Predictors of Successful Nipple-Sparing Mastectomy After Neoadjuvant Chemotherapy

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Background

- Neoadjuvant chemotherapy (NAC) is increasingly used for operable breast cancer, and rates of pathologic complete response have increased with targeted therapy.[1-2]
- Nipple-sparing mastectomy (NSM) utilization after NAC is increasing.[3-6]
- A 1 cm tumor-to-nipple distance (TND) is often used for NSM eligibility in the primary surgical setting, but its suitability after NAC is not well defined.

Study Objective

To examine factors associated with nipple involvement and evaluate the accuracy of TND ≥ 1 cm in predicting negative nipple pathology (NS-) in a cohort of women having total mastectomy after NAC

Methods

- Retrospective review of women with invasive breast cancer treated with NAC between 8/2014-4/2018
  - Underwent total mastectomy after NAC
  - Pre- and post-NAC MRIs available
- Excluded: Women with clinical T4 tumors, clinical nipple involvement, or pathologic nipple discharge
- Mammogram and pre/post NAC MRIs were reviewed by a dedicated breast radiologist
- Findings suggestive of nipple involvement such as retraction/invasion, mass and non-mass enhancement on MRI, or suspicious calcifications on mammogram were included in TND measurement
- Patients were stratified based on TND < 1 cm, 1-2 cm, or ≥ 2 cm
- Association of clinicopathologic, imaging variables, and TND with nipple involvement was examined using t-test or Wilcoxon's rank test for continuous variables, and Chi-square or Fisher's exact test for categorical variables
- Accuracy of ≥1 cm TND for estimating probability of nipple involvement was determined

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Results

- 175 eligible women undergoing 179 mastectomies met criteria and were analyzed.
- 18 nipples were positive on final pathology

TABLE 1. *Clinicopathologic characteristic of breasts with and without pathologic nipple involvement*

Variable	Overall n=179	Pathologic nipple involvement n=18	No pathologic nipple involvement (NS-) n=161	P-value
Age, years, median (IQR)	48 (41,57)	48 (42,66)	48 (41,57)	0.5
Tumor histology				0.06
Ductal	77%	56%	79%	
Lobular	6%	17%	5%	
Mixed ductal/lobular	12%	22%	11%	
Other	5%	5%	5%	
Grade				0.02
I/II	32%	62%	29%	
III	68%	38%	71%	
Clinical T				0.3
Tis-T2	74%	61%	76%	
T3	26%	39%	24%	
Clinical node positive	67%	67%	67%	>0.9
LVI present	49%	73%	45%	0.08
Pathologic T stage				0.02
Tis-T2	89%	67%	91%	
T3	11%	33%	9%	
Pathologic node positive	46%	80%	42%	0.01
Number of positive LNs, median (IQR)	0 (0,3)	6 (2,8)	0 (0,2)	<0.001
Subtype				<0.001
HR+/HER2-	42%	83%	37%	
HER2+	34%	17%	36%	
HR-/HER2-	24%	0%	27%	
Pre-NAC MRI largest extent suspected disease, median (IQR)	7.9 (5.7,10.1)	9.4 (8.6,11.4)	7.7 (5.5,9.9)	0.001
Post-NAC MRI largest extent suspected disease, median (IQR)	3.4 (0.8,6.9)	7.8 (6.2,8.9)	2.8 (0.5,6.2)	<0.001
Pre-NAC multifocal/multicentric	89%	100%	88%	0.2
Post-NAC multifocal/multicentric	55%	83%	52%	0.02
Pre-NAC skin thickening on mammogram	28%	56%	25%	0.015
Pre-NAC nipple retraction on MRI	25%	50%	22%	0.017
Post-NAC nipple retraction on MRI	23%	44%	14%	0.004
Pre-NAC skin thickening on MRI	45%	78%	42%	0.008
Post-NAC skin thickening on MRI	38%	72%	34%	0.004

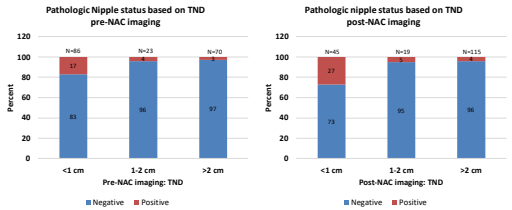
IQR, interquartile range; LVI, lymphovascular invasion; LN, lymph node; NAC, neoadjuvant chemotherapy; TND, tumor-to-nipple distance (includes mass and non-mass enhancement, and pathologic-appearing calcifications)

On univariate analysis, nipple involvement was associated with lower grade, HR+/HER2-, pT3, pN+, greater numbers of positive nodes, and a number of imaging variables such as greater tumor extent on pre- and post-NAC MRI, and multifocality/multicentricity on post-NAC MRI (p-values < 0.05)(Table 1).

Results

Likelihood of NS- was higher, with increasing TND on both pre- and post-NAC imaging. In breasts with pre-NAC TND < 1 cm, 83% had NS- compared to 96% with TND 1-2 cm and 97% with > 2 cm (p < 0.05). Similarly, on post-NAC imaging, 73%, 95%, and 96%, respectively, had NS- (p < 0.05).

Figure 1. *Pathologic nipple status based on increasing TND pre- and post-NAC imaging*

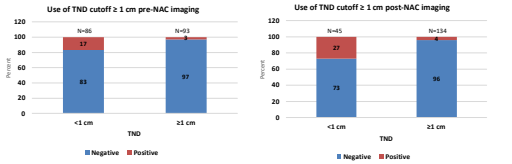


On multivariable analysis, increasing number of positive nodes, pre-NAC nipple retraction on MRI, and TND < 1 cm were associated with nipple involvement (p < 0.05).

TABLE 2. *Multivariable analysis demonstrating risk of pathologic nipple involvement based on clinical and radiologic variables*

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

Figure 2. *Pathologic nipple status based on use of TND cutoff ≥ 1 cm pre- vs post-NAC imaging*



Results

TABLE 3. *Measures of performance for cutoff TND ≥ 1 cm in predicting nipple status*

	n = 179	Final nipple pathology		Sensitivity	Specificity	NPV	PPV
		Positive	Negative				
Pre-NAC imaging							
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 imaging							
TND < 1 cm	45	12 (27%)	33 (73%)	66.7%	79.4%	95.5%	26.6%
TND ≥ 1 cm	134	6 (4%)	128 (96%)				

- A ≥ 1 cm TND on pre-NAC imaging had an NPV of 97% for NS- compared to 96% for post-NAC imaging.
- In 13 women with TND of < 1 cm on pre-NAC imaging and a complete response on post-NAC imaging, all had NS- (p = 0.4).

Summary

- On multivariable analysis, increasing number of positive lymph nodes, pre-NAC nipple retraction on MRI, and TND < 1 cm were associated with nipple involvement.
- Increasing TND pre- or post-NAC imaging was associated with a higher likelihood of NS-.
- Use of a TND ≥ 1 cm pre- *or post-NAC* imaging had a high predictive value for NS-.
- Further study of imaging accuracy in women with TND < 1 cm pre-NAC who achieve complete imaging response post-NAC is needed.

Conclusions

- A TND cutoff of ≥ 1 cm pre- or post-NAC imaging rules out nipple involvement in 97% and 96% of breasts, respectively, and could be used to determine eligibility for NSM post-NAC.

Selected References

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