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ORIGINAL ARTICLE – BREAST ONCOLOGY

How Often Does Modern Neoadjuvant Chemotherapy Downstage Patients to Breast-Conserving Surgery?

Oriana Petruolo, MD[1], Varadan Sevilimedu, MBBS, DrPH[2], Giacomo Montagna, MD[1], Tiana Le, BS[1], Monica Morrow, MD[1], and Andrea V. Barrio, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Background. Neoadjuvant chemotherapy (NAC) has been proven to increase breast-conserving surgery (BCS) rates, but data are limited on conversion rates from BCS-ineligible (BCSi) to BCS-eligible (BCSe), specifically, in patients with large tumors.

Methods. Consecutive patients with stage I–III breast cancer treated with NAC from November 2013 to March 2019 were identified. BCS eligibility before and after NAC was prospectively determined. Patients deemed BCSi before NAC due to large tumor size were studied. Statistical analyses were conducted using Student's t-test, Wilcoxon rank sum test, Chi-square test, Fisher's test, and logistic regression.

Results. In this study, 600 of 1353 cancers were BCSi with large tumors; 69% were non-BCS candidates, 31% were borderline-BCS (bBCS) candidates. Of non-BCS candidates, 69% became BCSe after NAC; 66% chose BCS, and 90% were successful. Among bBCS candidates, 87% were BCSe after NAC, 73% chose BCS, and 96% were successful. On univariate analysis, bBCS candidacy, lower cT stage, cN0 status, absence of calcifications, human epidermal growth factor receptor 2 positive (HER2+)/triple negative (TN) receptor status, poor differentiation, ductal histology, and breast pCR were associated with conversion to BCS eligibility. On multivariable analysis, receptor status (hormone receptor positive [HR+]/HER2– ref; odds ratio [OR] HER2+ 1.63, $P = 0.047$; HR–/HER2– OR, 2.26, $P = 0.003$) and breast pCR (OR 2.62, $P < 0.001$) predicted successful downstaging, while larger clinical tumor size (OR 0.86, $P = 0.003$), non-BCS candidacy (OR 0.46, $P = 0.003$), cN+ status (OR 0.54, $P = 0.008$), and calcifications (OR 0.56, $P = 0.007$) predicted lower downstaging rates.

Conclusion. In patients with large tumors precluding BCS, conversion to BCS eligibility was high with NAC, particularly in bBCS candidates. HER2+/TN receptor status predicted successful downstaging, while lower downstaging rates were observed with larger tumors, cN+ status, and calcifications. These factors should be considered when selecting patients for NAC.

Neoadjuvant chemotherapy (NAC), initially used in patients with inoperable breast cancer to improve resectability, is now commonly used in patients with large, operable breast cancer to downstage the primary tumor and to convert patients from mastectomy to breast-conservation candidates.[1,2] In a patient-level meta-analysis of 10 randomized trials performed in the pre-trastuzumab era comparing neoadjuvant to adjuvant chemotherapy in patients with early-stage operable breast cancer, rates of breast conservation were 65% with NAC compared to 49% with upfront surgery.[3] However, some patients were candidates for breast-conserving surgery prior to NAC, so the true rate of downstaging cannot be determined from these studies.

In patients receiving modern systemic chemotherapy and HER2 targeted therapy, response rates in the breast to NAC have improved, with breast pathologic complete

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A. V. Barrio, MD
e-mail: barrioa@mskcc.org

response (pCR) rates reported to be approximately 50% to 60% in HER2+ breast cancers, 30% to 50% in triple negative breast cancers, and 5% to 15% in hormone receptor positive (HR+)/HER2 negative (HER2–) breast cancers,[4,5] suggesting that a large number of patients will become eligible for breast conservation and will benefit from this approach. Breast pCR is not required for successful downstaging from mastectomy to BCS, and the presence of residual disease in the breast after NAC does not preclude breast conservation if the total volume of disease is limited.

