Does Tumor Size Predict Response to Neoadjuvant Chemotherapy in the Modern Era of Biologically Driven Treatment? A Nationwide Study of US Breast Cancer Patients

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Abstract

The effect of tumor size on response to neoadjuvant chemotherapy in patients with stage I to III breast cancer remains an open question. In this national study, tumor size was shown to be an independent predictor of complete pathologic response in patients with invasive breast cancer. However, cancer biology has a greater effect than tumor size.

Background: Tumor size has historically been used to stage breast cancer and guide treatment recommendations. The importance of tumor biology in long-term outcomes is increasingly being acknowledged. No large studies have examined the relative roles of tumor size and receptor status on response to neoadjuvant chemotherapy (NAC) in breast cancer. **Patients and Methods:** The National Cancer Database was queried for women who underwent NAC and surgery for unilateral clinical stage I to III (cT1-3) invasive breast cancer from 2010 to 2013. Multivariable logistic regression models were used to assess the relation between receptor status, tumor size, and pathologic complete response (pCR) while controlling for other biologic, sociodemographic, diagnosis, and treatment factors. **Results:** We included 38,864 women in this study, most presented with cT2 disease (55%). Patients predominantly had estrogen receptor (ER)/progesterone receptor (PR)-positive (ER/PR$^+$) HER2$^-$ (45%) or ER/PR$^-$ HER2$^-$ (28%) disease. Nineteen percent (7432 patients) had a pCR. cT3 (odds ratio [OR], 0.64; 95% confidence interval [CI], 0.59-0.70) but not cT2 cancers (OR, 0.95; 95% CI, 0.89-1.02) were associated with lower pCR rates compared with cT1 disease. HER2$^+$ (ER/PR$^+$ HER2$^+$: OR, 2.94; 95% CI, 2.72-3.18; ER/PR$^-$ HER2$^+$: OR, 6.45; 95% CI, 5.92-7.02) and ER/PR$^-$ HER2$^-$ cancers (OR, 3.94; 95% CI, 3.68-4.22) were more likely to experience pCR than those with ER/PR$^+$ HER2$^-$ cancers. Receptor status was more strongly associated with pCR than tumor size. **Conclusion:** Tumor size is independently associated with pCR after NAC after controlling for receptor status, although the effect of receptor status is stronger. These data reinforce the importance of receptor status as well as tumor size, each of which might act as surrogates for tumor biology, in setting expectations for outcomes in patients who undergo NAC.

Clinical Breast Cancer, Vol. 19, No. 6, e741-7
Keywords: Complete pathologic response, NAC, National Cancer Database, NCDB, TNM staging

Introduction

Neoadjuvant chemotherapy (NAC) has increasingly become a first-line treatment choice for some patients with node-positive breast cancer as well as for individuals with HER2/*neu*-positive and estrogen receptor (ER) and progesterone receptor (PR)-negative (PR$^-$) malignancies.[1] The benefits of NAC to the patient include

This work was presented, in part, at the 2018 American Society of Breast Surgeons conference in Orlando, Florida.

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Submitted: Apr 5, 2019; Revised: Apr 29, 2019; Accepted: May 27, 2019; Epub: Jun 6, 2019

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1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2019.05.014

acting as an in vivo test of the tumor's susceptibility to systemic therapies, which is highly prognostic and strongly associated with survival.[2,3] Additionally, NAC might increase the ability to perform breast conservation and less extensive axillary surgery.[4] Finally, patients with residual disease after NAC might have the opportunity to either enroll in clinical trials for novel adjuvant therapies or receive evidence-based additional adjuvant therapies.[5,6]

The most recent consensus guidelines on NAC state that age, tumor size, nodal status, Grade, proliferation, ER, PR, and HER2 status all influence the likelihood of a complete pathologic response (pCR) after NAC.[1] Tumor receptors (ER, PR, and HER2) are currently the best indicators of the biologic function of invasive breast cancer. When NAC is administered, less than 20% of ER^+ or PR^+ $HER2^-$ cancers experience a pCR, in contrast to upward of 30% to 40% of patients with triple-negative cancers and 20% to 50% of $HER2^+$ cancers regardless of ER or PR status.[3,7,8]

