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Tumor biology predicts pathologic complete response to neoadjuvant chemotherapy in patients presenting with locally advanced breast cancer

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Abstract

Background—Neoadjuvant chemotherapy (NAC) is used to convert patients with inoperable locally advanced breast cancer (LABC) to operability, but has not traditionally been used to avoid mastectomy or axillary dissection in this subset. The purpose of this study was to determine rates of pathologic complete response (pCR) in LABC patients and identify factors predictive of pCR to determine if responding patients might be suitable for limited surgery.

Methods—From 2006-2016, 1522 patients received NAC followed by surgery; 321 had advanced disease in the breast (cT4) and/or in the nodes (cN2/N3). pCR rates were assessed by T and N stage, and receptor subtype.

Results—Of 321 LABC patients, 223 were cT4, 77 cN2, and 82 cN3. 43% were hormone receptor (HR)+/HER2-, 23% triple negative, and 34% HER2+. The overall pCR rate was 25% and differed by receptor subtype (HR+/HER2- 7%; triple negative 23%; HER2+ 48%; $p<0.001$). Breast pCR occurred in 27% and was similar in T4 vs. non-T4 disease (29% vs. 22%, $p=0.26$). Nodal pCR was achieved in 38% of cN+ patients and did not differ by nodal stage (cN1 43%, cN2 36%, cN3 32%; $p=0.23$). Nodal pCR was significantly more common than breast pCR ($p=0.014$) across all tumor subtypes. Receptor subtype was the only predictor of overall pCR ($p<0.001$).

Conclusion—In patients with LABC, pCR after NAC was seen in 25%, and did not differ by T or N stage. Tumor biology, but not extent of disease, predicted pCR. Studies assessing feasibility of surgical downstaging with NAC in LABC patients are warranted.

Keywords

pathologic complete response; neoadjuvant chemotherapy; locally advanced breast cancer

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INTRODUCTION

Neoadjuvant chemotherapy (NAC) is increasingly used in patients with operable breast cancer to allow more limited surgery in the breast and axilla¹⁻³, with reported pathologic complete response (pCR) rates of 33-37% in the breast and 40-49% in the nodes.^{2,4} Patients presenting with locally advanced breast cancer (LABC), defined as disease in the breast with skin or chest wall involvement (cT4) and/or extensive disease in the nodes (cN2/N3), have not been considered candidates for surgical downstaging with NAC due to their heavy disease burden at presentation, although NAC is used in this group to render inoperable disease operable. These patients have traditionally been treated with modified radical mastectomy, as long-term local and regional control rates with more limited surgery are largely unknown⁵, and the accuracy of sentinel node mapping is also uncertain.^{6,7}

In addition, the magnitude of benefit of modern NAC in LABC patients is also uncertain. Studies evaluating response rates are primarily limited to patients with cT4 disease, with a paucity of data in cN2 and cN3 patients. In a pooled analysis of 12 neoadjuvant trials, Cortazar et al demonstrated overall pCR rates of 14.5% and 16% in T4a-c (n = 781) and T4d (n = 482) patients, respectively⁸; however, these pCR rates may be an underestimate, as studies were comprised of heterogeneous patient populations and therapies were not targeted to a specific tumor subtype. Understanding rates of overall, breast, and nodal pCR in patients with LABC becomes increasingly important given the success of NAC in operable breast cancer patients in improving rates of breast-conserving surgery in borderline conservation candidates³ and reducing the need for axillary lymph node dissection (ALND) in clinically node-positive patients², particularly in those with HER2 positive disease. The impact of tumor burden at presentation on pCR rates is uncertain, and adoption of more limited surgery in patients with LABC could be considered if pCR rates are similar to those seen in non-LABC patients. The purpose of this study was to determine overall, breast, and nodal pCR rates in patients with LABC, and to identify factors predictive of pCR.