While randomized and retrospective trials have assessed rates of BCS with NAC compared to upfront surgery, few studies have prospectively evaluated conversion rates from BCS-ineligible to BCS-eligible with NAC. The Cancer and Leukemia Group B (CALBG) 40601 and 40603 trials prospectively evaluated BCS conversion rates in HER2+ and triple negative breast cancer patients, respectively, with the most common reason for BCS ineligibility in these studies reported as "tumor too large" or "probable poor cosmetic outcome", but these studies also included patients with multicentric and T4 disease at presentation—characteristics which traditionally preclude surgical downstaging in the breast.[6,7] Therefore, an accurate assessment of BCS conversion rates in patients ineligible for BCS because of a large tumor size relative to breast size is needed to understand the clinical benefit of NAC in this population. We sought to prospectively evaluate rates of BCS conversion with modern NAC in BCS-ineligible patients presenting with a large clinical tumor size and assess factors associated with successful downstaging.

METHODS

Beginning in 2013, our team of 15 surgeons from the Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center prospectively collected data on all patients with invasive breast cancer treated with NAC at our institution into a prospective Health Insurance Portability and Accountability Act (HIPAA)-compliant database. Patients who had a clear indication for systemic chemotherapy because of tumor biology, receptor subtype, nodal status, or tumor size were considered for NAC, to allow downstaging for BCS or avoidance of axillary dissection. Patients in whom the selection of chemotherapy approach was felt to be dependent upon surgical pathology findings underwent primary surgery. Surgeons prospectively assessed BCS eligibility prior to NAC and at the completion of NAC, based on physical exam and imaging findings, and reasons for ineligibility were documented (Fig. 1). Patients considered BCS-ineligible prior to NAC were further categorized as non-BCS candidates versus borderline BCS candidates.

After institutional review board approval, consecutive patients with invasive breast cancer treated with NAC and subsequent surgery between November 2013 and March 2019 were identified. Patients with occult primary breast cancer and those with unknown pre- or post-NAC BCS eligibility were excluded. Patients who were determined by the treating surgeon to be BCS-ineligible before NAC because of a large tumor size relative to breast size comprised the study cohort. Prior to NAC, 99% of patients in the cohort had a mammogram and ultrasound, and 89% had a pre-treatment breast MRI. Following NAC, 81% had a mammogram, 25% had an ultrasound, and 81% had a breast MRI. NAC regimens included dose-dense doxorubicin, cyclophosphamide, and a taxane in 92%. Of HER2 overexpressing patients, 99% received dual blockade with trastuzumab and pertuzumab.

Clinical characteristics between non-BCS and borderline BCS candidates before NAC were compared in a univariate analysis using Student's t-test or the Wilcoxon rank sum test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. A similar univariate analysis was performed to identify clinicopathologic factors associated with conversion to BCS eligibility. Multivariable logistic regression analysis was used to study the association between post-NAC BCS candidacy and the clinicopathologic variables found to be significant in the univariate analysis. The final list of variables for the multivariable model was obtained by backward elimination using a p value of > 0.05 as being eligible for exclusion from the model. The type 1 error rate (α) was set to 0.05 for all the statistical tests. All statistical analyses were performed using R 3.5.3 (R Core Development Team, Vienna, Austria).

RESULTS

From November 2013 to March 2019, 1329 patients with 1353 stage I–III invasive breast cancers (24 bilateral cancers) received NAC followed by surgery at Memorial Sloan Kettering Cancer Center, with 96% having stage II or III breast cancer. Overall, 346 (26%) were BCS-eligible prior to NAC, 982 (73%) were BCS-ineligible, and 25 (1%) had occult primary breast cancer or unknown pre-or post-NAC BCS eligibility and were excluded. Of BCS-ineligible cancers, 600 (61%) had a large tumor size relative to breast size as the reason for ineligibility and comprised our study cohort; the remainder were ineligible for downstaging because of multicentric disease, inflammatory or other T4 disease, or contraindications to radiotherapy (Fig. 1).