Although tumor size is often considered when selecting patients for NAC, it is less clear how tumor size affects the likelihood of pCR after tumor receptors are considered. Recent studies have provided conflicting results. Baron et al[9] reported no contribution of tumor size when tumor biology was controlled for in a subset of the Neoadjuvant Breast Symphony Trial, whereas Goorts et al[10] reported a difference between these 2 tumor characteristics in their multivariable analysis of data from the Netherlands cancer registry. When clinicians discuss the potential for a pCR with their patients they often refer more to the biologic or receptor subtype rather than size,[11] yet there are no data on a direct comparison of the relative contributions of tumor size and receptor status to pCR. We sought to evaluate whether tumor size was independently associated with pCR after NAC after controlling for receptor status, using the National Cancer Database (NCDB).[12] On the basis of the importance of breast cancer biology and the associated response to chemotherapeutic agents we hypothesized that the underlying tumor biology (ER, PR, HER2 status) would have the strongest association with pCR in patients who undergo NAC, but that tumor size would still be an independent predictor.

Patients and Methods

The NCDB is a hospital-based cancer registry that is estimated to capture approximately 70% of all malignancies diagnosed in the United States.[12,13] All patient information in the participant user file is deidentified and was exempt from institutional review board review.

Study Population

The patient population included women 18 years of age or older with clinical stage I to III unilateral breast cancer who were diagnosed in 2010 to 2013 and underwent NAC with subsequent surgical excision of the breast excluding excisional breast biopsy (n = 64,252). This timeframe was selected to ensure consistent reporting of HER2 status and represents a time period when patients were most likely to have received guideline-recommended HER2-targeted therapy. The NCDB therapy timing variable that includes NAC treatment relies on the planned treatment and not what the patient actually received. To ensure women in this study received chemotherapy before surgery we defined NAC as patients who were coded as receiving chemotherapy before undergoing surgical excision. We further restricted the study cohort to the subgroup of women who were most likely to have completed their NAC regimen, by only including women with 75 to 252 days between starting NAC and undergoing surgical excision (n = 59,568). This lower limit was selected on the basis of the minimum amount of time to complete NAC (cyclophosphamide every 14 days for 4 cycles[14]) and schedule surgery (14 days). The upper limit was determined by the 95th percentile of NAC timing for women in the cohort. We also excluded women missing clinical T and N stage, pathologic T stage, and ER, PR, and HER2/*neu* status as well as women with cT4 disease because the T4 designation does not include any indication as to tumor size. The final sample size was 38,864.

The primary outcome variable was pCR after NAC. Patients with a pCR were defined as no identifiable tumor in the breast (ypT0). Patients with residual in situ disease were classified as not experiencing a pCR. Nodal response was not included in the definition of pCR used in this study. The primary predictor variables were receptor status and tumor size. ER/PR and HER2 receptor statuses were combined into 1 categorical variable with 4 groups: ER/PR^+ $HER2^-$, ER/PR^+ $HER2^+$, ER/PR^- $HER2^-$ (triple negative), and ER/PR^- $HER2^+$.[15] Tumor size was approximated using clinical T stage. Control variables associated with tumor size, receptor status, or pCR included age, race (white, nonwhite, and unknown), ethnicity (Hispanic and non-Hispanic), insurance, facility type for reporting (community, academic, cancer center, integrated center, or unknown), Charlson (comorbidity) index (categorized as 0, 1, $\geq$2), income, education, and clinical nodal stage as a dichotomous variable (positive/negative).

Analysis

Descriptive statistics were used to assess sociodemographic, diagnosis, and treatment characteristics overall. Multivariable logistic regression was used to assess the relation between clinical tumor stage and pCR after NAC controlling for receptor status. Additional models that stratified patients according to receptor status were also constructed. Control variables in the model included age, race, ethnicity, insurance, facility type, Charlson (comorbidity) index, income, education, and clinical nodal stage. Odds ratios (ORs), *P* values, 95% confidence intervals (CIs), and pseudo-R^2 values were calculated for each model. In addition, a model was estimated that included the interaction between tumor size and receptor status. To determine the comparative effect of tumor size and receptor status the percent change in logistic regression pseudo-R^2 (% ΔR^2) was calculated. This was performed by calculating the pseudo-R^2 for the model including all covariates (R^2_{tot}), and then repeating the pseudo-R^2 calculation for each of 3 different models that excluded either cT stage or receptor status individually or the 2 variables in combination. The % ΔR^2 was then calculated using the formula: $(R^2_{tot} - R^2_x)/R^2_{tot}$ where R^2_x is the pseudo-R^2 value for the model excluding the variable of interest.[16] Relative contributions of tumor size and receptor status were evaluated by comparing the calculated % ΔR^2 for the model with both variables excluded and models lacking the variables individually. All statistics were performed using STATA 14.0 (StataCorp LP, College Station, TX).

