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Authors

Moo, Tracy-Ann
Saccarelli, Carolina
Sutton, Elizabeth
et al.

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Tumor-Nipple Distance of ≥ 1 cm Predicts Negative Nipple Pathology After Neoadjuvant Chemotherapy

Tracy-Ann Moo, MD[1], **Carolina Rossi Saccarelli, MD**[2,5], **Elizabeth J. Sutton, MD**[2], **Varadan Sevilimedu, MBBS, DrPH**[3], **Kate R. Pawloski, MD**[1], **Timothy M. D'Alfonso, MD**[4], **Mary C. Hughes, MD**[2], **Jill S. Gluskin, MD**[2], **Almir Bitencourt, MD, PhD**[2], **Elizabeth A. Morris, MD**[2], **Audree Tadros, MD**[1], **Monica Morrow, MD**[1], **Mary L. Gemignani, MD**[1], **Virgilio Sacchini, MD**[1]

[1.]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[2.]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[3.]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[4.]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[5.]Department of Imaging, A.C. Camargo Cancer Center, São Paulo, SP, Brazil

Abstract

Background: As neoadjuvant chemotherapy (NAC) for breast cancer has become more widely used, so has nipple-sparing mastectomy. A common criterion for eligibility is a 1 cm tumor-to-nipple distance (TND), but its suitability after NAC is unclear. Here we examined factors predictive of negative nipple pathologic status (NS-) in women undergoing total mastectomy after NAC.

Methods: Women with invasive breast cancer treated with NAC and total mastectomy from Aug 2014 to Apr 2018 at our institution were retrospectively identified. Following review of pre- and post-NAC MRIs and mammograms, the association of clinicopathologic and imaging variables with NS- was examined and the accuracy of 1 cm TND on imaging for predicting NS- was determined.

Results: Among 175 women undergoing 179 mastectomies, 74% of tumors were cT1-T2 and 67% cN+ on pre-NAC staging; 10% (18/179) had invasive or in situ carcinoma in the nipple on final pathology. On multivariable analysis, after adjusting for age, grade, and tumor stage, three factors, namely number of positive nodes, pre-NAC nipple-areolar complex retraction, and decreasing TND, were significant predictors of nipple involvement ($p < 0.05$). Likelihood of NS- was higher with increasing TND on pre- and post-NAC imaging ($p < 0.05$). TND ≥ 1 cm predicted NS- in 97% and 95% of breasts on pre- and post-NAC imaging, respectively.

Corresponding author: Tracy-Ann Moo, MD, Memorial Sloan Kettering Cancer Center, Breast and Imaging Center, 300 E. 66th St., New York, NY 10065, moot@mskcc.org, Ph: 646-888-5360; Fax: 646-888-4921.

Conclusions: Increasing TND was associated with a higher likelihood of NS-. TND of ≥ 1 cm on pre- or post-NAC imaging is highly predictive of NS- and could be used to determine eligibility for nipple-sparing mastectomy after NAC.

Introduction

In women with invasive breast cancer, neoadjuvant chemotherapy (NAC) using modern chemotherapy and targeted therapy regimens is associated with improved pathologic complete response rates and is increasingly used to treat operable breast cancer.[1–3] As more women undergo NAC, interest in the use of nipple-sparing mastectomy in this population has also increased.[4–10] Among several recent institutional reports on outcomes following nipple-sparing mastectomy, 6–27% of these surgeries performed for therapeutic purposes were in patients who had received NAC.[7–9,11] Studies examining the proportion of patients undergoing nipple-sparing mastectomy after NAC show a steady increase in its use over the past 10 years.[4,9]

In the primary surgery setting, a 1 cm tumor to nipple distance (TND) on imaging is often used to determine nipple-sparing mastectomy eligibility,[12–17] and combined with intraoperative retroareolar biopsy has been reported to be the best criteria for achieving a negative nipple pathologic status (NS-).[12] However, the accuracy of these criteria for prediction of NS- pathology after NAC is unclear. Here we examine the accuracy of the 1 cm TND cutoff to predict NS- based on findings on pre- and post-NAC MRI and mammogram in a cohort of women undergoing total mastectomy after NAC.