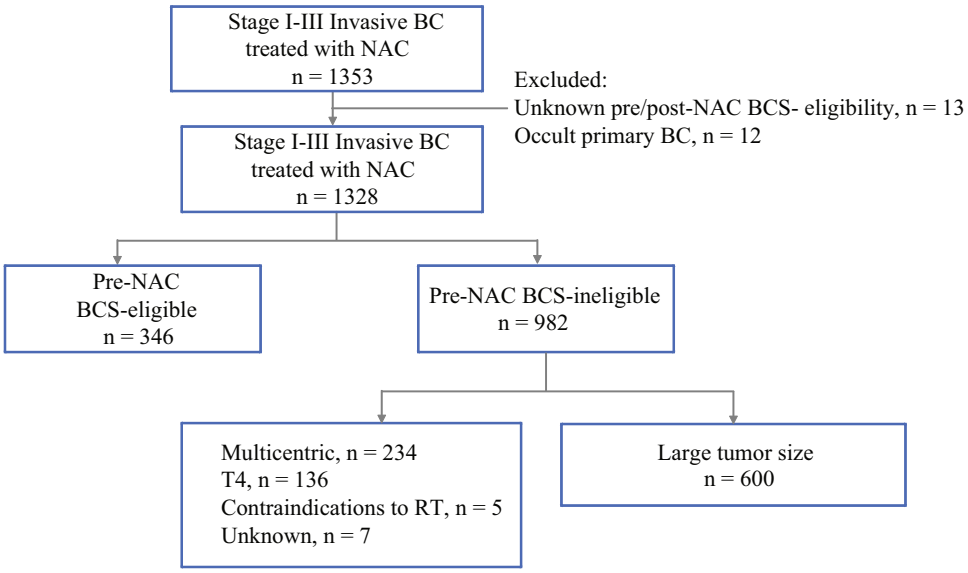

FIG. 1 Study selection. *NAC* neoadjuvant chemotherapy, *BCS* breast-conserving surgery, *BC* breast cancer, *RT* radiation therapy

Of the 600 cancers, the median clinical tumor size was 4.0 cm, with 94% having clinical T2/T3 tumors (Table 1). Overall, 62% of patients were clinically node positive, with a higher incidence of clinical nodal positivity observed among HR+/HER2– patients receiving NAC (72%) compared to HER2+ (61%) or triple negative (54%) patients.

Of patients with large tumors precluding BCS, 69% (n = 412) were non-BCS candidates and 31% (n = 188) were borderline BCS candidates, as determined by the treating surgeon. Compared to borderline BCS candidates, non-BCS candidates had larger tumors (median 4.5 cm vs. 3.5 cm, $P < 0.001$) and a higher proportion of clinical T3 tumors (38% vs. 8%, $P < 0.001$). Non-BCS candidates were also more likely to be clinically node positive (66% vs. 54%, $P = 0.006$) and have non-ductal histology (9% vs. 5%, $P = 0.03$; Table 1).

BCS Conversion Rates

Overall Cohort Among 600 BCS-ineligible cancers, 75% (n = 450) became BCS-eligible after NAC. Of these, 68% of patients (n = 308) elected BCS, which was successful in 93% (n = 285). Overall, 48% (285/600) of BCS-ineligible cancers with large clinical tumor size at presentation avoided mastectomy with preoperative chemotherapy.

Non-BCS Candidates Of 412 non-BCS candidates, 69% (n = 286) became eligible for BCS after NAC. One hundred and twenty-six remained BCS-ineligible due to a tumor size that was too large (n = 88, 70%) or scattered residual disease on imaging (n = 36, 29%) (1% unknown). Of the 286 BCS-eligible patients after NAC, 66% (n = 188) chose BCS and 90% (n = 170) were successful (Fig. 2). Reasons for mastectomy in BCS-eligible patients were primarily patient preference (79%) or high-risk status (20%) (1% unknown).