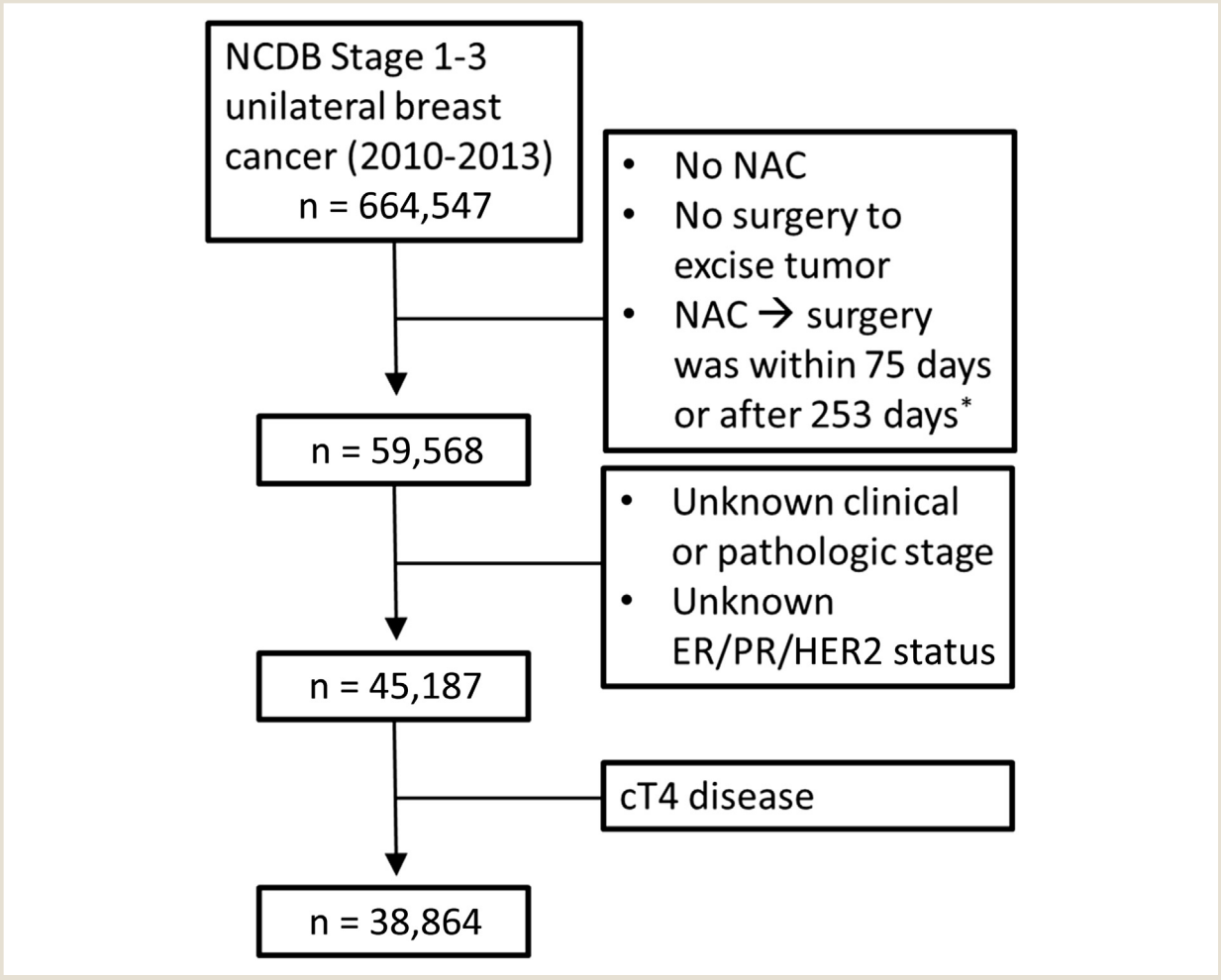
Results

The Consolidated Standards of Reporting Trials diagram for included patients who received NAC for stage I to III invasive breast cancer before definitive surgery is presented in Figure 1. We identified 38,864 individuals within the NCDB who fit our inclusion criteria (Table 1). The average age of these women was 52 years old and most were non-Hispanic and white with private insurance. More than half of these women had cT2 tumors (2-5 cm) and a slight majority had nodal disease before NAC. Approximately 63% of breast cancers in this cohort were ER/PR$^+$ and 28% were triple-negative. Within the total cohort the pCR rate was 19% after NAC. The pCR rate for women with cT1 and cT2 disease was 20% and 21%, respectively, whereas it was 15% for tumors >5 cm. Nine percent of women with ER/PR$^+$ HER2$^-$ cancers experienced pCR compared with 22% for ER/PR$^+$ HER2$^+$, 27% for triple-negative, and 38% for ER/PR$^-$ HER2$^+$. Surgery type was stratified according to cT stage and is presented in Table 2. Women with cT3 tumors underwent the lowest percentage of breast conserving surgery (22% vs. 38% for cT1 and 44% for cT2).