Methods

After approval by the IRB, we retrospectively collected clinicopathologic data from electronic medical records on women with invasive breast cancer treated with NAC and total mastectomy (non-nipple sparing) at Memorial Sloan Kettering Cancer Center between August 2014 and April 2018. Total mastectomy cases were selected for study to allow complete pathologic examination of the nipple. Women with clinical T4 tumors, clinical nipple involvement, or pathologic nipple discharge were excluded. We also excluded women who did not have both a pre- and post-NAC MRI available for review, whose pre- and post-NAC MRI were < 12 weeks apart, and those with technically inadequate MR image quality.

Pre- and post-NAC mammograms and MRIs were reviewed by three radiologists specializing in breast imaging, who were blinded to final nipple pathology results. Performance of post-NAC mammogram was based on the presence of pre-NAC calcifications and surgeon discretion.

Pre- and post-NAC imaging review documented suspected tumor size, nipple-areolar complex thickening, nipple-areolar complex retraction or invasion, presence of multifocal or multicentric disease, and distances of biopsy clip, mass and non-mass enhancement, and calcifications from the nipple. Findings of nipple retraction or invasion, mass and non-mass enhancement, or suspicious calcifications were classified as suspected disease and included

in TND measurement. Mastectomy specimens were stratified according to TND into the following categories: < 1 cm, 1–2 cm, or ≥ 2 cm.

Routine processing of all mastectomy specimens began with inking and sectioning at approximately 0.5 cm intervals. If the nipple appeared grossly normal and uninvolved by tumor, the nipple-areolar complex was amputated in a plane parallel to the skin surface and sectioned perpendicularly. The entire nipple was submitted for examination. A second deeper section was taken in the plane parallel to the skin surface to demonstrate a cross-section of lactiferous ducts approaching the nipple. If the tumor grossly extended to or was within 1 cm of the nipple, perpendicular sections showing the interface between tumor and nipple were submitted for examination. For this study, only ductal carcinoma in situ (DCIS) or invasive carcinoma reported in the nipple sections were considered positive pathology findings.

The association between clinicopathologic and imaging variables and nipple involvement was examined using the t-test or Wilcoxon rank-sum test for continuous variables, and the chi-square or Fisher's exact test for categorical variables. The accuracy of 1 cm TND for estimating probability of negative nipple pathology was determined using the epidemiological parameters sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Sensitivity was defined as the ability of imaging studies to detect nipple involvement in women who had positive nipple pathology, specificity as the ability to exclude nipple involvement in individuals who had negative nipple pathologic status, PPV as the ability of a positive imaging finding to correctly predict nipple involvement, and NPV as the ability of a negative finding to correctly exclude nipple involvement. All statistical tests were performed using R 3.5.3 (R Core Development Team, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

We identified 298 mastectomies in 292 women who had undergone neoadjuvant chemotherapy followed by total mastectomy during the study period. Of these, 209 women had both pre- and post-NAC MRIs available for review. After excluding T4 tumors and those with clinical nipple involvement or pathologic nipple discharge, 175 eligible women who had undergone 179 mastectomies were analyzed. Median age was 48 years (IQR 41–57) (Table 1). Based on pre-NAC staging, 74% of tumors were cT1-T2, 67% were clinically node-positive, and 77% were of ductal histology. With respect to molecular subtype, 42% of tumors were hormone receptor (HR)-positive and HER2-negative, 24% were triple negative, and 34% were HER2-positive.

On final pathologic examination, 10% (18/179) of mastectomy specimens had invasive carcinoma or DCIS detected in the nipple. On univariate analysis, multiple pathologic variables were significantly associated with nipple involvement including lower grade, HR+/HER2− subtype, pT3, pN+, and greater numbers of positive nodes (Table 1). On univariate analysis of imaging findings, nipple involvement was associated with nipple-areolar complex thickening on pre-NAC mammogram, greater tumor extent, nipple retraction,

and nipple-areolar complex thickening on pre- and post-NAC MRI, and multifocality/multicentricity on post-NAC MRI ($p < 0.05$).