METHODS

Following institutional review board approval, patients with locally advanced cancer, defined as disease in the breast with skin or chest wall involvement (cT4), or extensive disease in the regional lymph nodes (cN2/N3) were identified from our institutional database. LABC patients who had NAC followed by surgery at Memorial Sloan Kettering Cancer Center (MSK) between September 2006 and May 2016 comprised the study cohort. Patients diagnosed with distant metastatic disease prior to surgery or who did not have surgery at MSK were excluded. Clinicopathologic and treatment data were collected from the medical record. Hormone receptor positivity was defined as > 1% of cells staining positive for estrogen or progesterone receptor, and HER2 receptor was considered positive with immunohistochemical staining of 3+ or fluorescence in situ hybridization that was amplified.

The primary endpoint was overall pCR defined as no residual invasive disease in the breast and the lymph nodes (in situ disease allowed).⁸ Patients who presented with an occult primary breast cancer (n = 8) were excluded from the breast pCR endpoint calculation, and

patients who were clinically node negative ($n = 11$) at presentation were excluded from the nodal pCR endpoint calculation.

Overall rates of breast and nodal pCR, as well as rates stratified by subtype, were compared using robust standard error estimates to account for correlation between paired observations and to allow for some pairs with missing data, which can occur when a patient was not eligible for analysis of both the breast and the nodal pCR endpoint. All other univariable comparisons were performed using the Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Multivariable analyses of associations with pCR were conducted using logistic regression models. A p -value < 0.05 was considered statistically significant. All statistical analyses were conducted using R software version 3.2.5 (R Core Development Team, Vienna, Austria).

RESULTS

Between September 2006 and May 2016, 1522 patients received NAC followed by surgery; 321 patients had locally advanced disease in the breast (cT4) and/or in the nodes (cN2/N3). Two hundred and sixty patients had advanced disease in either the breast or axilla while 61 had advanced disease in both. Clinicopathologic and treatment characteristics are summarized in Table 1. Overall, 223 patients had cT4 disease, 77 had cN2 disease, and 82 had cN3 disease. Median age was 52 years and median tumor size was 6 cm. Eighty-six percent had ductal histology, 43% were hormone receptor (HR) positive/human epidermal growth factor receptor 2 (HER2) negative, 23% were triple negative, and 34% were HER2 positive. The majority of patients (85%) were treated with mastectomy; all patients had an ALND. The most common chemotherapy regimen was doxorubicin, cyclophosphamide, and a taxane received by 85% of patients. All HER2 positive patients received HER2 targeted therapy, with 29% treated with dual anti-HER2 therapy with trastuzumab and pertuzumab (Table 2).

The overall pCR rate was 25% and differed significantly by receptor subtype (HR positive/HER2 negative 7%; triple negative 23%; HER2 positive 48%; $p < 0.001$). Age, tumor size, histology, clinical T stage, and clinical N stage were not significantly associated with pCR (Table 1). On multivariable analysis, after adjusting for clinicopathologic factors selected *a priori*, receptor subtype remained the only significant predictor of overall pCR with HER2 positive cancers having increased odds of pCR (odds ratio [OR], HER2 positive 11.52 [95% confidence interval [CI], 5.25–25.1]) compared with HR positive/HER2 negative tumors ($p < 0.001$) (Table 3).

Breast pCR occurred in 27% of patients and was similar in T4 ($n = 223$) vs. non-T4 ($n = 90$) disease (29% versus 22%, $p = 0.26$). Among clinically node-positive patients ($n = 310$), nodal pCR was achieved in 38%, with similar nodal pCR rates in patients with cN1 (43%) compared to cN2 (36%) or cN3 (32%) disease ($p = 0.23$). Nodal pCR was significantly more common than breast pCR ($p = 0.014$), and this was true across all tumor subtypes (Table 4).

In the subset of patients with inflammatory breast cancer (T4d, $n = 131$), overall pCR rates were 33% in T4d patients compared to 20% in those with non-inflammatory T4 disease ($n =$

92) ($p = 0.033$), and breast pCR rates were 35% vs. 21%, respectively ($p = 0.024$). Notably, T4d and non-inflammatory T4 patients differed in subtype frequency ($p = 0.001$), such that T4d patients were more likely to be HER2 positive than non-inflammatory T4 breast cancer patients (50% vs. 25%). After adjusting for receptor subtype, the association between inflammatory breast cancer and overall pCR was no longer significant ($p = 0.52$) (Table 5).