Tumors >5 cm were independently associated with a decrease in likelihood of pCR after NAC (OR, 0.64; 95% CI, 0.59-0.70) in our multivariable analysis (Table 3). Receptor status was also strongly associated with likelihood of pCR with ORs of 2.94 (95% CI, 2.72-3.18), 3.94 (95% CI, 3.68-4.22), and 6.45 (95% CI, 5.92-7.02) for ER/PR$^+$ HER2$^+$, triple-negative, and ER/PR$^-$ HER2$^+$ cancers, respectively. Clinical stage III tumors, >5 cm were associated with decreased likelihood of pCR with ORs of 0.52 (95% CI, 0.44-0.62) for ER/PR$^+$ HER2$^-$, 0.68 (95% CI, 0.57-0.82) for ER/PR$^+$ HER2$^+$, 0.67 (95% CI, 0.58-0.77) for triple-negative, and 0.75 (95% CI, 0.61-0.92) for ER/PR$^-$ HER2$^+$ disease.

The relative contributions of cT stage and receptor status to pCR are shown in Table 4. Receptor status had the largest effect on pCR as evidenced by a % ΔR^2 of 88.7% compared with cT stage

Figure 1 Consolidated Standards of Reporting Trials Diagram of Study Criteria. * To Enrich for Patients Who Completed a Full Course of NAC: on the Basis of Minimum Time to Complete NAC (75 Days) and 95th Percentile of NAC to Surgery Time in the Cohort (253 Days)



Abbreviations: ER = estrogen receptor; NAC = neoadjuvant chemotherapy; NCDB = National Cancer Database; PR = progesterone receptor.

Table 1 Patient Demographic Characteristics

Characteristic	All (n = 38,864), n (%)	pCR (n = 7432), n (% of All)
cT Stage		
1	7958 (21)	1631 (20)
2	21,406 (55)	4393 (21)
3	9500 (24)	1408 (15)
Receptor Status		
ER/PR$^+$ HER2$^-$	17,424 (45)	1519 (9)
ER/PR$^+$ HER2$^+$	6871 (18)	1537 (22)
ER/PR$^-$ HER2$^-$	10,756 (28)	2934 (27)
ER/PR$^-$ HER2$^+$	3813 (10)	1442 (38)
Clinical Nodal Disease		
Absent	16,783 (43)	3086 (18)
Present	22,081 (57)	4346 (20)
Age		
<45	10,819 (28)	2277 (21)
45-55	13,783 (36)	2610 (19)
>55	14,262 (37)	2545 (18)
Race		
White	29,731 (77)	5637 (19)
Nonwhite	8805 (23)	1734 (20)
Unknown	325 (1)	61 (19)
Ethnicity		
Non-Hispanic	36,035 (93)	6885 (19)
Hispanic	2829 (7)	547 (19)
Insurance		
Private	25,889 (67)	5147 (20)
Uninsured	1612 (4)	323 (20)
Medicaid	4649 (12)	820 (18)
Government/Medicare	6257 (16)	1058 (17)
Unknown	457 (1)	84 (18)

Abbreviations: cT = clinical tumor; pCR = pathologic complete response.

(% $\Delta R^2 = 5.1\%$). There was no statistically significant interaction between tumor size and receptor status ($\chi^2 = 8.91$; $P = .18$).

Discussion

This study showed that tumors >5 cm are associated with a lower likelihood of having a pCR after NAC even when accounting for receptor status. Not surprisingly, receptor status had a larger effect on pCR than tumor size. To our knowledge, this is the largest study specifically to examine the role of tumor size in response to NAC performed in the modern era.

Table 2 Definitive Surgery Type and Clinical Tumor Stage

	cT1	cT2	cT3
BCS	3000 (38)	9353 (44)	2041 (21)
Mastectomy	4958 (62)	12,051 (56)	7459 (79)
Unknown	0 (0)	2 (0)	0 (0)

Data are presented as n (%).
Abbreviations: BCS = breast-conserving surgery; cT = clinical tumor.