When breasts were classified based on TND on imaging, we found that the likelihood of having a NS- pathology was higher with increasing TND on both pre- and post-NAC imaging (Figure 1). In breasts with a pre-NAC TND < 1 cm, 83% had NS-, compared to 96% of breasts with TND of 1–2 cm and 97% with a TND of > 2 cm ($p = 0.006$). We found a similar pattern of nipple involvement on examination of post-NAC TND: 73% of breasts with a TND of < 1 cm had NS-, compared to 95% with TND of 1–2 cm and 96% of those with TND > 2 cm ($p < 0.001$). On multivariable analysis, after adjusting for age, histologic grade, and tumor stage, significant ($p < 0.05$) predictors of nipple involvement remained the number of positive nodes, nipple-areolar complex retraction on pre-NAC MRI, and decreasing TND (Table 2).

We further examined measures of accuracy for TND in predicting nipple pathologic status (Table 3). Using a cutoff of ≥ 1 cm, TND had a sensitivity and specificity of 84% and 56% in the pre-NAC settings, respectively. When applying this cutoff in the post-NAC setting, sensitivity decreased to 67% and specificity increased to 79%. A ≥ 1 cm TND on pre-NAC imaging had an NPV of 97%. In other words, if we applied imaging eligibility criteria for nipple-sparing mastectomy of ≥ 1 cm TND, of 93 breasts in this cohort, 90 would go on to have a negative nipple pathology. On post-NAC imaging, the NPV of ≥ 1 cm TND cutoff decreased very slightly to 95%. We further examined those breasts that had a complete imaging response post-NAC, defined as no residual tumor enhancement seen on MRI or suspicious calcification/masses on mammogram. In the 13 breasts with TND of < 1 cm on pre-NAC imaging and a complete response on post-NAC imaging, all were NS- ($p = 0.4$).

Discussion

In this study we used findings on both pre- and post-neoadjuvant mammogram and MRI to categorize women based on TND < 1 cm, 1-2 cm and > 2 cm from the nipple. We found that increasing TND was associated with a higher likelihood of having a negative nipple status on final pathology and use of a cutoff TND of ≥ 1 cm on pre- or post-NAC mammogram and MRI could rule out nipple involvement in 97% and 95% of breasts, respectively.

To our knowledge this is the first study to examine this question in the neoadjuvant setting. Prior studies have evaluated the optimal TND cutoff on MRI to determine nipple-sparing mastectomy eligibility in the upfront surgery setting. In one such study by Koh et al., among 249 patients who had pre-operative MRI, 24 (9.6%) had nipple involvement on final pathology.[17] Nipple enhancement and TND of ≤ 1 cm showed the best performance (AUC 0.88) in predicting nipple-areolar complex involvement, with a sensitivity of 92%, specificity of 84%, PPV of 38%, and NPV of 99%. However, this study also included patients having breast conservation who may have had undetected nipple pathology, likely explaining the higher reported PPV in that study compared with ours (27% on post-NAC MRI). Mariscotti et al., in a retrospective study of 195 patients, also found a TND distance of 1 cm to be most appropriate for selecting patients likely to have negative nipple pathology.[12] TND of 1 cm had a sensitivity of 82%, specificity of 72%, PPV of 84%,

and NPV of 69%. Increasing this threshold to 1.5 cm decreased the sensitivity to 69% and increased specificity to 77%, while decreasing the threshold to 0.5 cm increased the sensitivity to 92% and decreased specificity to 57%. Using a TND cutoff of ≥ 1 cm to select patients for nipple-sparing mastectomy would have correctly identified 81% of patients without nipple involvement. These results are consistent with other studies[16,18] that sought to identify a threshold lower than the previously accepted cutoff TND of 2 cm, which excluded many patients without nipple involvement from having nipple-sparing mastectomy. Our study found that this cutoff had a sensitivity and specificity of 84% and 56% for pre-NAC imaging, with an NPV of 97%, compared to 67%, 79%, and 95%, respectively, on post-NAC imaging.