DISCUSSION

NAC in LABC patients has traditionally been used to improve resectability, without altering surgical treatment recommendations. The National Comprehensive Cancer Network guidelines still advise modified radical mastectomy for most patients with LABC following preoperative systemic therapy, with consideration of breast-conserving surgery in a select group of patients with non-inflammatory T4 disease and a complete response after NAC.⁹ However, the success of NAC in allowing more limited surgery in the breast and axilla in patients with operable breast cancer¹⁻³ raises the possibility that LABC patients could similarly be considered for surgical downstaging, provided that the pCR rates between early-stage and advanced cancers are comparable.

Improvements in systemic therapy and targeted therapies have improved overall pCR rates in operable breast cancer patients; early neoadjuvant trials reported pCR rates of 13% with 4 cycles of doxorubicin and cyclophosphamide (AC)³, which improved to 24-28% in more recent studies with the addition of a taxane (T) to AC.^{2,4,10} In our patient cohort of LABC patients, of whom 85% were treated with AC-T, we observed a similar overall pCR rate of 25%, suggesting that a tumor's drug sensitivity is far more important than the initial tumor burden.

As expected, receptor subtype was the most important predictor of pCR on univariable and multivariable analysis ($p < 0.001$). Increasing tumor burden in the breast and regional nodes had no impact on overall, breast, or nodal pCR. HER2 positive patients had the highest rates of pCR (48%), similar to the 45% pCR rates seen in early-stage HER2 positive breast cancer patients enrolled in ACOSOG Z1071.¹¹ Contributing to the high pCR rate observed in HER2 positive patients was the use of dual anti-HER2 therapy with trastuzumab and pertuzumab in addition to chemotherapy in 29% of our patients. The use of dual HER2 blockade has been demonstrated in two neoadjuvant trials to almost double the pCR rate compared to treatment with trastuzumab monotherapy^{12,13}, emphasizing the importance of optimal systemic and targeted therapy to achieve maximal treatment response.

Our data also demonstrate that breast pCR rates do not differ significantly based upon tumor burden in the breast, with similar breast pCR rates observed in T4 (29%) vs. non-T4 (22%, $p = 0.26$) disease, suggesting that surgical downstaging in select patients may be feasible. However, it is unknown whether local control with breast-conserving surgery is equivalent to mastectomy in this population. Studies evaluating long-term outcomes in T4 patients undergoing breast-conserving surgery after NAC are limited. Shen et al reported on 33 patients with T4 breast cancer treated with NAC followed by lumpectomy and radiation therapy; complete resolution of skin changes occurred in 29 patients, and the 5-year local recurrence rate was 6%.¹⁴ In a more recent study, Murphy et al reported surgical

management and outcomes in a contemporary cohort of 98 T4 patients; 85 patients had conventional mastectomy, while 13 had either skin sparing mastectomy (n = 9) or breast-conserving surgery (n = 4), with no difference in breast cancer-specific survival between patients receiving standard surgical therapy compared to non-standard surgical therapy (p = 0.24).¹⁵

When considering surgical downstaging in the breast in patients with LABC, there are important considerations. One is the optimal volume of tissue to be excised. Although we know from trials in operable cancer patients that removal of the entire original tumor volume is not needed after NAC to optimize local control¹⁶, it's uncertain how this translates to patients with a heavier, more diffuse disease burden at presentation. Radiologic determination of pCR has a positive predictive value of 47-73%¹⁷, and, unlike the situation of a patient with a large unifocal tumor who downstages to breast conservation where residual disease is likely to be within the radiation boost volume, the same is not true for diffuse T4 lesions. For these reasons, initial trials of breast conservation in patients presenting with T4 lesions should be limited to patient subgroups with the highest response rates to NAC. Patients with HER2 positive tumors in our study had a breast pCR rate that exceeded 50%. The exquisite sensitivity of HER2 positive tumors to NAC and targeted therapy, combined with the administration of additional anti-HER2 therapy postoperatively, makes them ideal candidates for trials of surgical downstaging in the future. At present, mastectomy remains the standard of care for diffuse T4 lesions, particularly inflammatory cancer, and attempts at breast conservation in patients with diffuse T4 disease should not be considered outside of a well-designed clinical trial.