Two recently published studies on this issue showed conflicting results. When controlling for tumor biology (receptor status and tumor grade), Goorts et al[10] identified cT3/cT4 disease as an independent predictor of decreased pCR likelihood whereas Baron et al[9] reported no association between tumor size and pCR in their multivariable analysis. Neither of these studies compared cT1 with cT2 disease and both used smaller homogenous populations. Goorts et al[10] investigated data from a time period (2005-2008) in which breast cancer treatments, specifically the adoption of HER2-targeted therapies, was inconsistent. This study from the Netherlands also examined ER, PR, and HER2 receptor status as 3 independent variables and reported an association between PR and HER2 status, but not ER status, with pCR; whereas our study combined receptor status into 1 variable and identified an interaction between the composite of ER, PR, and HER2 with pCR. Through analysis of the NCDB we were able to independently compare cT1, cT2, and cT3 stages in a broad range of breast cancer patients from across the United States during the modern era of breast cancer treatment and highlighted that although tumor size has a smaller effect on pCR than receptor status, both were influential.

Recent studies that developed predictive models for axillary pCR after NAC have also evaluated the effect of tumor size on pCR.[17-20] These studies differ from ours in several important features. Their outcome of interest, axillary pCR (ypN0) was different from ours (ypT0). Different definitions of pCR are associated with differences in patient outcomes[21] and in-breast and nodal response rates to NAC differ likely reflecting distinct biological niches within each anatomic location as well as biological heterogeneity.[22] Studies on axillary response to NAC either only included node-positive patients[18-20] or analyzed cN0 patients separately from patients with nodal disease[17] whereas we included patients with and without nodal involvement in our models. Additionally, these studies were not designed to answer the question of whether tumor size affects pCR; they were designed to develop tools to help clinicians predict which patients might not require axillary dissection and using results of individual covariates from these models can fall into the table 2 fallacy.[23] The study presented herein was specifically designed to examine the effect of tumor size on breast pCR after NAC, a question of clinical importance that has not been fully addressed in the literature to date.

Although the intrinsic biology of a breast cancer is perhaps best understood through its receptor status, tumor size might also provide a different or additive window into a cancer's internal biology. Breast cancer screening studies have highlighted the improved outcomes for patients whose cancers are identified at an earlier stage.[24] Although tumor size might simply be a function of a cancer that has been existent in the breast for a longer period of time and therefore less responsive to cytotoxic treatments, it might more importantly provide an understanding of biologic properties that are not reflected in the receptors. A meta-analysis of circulating tumor cells (CTCs) in early stage breast cancer patients who underwent NAC revealed that 25.2% of patients had CTCs before NAC and the presence of CTCs was associated with tumor size but not receptor status.[25] Increasing numbers of CTCs resulted in a decrease in overall survival as well as locoregional relapse-free survival but was not associated with pCR.[25] This highlights the fact that although receptor status is a key component of a cancer's response to therapy

Table 3 Multivariable Logistic Regression Models for Evaluating Clinical Tumor Stage and pCR[a]

	All Patients (n = 38,732)		ER/PR$^+$ HER2$^-$ (n = 17,424)		ER/PR$^+$ HER2$^+$ (n = 6871)		ER/PR$^-$ HER2$^-$ (n = 10,756)		ER/PR$^-$ HER2$^+$ (n = 3813)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
cT Stage										
1	REF	[b]	REF	[b]	REF	[b]	REF	[b]	REF	[b]
2	0.95 (0.89-1.02)		0.89 (0.78-1.01)		0.96 (0.84-1.11)		0.96 (0.86-1.08)		1.02 (0.85-1.21)	
3	0.64 (0.59-0.70)		0.52 (0.44-0.62)		0.68 (0.57-0.82)		0.67 (0.58-0.77)		0.75 (0.61-0.92)	
Receptors										
ER/PR$^+$ HER2$^-$	REF	[b]								
ER/PR$^+$ HER2$^+$	2.94 (2.72-3.18)									
ER/PR$^-$ HER2$^-$	3.94 (3.68-4.22)									
ER/PR$^-$ HER2$^+$	6.45 (5.92-7.02)									
Age										
<45	REF	[b]	REF	[b]	REF	ns	REF	[b]	REF	[c]
45-55	0.89 (0.82-0.97)		0.80 (0.68-0.95)		0.93 (0.78-1.12)		0.91 (0.80-1.05)		0.93 (0.74-1.17)	
>55	0.85 (0.78-0.93)		0.70 (0.58-0.83)		1.05 (0.87-1.28)		0.74 (0.64-0.86)		1.17 (0.93-1.49)	
Clinical Nodal Disease										
No	REF	[b]	REF	[b]	REF	[b]	REF	[b]	REF	[c]
Yes	1.23 (1.16-1.30)		1.20 (1.07-1.34)		1.33 (1.18-1.50)		1.21 (1.10-1.32)		1.19 (1.03-1.37)	