Borderline BCS Candidates Of 188 borderline BCS candidates, 87% (n = 164) became eligible for BCS after NAC and 13% (n = 24) remained BCS-ineligible due to large tumor size (n = 12, 50%), scattered residual disease (n = 8, 33%), or disease progression (n = 4, 17%). Of BCS-eligible patients after NAC, 73% (n = 120) chose BCS and 96% (n = 115) were successful (Fig. 2). Reasons for mastectomy in BCS-eligible patients were patient preference (86%) and high-risk status (14%).

Predictors of Conversion to BCS Eligibility

On univariate analysis, smaller clinical tumor size at presentation, borderline BCS candidacy (versus non-BCS candidacy), lower clinical T stage, HER2+/triple negative receptor status, poor differentiation, ductal histology, and breast pCR were associated with conversion to BCS, while clinical node positivity and presence of pre-NAC mammographic calcifications were associated with a lower likelihood of conversion (Table 2). Notably, although patients who achieved breast pCR were more likely to become BCS-eligible (87%), approximately 70% of patients who did not achieve pCR also became BCS-eligible after NAC.

On multivariable analysis, receptor status (HR+/HER2- ref, odds ratio [OR] HER2+ 1.63, $P = 0.047$; HR-/HER2- OR 2.26, $P = 0.003$) and achievement of breast pCR (OR 2.62, $P < 0.001$) were independently associated with post-NAC BCS eligibility. Larger clinical tumor size, non-BCS candidacy, clinical node positivity, and pre-NAC

TABLE 1 Clinicopathologic characteristics of the study cohort stratified by non-BCS versus borderline-BCS candidacy

	Overall (n = 600)	Non-BCS candidate (n = 412)	Borderline BCS candidate (n = 188)	P value
Median age: years (range)	49 (25–87)	48 (25–87)	51 (26–82)	0.2
Median clinical tumor size: cm (range)[a]	4.0 (0.9–12.0)	4.5 (1.1–12.0)	3.5 (0.9–10.7)	< 0.001
Clinical T stage				< 0.001
T1	37 (6)	20 (5)	17 (9)	
T2	393 (66)	237 (57)	156 (83)	
T3	170 (28)	155 (38)	15 (8)	
Clinical N stage				0.006
N0	225 (38)	139 (34)	86 (46)	
N+	375 (62)	273 (66)	102 (54)	
Calcifications on pre-NAC MMG				0.2
No	413 (69)	277 (67)	136 (72)	
Yes	187 (31)	135 (33)	52 (28)	
Receptors				0.14
HR+/HER2–	196 (32)	145 (35)	51 (27)	
HER2+	227 (38)	149 (36)	78 (41)	
TN	177 (30)	118 (29)	59 (31)	
Differentiation				0.2
Well	7 (1)	3 (1)	4 (2)	
Moderate	141 (24)	101 (24)	40 (21)	
Poor	452 (75)	308 (75)	144 (77)	
Histology[b]				0.030
Ductal	554 (93)	376 (91)	178 (95)	
Lobular	20 (3)	16 (4)	4 (2)	
Mixed	19 (3)	17 (4)	2 (1)	
Other[c]	6 (1.0)	2 (1)	4 (2)	
pCR				0.97
No	433 (72)	298 (72)	135 (72)	
Yes	167 (28)	114 (28)	53 (28)	

All categorical variables are expressed as n (%) except where otherwise indicated

BCS breast-conserving surgery, *NAC* neoadjuvant chemotherapy, *MMG* mammogram, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *TN* triple negative, *pCR* pathologic complete response

[a]Unknown tumor size (n = 16)

[b]Unknown histology (n = 1)

[c]Other (4 metaplastic, 1 anaplastic, 1 mucinous)

mammographic calcifications were associated with a lower likelihood of downstaging (Table 2).