The relatively high NPV seen in our study compared with both Mariscotti et al. and Ponzone et al. is perhaps explained by the high sensitivity of MRI and imaging criteria set for suspected disease, where we considered as suspicious any focus of non-mass enhancement on pre- and post-NAC images. We also included distance of mammographic calcifications to the nipple when accounting for the proximity to the nipple of suspicious imaging findings. Although the NPV for both pre- and post-NAC imaging are comparable, the most stringent method of selecting patients without nipple involvement would be ≥ 1 cm TND cutoff on pre-NAC imaging. However, using the pre-NAC cutoffs would also lead to exclusion of a larger proportion of patients with negative nipple status from undergoing nipple-sparing mastectomy.

We found a low PPV for both pre- and post-NAC MRI in determining nipple involvement: 17% and 26%, respectively. In patients having upfront surgery there is also variation in the PPV of MRI, ranging from 36–84%,[12,17] indicating that a large proportion of patients deemed ineligible for nipple-sparing mastectomy on this basis will have NS-. In our cohort, based on the pre-NAC imaging cutoff of ≥ 1 cm TND, 86 breasts were ineligible, and only 15 of these had positive nipple pathology. Similarly, using post-NAC imaging, 45 patients would have been ineligible, of whom 12 had positive pathology. This is an area which requires further study, as offering nipple-sparing mastectomy to patients with a TND < 1 cm relies heavily on a negative retroareolar biopsy result. A negative retroareolar biopsy is considered mandatory in addition to imaging selection criteria for nipple-sparing mastectomy. In a study including 232 prospectively collected therapeutic mastectomy specimens with grossly uninvolved nipples, Brachtel et al. found a sensitivity of 80% and NPV of 96% for the retroareolar biopsy with respect to ruling out nipple involvement.[19] These studies have not yet been replicated in the neoadjuvant setting, so although using a ≥ 1 cm TND cutoff on post-NAC imaging overestimates extent of disease, at present it may be the most oncologically sound method of selecting women without suspected disease for sparing the nipple areolar complex.

On multivariable analysis increasing number of positive lymph nodes and increasing TND were significantly associated with nipple involvement. This is consistent with prior studies in patients having upfront surgery[16,20] and suggests that increasing tumor burden as manifested by residual nodal disease after NAC is correlated with nipple involvement. Thus, careful consideration should be given to attempting nipple-sparing mastectomy in patients with clinical evidence of persistent nodal disease after NAC. An interesting finding in this

study was that 13 patients who had suspicious disease within 1 cm of the nipple on pre-NAC imaging showed complete resolution on mammogram and MRI after NAC, and none of these patients had nipple involvement on final pathology. Although this is a small number of patients, it suggests that in patients with an excellent response to chemotherapy it may be possible to further reduce the ≥ 1 cm TND cutoff, though this requires further study in a larger population.

Limitations of our study include the retrospective design. In addition, although MRIs were reviewed by radiologists specializing in breast imaging, determination of what constitutes a suspicious finding can be subjective and therefore may differ based on radiologist. A strength of this study is the inclusion of mammographic findings in determination of TND, because, particularly in the post-neoadjuvant setting, evidence of residual disease such as calcifications may not be detected on MRI. Further, although TND is an important factor in determining whether the nipple-areolar complex can be successfully spared, it is important to choose appropriate candidates for nipple-sparing mastectomy such that the entire breast parenchyma and disease can be adequately removed from all quadrants. Most recurrences occur not at the nipple-areolar complex, but along the superior and lateral borders of the mastectomy flaps.[21] Therefore, even if the patient meets criteria for nipple-sparing mastectomy based on radiologic TND cutoffs, eligibility remains a clinical decision that should take into account factors such as disease volume and location, breast size, and incision size and location.

Conclusion

We found that increasing TND on pre- or post-NAC imaging was associated with a higher likelihood of having a negative nipple pathologic status. A TND of ≥ 1 cm on pre- or post-NAC imaging had a high NPV and could be used to determine eligibility for nipple-sparing mastectomy after NAC. Further study of imaging accuracy in women with TND < 1 cm pre-NAC who achieve complete imaging response post-NAC is needed.