Abbreviations: ER = estrogen receptor; pCR = pathologic complete response; PR = progesterone receptor; REF = reference.
[a]Ethnicity, race, insurance, facility type, education, income, Charlson Comorbidity Index, and geographic location were also included in these models.
[b]$P < .005$.
[c]$P < .05$.

Table 4 Relative Contributions of Staging Variables to pCR After NAC

Baseline Model $R^2 = 0.0780$			
Variable(s) Removed	R^2	ΔR^2	% ΔR^2
cT stage	0.0740	0.0040	5.1%
Receptor status	0.0088	0.0692	88.7%
cT and receptor status	0.0041	0.7390	94.7%

Abbreviations: NAC = neoadjuvant chemotherapy; pCR = pathologic complete response.

it is not the only component that will influence treatment response. Further studies into how a cancer achieves a certain size in its breast microenvironment will assist in the expectations for response to NAC as well as guide future changes in NAC treatment options.

This study has several limitations. The NCDB collects data on whether patients receive chemotherapy, but does not record whether they completed their course or what agents were received. We attempted to enrich our study population with individuals who had completed NAC by ensuring that only patients with at least 75 days between starting NAC and undergoing surgery were included. We were unable to evaluate whether women with $HER2^+$ cancers received trastuzumab because in the NCDB it is classified with other chemotherapy and was not entered as a separate category until 2013. We addressed this potential limitation by including patients diagnosed with breast cancer after 2010 when HER2 status was a required measure in the NCDB and HER2-directed therapies were widely administered. Other limitations to this study resulted from how variables were coded in the NCDB. We were not able to include tumor grade in our analysis because that variable is most commonly taken from the surgical pathology and not the initial biopsy report. Lower tumor grade has been associated with a decrease in pCR after NAC[9] and it is possible that the larger cancers in our study were disproportionately lower grade as well. We were unable to use the continuous variable tumor size and relied on the categorical cT stage for our variable of interest because tumor size in the NCDB is sometimes populated from post-NAC pathologic evaluation and it is not possible to know when that occurred. We were still able to compare tumors <1 cm with those 2 to 5 cm and >5 cm, a more clinically useful comparison than the 5-cm cutoff previously published.[9,10]

Conclusion

This study showed the importance of continuing to incorporate tumor size into the shared decision-making discussion around expected outcomes for NAC in patients with nonmetastatic invasive breast cancer. For patients with smaller tumors that are more responsive to chemotherapy, such as those with triple-negative and $HER2^+$ cancers, a higher likelihood of pCR can be described during decision-making discussions with the patient. Patients with large tumors, however, would benefit from counseling that despite the lower likelihood of a pCR with NAC, this treatment approach offers the opportunity to perform more minimally invasive surgery and the lack of a pCR might or might not reflect a worse long-term outcome.

Clinical Practice Points

- With the growing understanding of the important role tumor receptors and tumor biology play in breast cancer response rates to NAC, the contributions of tumor size to pCR rates remains unknown.
- In this large national study we examined the influence of clinical tumor stage and receptor status on pCR rates and showed that patients with cT3, but not cT2, tumors are less likely to experience pCR whereas hormone and HER2 receptor status have a much larger effect on pCR.
- These data reinforce the importance of receptor status as well as tumor size, each of which might act as surrogates for tumor biology, in setting expectations for outcomes in patients who undergo NAC.
- This study showed the continued importance of incorporating tumor size into the shared decision-making discussion regarding NAC in patients with nonmetastatic invasive breast cancer.

Acknowledgments

The NCDB is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society. The hospitals participating in the NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis of the conclusions derived by the authors. This work was supported by the National Institutes of Health (T32 CA090217 to D.L.-R., T.S.-D., and K.V.W.) and American College of Surgeons (Resident Research Scholarship to D.L.-R.).

Disclosure

L.G.W. is a founder of Elucent Medical. C.C.G. is a consultant for Johnson & Johnson. The remaining authors have stated that they have no conflicts of interest.

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