DISCUSSION

In patients with clinical T1-3 breast cancer, BCS eligibility is based on tumor location and tumor size relative to the breast size, and requires surgeon judgment to determine whether a cosmetically acceptable BCS can be performed. In patients who are not candidates for BCS at initial presentation because of a large tumor size in relation to breast size, NAC can be used to downstage the breast and facilitate breast conservation.[2–4] Patients with large primary tumors that preclude breast conservation are ideal candidates for consideration of NAC, as a decrease in tumor size allows for a smaller volume of tissue to be removed commensurate with the residual volume of disease.[8] The majority of NAC trials examined survival or pCR as end points, and did not distinguish between patients eligible for BCS at presentation and those who required downstaging to undergo BCS. Thus, data on differences in rates of BCS from these studies underestimate the benefit of NAC for downstaging. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B18 and the European

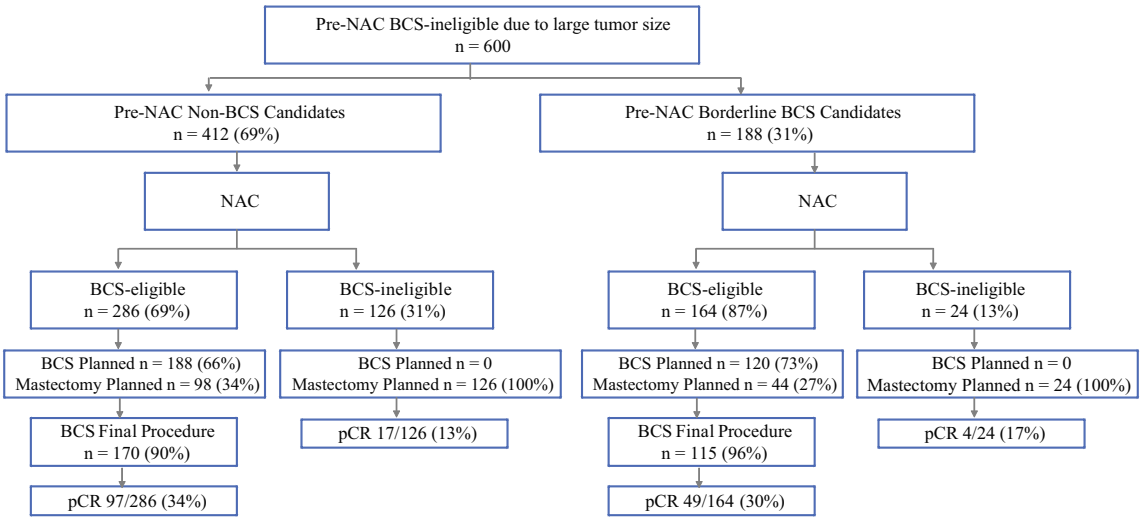

FIG. 2 Conversion to breast-conserving surgery (BCS) eligibility after neoadjuvant chemotherapy (NAC) stratified by borderline versus non-BCS candidates. *pCR* pathologic complete response

Organisation for Research and Treatment of Cancer (EORTC) 10902 trials specifically examined conversion to BCS in patients felt to require mastectomy after four cycles of an anthracycline and cyclophosphamide, and reported conversion to BCS in 27% and 23%, respectively.[9,10] In more recent trials in triple negative and HER2+ patients, Golshan et al.[6,7,11] reported 42% to 53% conversion rates from BCS-ineligible to BCS-eligible with NAC, with BCS ineligibility inclusive of patients with large tumors, multicentric disease, and cT4 disease.

We chose to examine the subset of women ineligible for BCS secondary to large clinical tumor size, since this was the most common reason for BCS ineligibility in our study, observed in 61% of the BCS-ineligible patients. The conversion rate of 75% from BCS-ineligible to BCS-eligible with NAC observed in our study is higher than that reported in other studies, reflecting improvements in systemic therapy as well as the exclusion of patients from our study with multicentric or T4 disease who were not eligible for downstaging.