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Synopsis

We reviewed eligibility criteria for nipple-sparing mastectomy in women undergoing neoadjuvant chemotherapy (NAC) for breast cancer. Tumor-to-nipple distance ≥ 1 cm on pre- or post-NAC imaging is highly predictive of negative nipple pathology and could be used to determine eligibility.

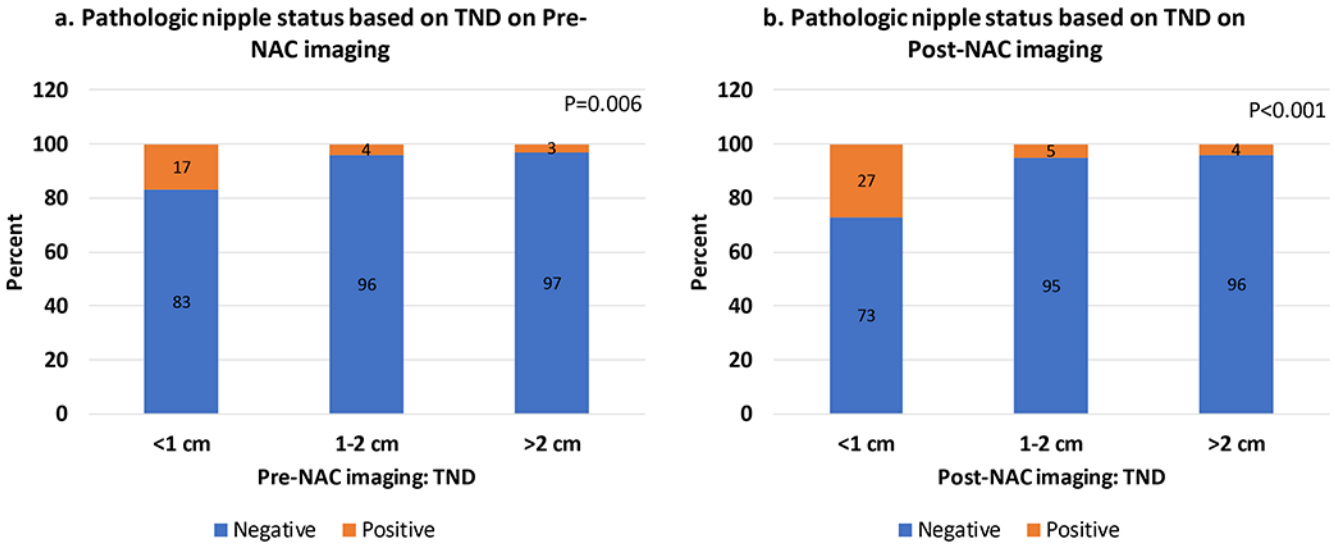

Figure 1.

Pathologic nipple status based on tumor-to-nipple distance (TND) on (a) pre- and (b) post-neoadjuvant chemotherapy (NAC) imaging.

Table 1.

Clinicopathologic characteristics of patients with and without pathologic nipple involvement.