Nodal pCR in our cohort was achieved in 38% of node-positive patients and was more common than breast pCR, a trend also observed in early-stage cancer patients.² Similar to the breast, where tumor burden did not impact pCR, we saw no difference in nodal pCR based on nodal burden at presentation (p = 0.23), and nodal pCR rates in cN2 and cN3 patients were 36% and 32%, respectively. Boughey et al similarly observed a 46% nodal pCR rate among 26 women with cN2 disease enrolled in ACOSOG Z1071⁴, raising the question as to whether sentinel lymph node biopsy (SLNB) can be considered in LABC patients who have a complete clinical response in the nodes after NAC. In cN1 patients, three recently published single-arm, prospective studies have demonstrated that SLNB is accurate after NAC, with a false-negative rate of < 10% provided that 3 or more negative SLNs are removed.^{11,18,19} Data on the feasibility of SLNB after NAC in patients presenting with LABC are limited. Among 26 women with cN2 disease in ACOSOG Z1071 with at least 2 SLNs removed, the false-negative rate of SLNB in the 14 patients with residual nodal disease was 0% (95% confidence interval, 0-23.2%).¹¹ These numbers are promising, but are too small to draw definitive conclusions regarding the accuracy of SLNB for cN2 disease. To the best of our knowledge, studies evaluating the feasibility of SLNB in patients presenting with either cN3 or cT4 disease have not been performed. The magnitude of reduction in tumor burden in the nodes with modern NAC suggests that a substantial number of LABC patients may not benefit from ALND. However, long-term data regarding regional recurrence rates in patients presenting with clinically node-positive disease and treated with SLNB after NAC are limited. Galimberti et al reported outcomes in clinically node positive (cN1/N2) patients with complete clinical response after NAC undergoing SLNB alone. At a

median follow-up of 61 months, there were no axillary failures in the 70 patients who initially presented with cN1/N2 disease, had negative sentinel nodes after NAC, and received SLNB alone.²⁰ Although these results are promising, the safety of lesser surgery in the axilla after NAC in clinically node-positive patients remains uncertain, and the ultimate utility of this approach in LABC patients can only be determined in a clinical trial.

In conclusion, overall pCR rates in patients with LABC are comparable to those seen in early-stage breast cancer, suggesting that sensitivity to chemotherapy is not a function of tumor burden. Tumor biology, but not extent of disease, predicts pCR. Substantial pCR rates in the breast and axilla suggest that select LABC patients with an excellent response to NAC may be considered for clinical trials of surgical downstaging in the future.

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Synopsis

Of 321 patients with locally advanced breast cancer treated with neoadjuvant chemotherapy followed by definitive surgery, overall pCR was 25%, and did not differ by T and N stage. We conclude that tumor biology, but not extent of disease, predicts pCR.

Table 1

Clinicopathologic characteristics and association with overall pCR (n = 321)

Characteristic	All Patients(n = 321)	No pCR (n = 241)	pCR (n = 80)	p value
Age, years, median (range)	52 (28, 84)	52 (28, 81)	52 (28, 84)	0.94
Tumor size, cm, median (range)	6 (0.7,28)	6 (1, 28)	6.5 (0.7, 15)	0.55
Histology				0.23
	Ductal	276	26%	
	Lobular	22	9%	
	Mixed ductal/lobular	12	17%	
	Other [*]	11	36%	
cT [‡]				0.17
	T1	11	18%	
	T2	46	17%	
	T3	33	12%	
	T4	223	27%	
cN [§]				0.40
	N1	151	28%	
	N2	77	25%	
	N3	82	21%	
Receptor subtype				<0.001
	HR+/HER2–	138	7%	
	Triple negative	73	23%	
	HER2+	110	48%	

pCR, pathologic complete response; cT, clinical tumor stage; cN, clinical nodal stage; HR, hormone receptor