Despite increased eligibility for BCS after NAC, others have demonstrated low rates of acceptance of BCS among patients after NAC.[6,7,11] Golshan et al. prospectively evaluated the role of NAC in facilitating BCS and found that only 56% of BCS-eligible patients chose BCS after NAC, with a lower BCS rate in North American patients (55%) than in European and Asian patients (80%).[11] Furthermore, BCS-eligible patients after NAC who opt for mastectomy often choose bilateral over unilateral mastectomy, with Christian et al. demonstrating a threefold higher incidence of bilateral versus unilateral mastectomy among post-NAC BCS candidates.[12] In our study, 68% of BCS-eligible patients opted for BCS after NAC, higher than the rate reported by Golshan et al., and mastectomy was avoided in 48% of patients deemed BCS-ineligible at presentation. Surgical de-escalation and avoidance of mastectomy with the use of NAC has the potential to reduce surgical morbidity and improve long-term quality of life for patients, with accumulating evidence demonstrating improved satisfaction with breasts among patients treated with BCS versus mastectomy.[13,14] These findings reinforce that NAC should be considered for downstaging in BCS-ineligible patients with large tumors who are desirous of breast conservation, provided that chemotherapy is otherwise indicated.

In selecting patients for NAC, our study demonstrated high rates of conversion to BCS eligibility among triple negative and HER2+ breast cancer patients with large primary tumors (84% and 79%, respectively), underscoring that these aggressive subtypes are ideally suited for downstaging with NAC, especially in the absence of mammographic calcifications. While the decision to give NAC as an initial treatment in stage II–III triple negative and HER2+ breast cancer patients is relatively straightforward due to their high-risk biology and excellent response rates, the decision for NAC versus upfront surgery among patients with HR+/HER2– cancers is more complex. Central to this decision is the understanding that NAC should only be considered for surgical downstaging in HR+/HER2– patients in whom chemotherapy would otherwise be indicated, highlighted by the fact that over 70% of HR+/HER2– patients in our study cohort receiving NAC were also clinically node positive. Among our cohort of patients with HR+/HER2– cancer selected for NAC, 62% of BCS-ineligible patients became BCS-eligible with NAC, emphasizing that pCR is not required for successful

TABLE 2 Predictors of conversion to breast-conserving surgery (BCS) eligibility with neoadjuvant chemotherapy (NAC)

Characteristic	Overall (n = 600)	Post-NAC BCS candidate		Univariable	Multivariable		
		No (n = 150)	Yes (n = 450)	P value	OR	95% CI	P value
Median age at diagnosis: years (range)	49 (25–87)	49 (27–87)	49 (25–82)	0.3	–	–	
Median clinical tumor size: cm (range)[a]	4.0 (0.9–12)	5.0 (0.9–12)	4.0 (1.0–12)	< 0.001	0.86	0.78–0.95	0.003
Pre-NAC BCS candidate				< 0.001			0.003
Borderline	188	24 (13)	164 (87)		Ref		
No	412	126 (31)	286 (69)		0.46	0.27–0.76	
Clinical T stage				< 0.001	–	–	
T1	37	8 (22)	29 (78)				
T2	393	81 (21)	312 (79)				
T3	170	61 (36)	109 (64)				
Clinical nodal status				< 0.001			0.008
cN0	225	36 (16)	189 (84)		Ref		
cN+	375	114 (30)	261 (70)		0.54	0.34–0.84	
Pre-NAC calcifications				< 0.001			0.007
No	413	83 (20)	330 (80)		Ref		
Yes	187	67 (36)	120 (64)		0.56	0.36–0.85	
Receptor status				< 0.001			
HR+/HER2–	196	74 (38)	122 (62)		Ref		
HER2+	227	47 (21)	180 (79)		1.63	1.01–2.65	0.047
HR–/HER2–	177	29 (16)	148 (84)		2.26	1.33–3.91	0.003
Differentiation	7	4 (57)	3 (43)	0.009	–	–	
Well	141	45 (32)	96 (68)				
Moderate	452	101 (22)	351 (78)				
Poor							
Histology[b]				0.015	–	–	
Ductal	554	130 (23)	424 (77)				
Lobular	20	9 (45)	11 (55)				
Mixed	19	9 (47)	10 (53)				
Other[c]	6	2 (33)	4 (67)				
Breast pCR				< 0.001			< 0.001
No	433	129 (30)	304 (70)		Ref		
Yes	167	21 (13)	146 (87)		2.62	1.54–4.66	