Variable	Overall n = 179	Nipple involvement n = 18	No nipple involvement (NS-) n = 161	*p*
Age, years	48 (41–57)	48 (42–66)	48 (41–57)	0.5
Tumor histology				0.06
Ductal	137 (77%)	10 (56%)	127 (79%)	
Lobular	11 (6%)	3 (17%)	8 (5%)	
Mixed ductal/lobular	22 (12%)	4 (22%)	18 (11%)	
Other	9 (5%)	1 (5%)	8 (5%)	
Grade				**0.02**
Well or moderate	55 (32%)	10 (62%)	45 (29%)	
Poor	117 (68%)	6 (38%)	111 (71%)	
Clinical T				0.3
T1-T2	125 (74%)	11 (61%)	114 (76%)	
T3	43 (26%)	7 (39%)	36 (24%)	
Clinically node-positive	113 (67%)	12 (67%)	101 (67%)	> 0.9
Lymphovascular invasion present	53 (49%)	11 (72%)	42(45%)	0.08
Pathologic T stage				**0.02**
Tis-T2	142 (89%)	10 (67%)	132 (91%)	
T3	18 (11%)	5 (33%)	13 (9%)	
Pathologically node-positive	74(46%)	12 (78%)	62 (42%)	**0.01**
Number of positive lymph nodes	0 (0–3)	6 (2–8)	0 (0–2)	< **0.001**
Subtype				< **0.001**
HR+/HER2−	75 (42%)	15 (83%)	60 (37%)	
HR−/HER2−	43 (24%)	0 (0%)	43 (27%)	
HER2+	61 (34%)	3 (17%)	58 (36%)	
Largest extent of suspected disease on MRI, cm				
Pre-NAC	7.9 (5.7–10.1)	9.4 (8.6–11.4)	7.7 (5.5–9.9)	**0.001**
Post-NAC	3.4 (0.8–6.9)	7.8 (6.2–8.9)	2.8 (0.5–6.2)	< **0.001**
Multifocal or multicentric				
Pre-NAC	160 (89%)	18 (100%)	142 (88%)	0.2
Post-NAC	99 (55%)	15 (83%)	84 (52%)	**0.02**
Distance of calcifications to nipple, cm				
Pre-NAC mammogram	3.5 (1.7–5.5)	1.8 (0.0–5.0)	3.5 (2.1–5.5)	0.2
Post-NAC mammogram	2.5 (1.0–5.1)	1.3 (0.0–2.0)	2.8 (1.2–5.2)	**0.03**

Variable	Overall n = 179	Nipple involvement n = 18	No nipple involvement (NS-) n = 161	*p*
Skin thickening				
Pre-NAC on mammogram	46 (28%)	9 (56%)	37 (25%)	**0.015**
Pre-NAC on MRI	81 (45%)	14 (78%)	67(42%)	**0.008**
Post-NAC on MRI	68 (38%)	13 (72%)	55 (34%)	**0.004**
Nipple retraction on MRI				
Pre-NAC	44 (25%)	9 (50%)	35 (22%)	**0.017**
Post-NAC	31 (17%)	8 (44%)	23 (14%)	**0.004**

Continuous data presented as n (%) and categorical as median (interquartile ratio).

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NAC, neoadjuvant chemotherapy.

Table 2.

Multivariable analysis of clinical and radiologic factors' influence on risk of pathologic nipple involvement.

Variable	OR	95% CI	*p*
Age	1.00	0.94–1.07	0.92
Number of positive axillary nodes	1.6	1.03–1.34	**0.018**
Histologic grade III (vs. I or II)	0.31	0.06–1.32	0.12
Clinical T3 vs. T1 or T2	0.32	0.06–1.5	0.15
Post-NAC TND ≥ 1 cm vs. < 1 cm	0.17	0.03–0.78	**0.03**
Pre-NAC nipple retraction on MRI	6.22	1.29–37.3	**0.029**

NAC, neoadjuvant chemotherapy; TND, tumor-to-nipple distance (includes mass and non-mass enhancement, and pathologic-appearing calcifications).

Table 3.

Measures of performance for a cutoff TND of ≥ 1 cm on imaging in predicting final nipple pathology status.

	n	Final Nipple Positive	Pathology Negative	Sensitivity	Specificity	NPV	PPV
Pre-NAC							
TND < 1 cm	86	15 (17%)	71 (83%)	83.4%	55.9%	96.7%	17.4%
TND ≥ 1 cm	93	3 (3%)	90 (97%)				
Post-NAC							
TND < 1 cm	45	12 (27%)	33 (73%)	66.7%	79.5%	95.5%	26.6%
TND ≥ 1 cm	134	6 (4%)	128 (96%)				

NAC, neoadjuvant chemotherapy; NPV, negative predictive value; PPV, positive predictive value; TND, tumor-to-nipple distance (includes mass and non-mass enhancement, and pathologic-appearing calcifications).