^{*} includes mammary (n = 4), mammary with lobular features (n = 3), metaplastic (n = 2), micropapillary (n = 2)

[‡] excludes patients with occult cancer (Tx) at presentation (n = 8)

[§] excludes patients who were cN0 at presentation (n = 11)

Table 2

Treatment characteristics of study cohort (n = 321)

		Total n = 321
Breast Surgery [‡]		
	Lumpectomy	47 (15%)
	Mastectomy	272 (85%)
Axillary Lymph Node Dissection		321 (100%)
Chemotherapy		
	AC-T	274 (85%)
	CMF	1 (< 1%)
	TC	26 (8%)
	Taxane only	13 (4%)
	Other [*]	7 (2%)
Anti-HER2 Therapy [§]		
	Trastuzumab	70 (64%)
	Trastuzumab/pertuzumab	32 (29%)
	Other ^{**}	8 (7%)

AC-T, doxorubicin and cyclophosphamide with the addition of a taxane; CMF, cyclophosphamide, methotrexate, 5 fluorouracil; TC, taxane and cyclophosphamide

[‡] 2 patients with occult primary breast cancer had no primary breast surgery

^{*} includes AC (n = 4), TC-vinorelbine (n = 1), cisplatin (n = 1), AT (n = 1)

^{**} includes trastuzumab/lapatinib (n = 7), lapatinib (n = 1)

[§] calculated for 110 HER2 positive patients

Table 3

Predictors of overall pCR in locally advanced breast cancer patients

		Odds ratio (95% CI)*	p value
Age		1.00 (0.98-1.03)	0.69
Ductal vs other histology		1.90 (0.59-6.07)	0.28
cT4 vs. non-T4		1.52 (0.63-3.64)	0.35
cN2/N3 vs. cN1/N0		0.86 (0.42-1.78)	0.69
Receptor subtype			< 0.001
	HR+/HER2–	1.00 (referent)	
	Triple negative	3.77 (1.53-9.29)	
	HER2+	11.52 (5.25-25.31)	

pCR, pathologic complete response; CI, confidence interval; HR, hormone receptor

* multivariable analysis includes patients with complete data for all clinicopathologic factors (n = 313)

Overall, breast, and nodal pathologic complete response rates for the entire population and stratified by receptor subtype

Table 4

Receptor subtype	Overall pCR		Breast pCR*		Nodal pCR [§]		p value [¶]
	n	%	n	%	n	%	
Any	321	25	313	27	310	38	0.014
HR positive/HER2 negative	138	7	135	9	132	17	0.014
Triple negative	73	23	70	24	70	41	0.002
HER2 positive	110	48	108	52	108	63	0.009

pCR, pathologic complete response; HR, hormone receptor; HER2, human epidermal growth factor receptor

* excludes patients with occult primary breast cancer (n = 8)

[§] excludes patients that were cN0 (n = 11)

[¶] p value calculations compare breast vs. nodal pCR

Table 5

Inflammatory breast cancer and overall pCR

Univariable analysis				
	Total n = 223	No pCR	pCR	P value
Other T4	92	80%	20%	0.033
T4d	131	67%	33%	
Multivariable analysis				
		OR (95% confidence interval)		p-value
T stage				0.52
	Other T4	1.00		
	T4d	1.27 (0.62-2.58)		
Receptor subtype				
	HR positive/HER2 negative	1.00		< 0.001
	Triple negative	3.47 (1.19-10.12)		
	HER2 positive	12.3 (5.06-29.94)		

pCR, pathologic complete response; HR, hormone receptor; HER2, human epidermal growth factor receptor 2