8.82)		6.46 (3.14–13.33)		3.20 (1.24–8.30)	
T4	—		—		4.87 (0.63–37.48)		2.11 (0.23–19.30)	
Pathologic Nodal category								
N0	1.00 (ref)	<0.0001	1.00 (ref)	0.007	1.00 (ref)	<0.0001	1.00 (ref)	0.0011
N1	2.48 (1.34–4.60)		1.54 (0.76–3.12)		2.28 (1.30–3.97)		1.51 (0.79–2.87)	
N2	4.60 (2.46–8.57)		2.38 (1.11–5.14)		4.04 (2.29–7.12)		2.25 (1.11–4.57)	
N3	7.36 (3.55–15.25)		4.21 (1.72–10.31)		7.93 (4.20–14.97)		4.56 (2.03–10.27)	
pCR								
Residual disease	1.00 (ref)	<0.0001			1.00 (ref)	<0.0001		
pCR	0.26 (0.12–0.53)				0.30 (0.16–0.56)			
Surgery Performed								
BCS	1.00 (ref)	0.26	1.00 (ref)	0.80	1.00 (ref)	0.15	1.00 (ref)	0.80

Variable	Breast Cancer-Specific Survival				Overall Survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Mastectomy	1.29 (0.83–1.99)		1.06 (0.67–1.70)		1.34 (0.90–2.00)		1.06 (0.68–1.63)	
Radiation								
Yes	1.00 (ref)	0.96	1.00 (ref)	0.20	1.00 (ref)	0.94	1.00 (ref)	0.21
No	0.98 (0.55–1.77)		1.46 (0.82–2.61)		1.02 (0.60–1.74)		1.41 (0.82–2.42)	
Residual Cancer Burden class								
0	1.00 (ref)	<0.0001			1.00 (ref)	<0.0001		
I	2.17 (0.58–8.18)				1.56 (0.44–5.60)			
II	2.13 (0.89–5.08)				1.63 (0.75–3.56)			
III	7.75 (3.65–16.44)				6.85 (3.58–13.10)			

Abbreviations: pCR = Pathologic complete response; BCS= breast conserving surgery; RCB=Residual cancer burden.

Breast Cancer-Specific Survival (BCSS) and Overall survival (OS) by approximated clinical tumor subtype and pathologic response

Table 3

	pCR			Residual Disease		
	HR pos/HER2 neg	HER2 positive	Triple negative	HR pos/HER2 neg	HER2 positive	Triple negative
BCSS						
HR	1.00	—	—	1.00	0.11	2.35
95% CI	ref	—	—	ref	0.03 – 0.44	1.50 – 3.68
5 yr	100%	96.0%	89.8%	78.3%	95.8%	65.8%
p value	0.018			<0.0001		
OS						
HR	1.00	1.14	4.02	1.00	0.32	2.18
95% CI	ref	0.12 – 10.96	0.50 – 32.71	ref	0.15 – 0.71	1.42 – 3.34
5 yr	97.1%	94.6%	87.8%	74.4%	92.8%	64.4%
p value	0.086			<0.0001		

Abbreviations: pCR = Pathologic complete response.