All categorical variables are expressed as n (%) except where otherwise indicated

OR odds ratio, *CI* confidence interval, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *pCR* pathologic complete response

[a]Unknown tumor size (n = 16)

[b]Unknown histology (n = 1)

[c]Other (4 metaplastic, 1 anaplastic, 1 mucinous)

downstaging to breast conservation. While the rate of downstaging to BCS is lower compared to triple negative and HER2+ patients, if chemotherapy is otherwise indicated because of clinical nodal positivity or other high-risk factors, our study provides evidence that a substantial proportion of high-risk HR+/HER2– patients with large tumors that preclude breast conservation will convert to BCS-eligible and may derive a substantial clinical benefit from NAC.

Patients who are borderline for BCS at presentation in whom upfront surgery would result in a poor cosmetic outcome represent a subgroup of patients in whom the decision for upfront surgery versus NAC is more

challenging, given their smaller tumor size compared to non-BCS candidates. However, we observed a high conversion rate to BCS eligibility among borderline BCS patients (87%), reflecting that only a small reduction in tumor volume is needed to convert these patients into BCS candidates. Furthermore, among patients who chose BCS, 96% were successful, allowing for 61% of the borderline BCS patients to avoid mastectomy with NAC. In borderline BCS candidates who have a clear indication to receive chemotherapy, there is little rationale to proceeding with upfront mastectomy if the patient is desirous of breast conservation.

Our study had several limitations. First, prospective assessment of BCS eligibility before and after NAC for an individual patient was determined by the patient's treating surgeon and therefore remains a subjective assessment. Because no standard cutoff for tumor size exists for determining BCS eligibility, it is possible that variability exists between surgeons in judging appropriateness for breast conservation. While we did not analyze individual surgeon biases and decision making, 94% of patients considered ineligible for BCS had clinical T2/3 tumors at presentation, with a median clinical tumor size of 4.0 cm, suggesting some consistency in what individual surgeons considered a tumor size too large for BCS. In assessing BCS eligibility after NAC, Golshan et al. observed a 35% pCR rate among patients deemed to be poor BCS candidates,[11] while we observed a 14% pCR rate among our patients determined to be BCS-ineligible after NAC, underscoring that surgeon assessment sometimes fails to identify patients who could potentially be candidates for BCS. However, surgeon assessment relies strongly on post-NAC imaging, which may demonstrate persistent abnormalities in the breast, such as calcifications, that may require more extensive surgery due to uncertainty surrounding the presence of residual disease.[15,16] Secondly, statistical analysis to identify factors associated with BCS eligibility was performed for the entire cohort. Even though a statistical analysis stratified by pre-NAC candidacy would have been ideal to uncover the favorable factors associated with conversion to BCS candidacy in borderline candidates and non-BCS candidates, it was not feasible because of the small number of pre-NAC borderline candidates who did not convert (13%).

In conclusion, among BCS-ineligible patients with a large tumor size relative to breast size, rates of conversion to BCS eligibility with NAC were high, particularly in borderline BCS candidates. HER2+ and triple negative receptor status predict for successful conversion to BCS, although, notably, more than 60% of HR+/HER2– breast cancer patients selected for NAC also became BCS-eligible. Overall, mastectomy was avoided in 48% of BCS-ineligible patients with the use of preoperative systemic therapy, suggesting that NAC can be used successfully for breast surgery de-escalation with a substantial clinical benefit, provided that systemic chemotherapy is otherwise indicated.

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