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Impact of clipped node as a sentinel lymph node on axillary staging following neoadjuvant chemotherapy in clinically node-positive breast cancer

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Abstract

Background: Residual disease after neoadjuvant chemotherapy (NAC) is prognostic and informs adjuvant treatment. Targeted axillary dissection (TAD) following NAC has low false-negative rates (FNR), facilitating accurate axillary staging. This study evaluates the clipped node status in axillary staging utilizing TAD.

Methods: Retrospective review identified cN1 breast cancer patients treated with NAC and TAD from 7/2013-6/2023. Nodal ultrasound and biopsy defined cN1 status. Patient, tumor and treatment characteristics were compared based on clipped node status (SLN or non-SLN). Multivariate analysis of factors associated with clipped node as non-SLN was performed.

Results: 680 patients underwent TAD, 94.6% with dual-tracer mapping. In 3 patients (0.4%) no SLN was identified. The clipped node was a SLN in 610 patients (90%) and non-SLN in 70

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(10.3%). When the clipped node was a non-SLN, 42 (60%) were positive for metastasis. In 22 of 42 patients (52%), the clipped non-SLN was the only positive node. The clipped non-SLN cohort had a higher proportion with >3 suspicious nodes at presentation ($p=0.003$), fewer SLNs excised (mean 2.2 vs 3.5, $p<0.001$) and fewer positive SLNs ($p<0.001$). On multivariate analysis, >3 suspicious nodes on US (OR 3.0, $p=0.001$) and tumor size at presentation (OR 0.9, $p=0.02$) were significantly associated with clipped node as non-SLN.

Conclusions: When the clipped node was a non-SLN, half of the time it was the only positive node and only residual disease on TAD. Given implications for adjuvant therapy, selective clipped node excision is recommended for precise identification of residual disease after NAC.

Keywords

Targeted axillary dissection; node-positive breast cancer; neoadjuvant chemotherapy; clipped node

Introduction

Surgical management of the axilla in patients with cN1 breast cancer treated with neoadjuvant chemotherapy (NAC) has evolved over the past decade. While historically, patients were recommended to undergo axillary dissection (ALND), improvements in systemic therapy have resulted in a higher rate of axillary pathologic complete response (pCR), which has facilitated de-escalation of axillary surgery.¹ Several studies evaluating sentinel lymph node (SLN) staging in this population highlighted the importance of operative technique in obtaining an acceptably low false negative rate (FNR) and improving accuracy of the procedure.²⁻⁶ Within a multidisciplinary context, accurate post-NAC axillary staging remains a critical component of the assessment of residual disease, thus informing adjuvant systemic therapy, and more recently radiation therapy, in cN1 disease.⁷⁻¹⁰

In 2016, seminal work by Caudle and colleagues demonstrated that the lowest FNR (2%) was achieved when the biopsy proven node was marked pre-NAC with a clip and selectively removed in addition to SLN dissection following NAC, thus defining targeted axillary dissection (TAD).¹¹ In fact, the FNR of the removing the clipped node alone was 4%, highlighting that pathologically re-evaluating the biopsy-proven clipped node is highly informative in determining if residual disease is present following NAC. Interestingly, several studies have previously demonstrated that the clipped node was a non-SLN in approximately 25% of cases, which further strengthened the importance of selectively localizing and excising this node.^{11,12} Over the past decade, several groups have pioneered multiple techniques to identify the biopsy-proven positive node including marking pre-NAC with a seed (MARI procedure),¹² tattooing of the biopsy-proven positive node,¹³ and use of intraoperative ultrasound for localization.¹⁴

After initial data established the accuracy of TAD, its use became incorporated into clinical practice at our institution with the intent to omit ALND when TAD nodes were negative. This study sought to evaluate the institutional experience at the University of Texas MD Anderson Cancer Center in patients impacted by this change in practice. The objectives were to identify the incidence of the clipped node as a non-SLN, factors associated with the

clipped node being a non-SLN, as well as to determine the impact of the clipped node being a non-SLN on adjuvant therapy decisions following surgery.

Methods

A retrospective review of an institutional database was conducted. Patients included those diagnosed with cN1 breast cancer at presentation who were treated with NAC followed by TAD from July 2013 to June 2023. Patients who underwent a planned ALND were excluded as many of these patients were treated during the development of the TAD technique and the database does not include patients with more extensive nodal involvement at presentation. All patients underwent a regional nodal ultrasound (US) at diagnosis including axillary levels I-III, internal mammary, and supraclavicular nodal basins. Fine needle aspiration (FNA) biopsy was performed of abnormal-appearing nodes. If the cytology was positive, a clip was placed at the time of biopsy in the biopsy-proven positive axillary node to facilitate subsequent identification. After completion of NAC, the clipped node was localized preoperatively for planned TAD. The most commonly used technique for dual-tracer mapping for sentinel lymph node biopsy at our institution is to inject technetium-labeled sulfur colloid the day of surgery (0.5 mCi) or the day prior to surgery (2.5 mCi). On the day of surgery in the operating room, between 3-5cc of isosulfan blue dye is injected into the breast followed by massage. Lymph nodes that are hot, blue, or both are excised. The clipped node is also selectively excised after preoperative localization with seed technology to complete the targeted axillary dissection (TAD) and noted at the time of excision to be a SLN or non-SLN.

Patient, tumor, and treatment characteristics were evaluated and compared between patients where the clipped node was a SLN and patients where the clipped node was a non-SLN. The student *t* test was used to compare the means of continuous variables with equal variances. The Wilcoxon rank-sum test was used to compare the median of continuous variables without equal variances. The X^2 test or Fisher exact test was used for univariate comparison of categorical variables. Multivariate logistical regression models were used with backward stepwise exclusion of factors, to test the significance of adding candidate predictive factors associated with the clipped node not being a SLN: age, race, sex, clinical T stage (or size of tumor at diagnosis), subtype, tumor grade, histology, number of suspicious clinical nodes on original US, surgery types and tracer used. Stata statistical software (SE, 16.1StataCorp LP, College Station, TX) was used for statistical analyses. All p-values were 2 tailed, and $p \leq 0.05$ was considered significant.

Results

A total of 902 patients undergoing TAD were identified. 222 patients underwent a planned ALND and were excluded. There were 680 patients included in the final analysis. The clipped node was a non-SLN in 70 patients (10.3%) and the clipped node was a SLN in 610 patients (89.7%). Of the 70 patients in whom the clipped node was a non-SLN, the clipped node was negative in 28 patients (40%) and positive in 42 patients (60%). Of the 42 patients in whom the clipped node was a positive non-SLN, 26 patients were found to have macrometastases, 13 with micrometastases, and 3 patients had isolated tumor cells

(ITCs) present in the clipped node. In 22 (52%) of the patients in whom the clipped node was a positive non-SLN, all of the remaining SLNs identified during TAD were negative for metastasis, making the clipped node the only evidence of residual disease in the axilla on TAD. [Figure 1]

The majority of patients underwent dual tracer mapping (n=643, 94.6%). In 3 patients (0.4%) no SLN was identified. There were no differences in demographic, clinical or pathologic factors including age, gender, race, tumor histology, clinical T category, tumor biomarkers, grade, Ki-67, type of tracer used, the size of the residual tumor, the size of residual nodal metastases, and the presence of a breast pCR or axillary pCR when comparing the clipped node as SLN status. [Table 1]

On univariate analysis, the clipped node as a non-SLN cohort had a higher proportion of patients with >3 suspicious nodes on US at presentation (p=0.003), fewer SLNs excised (mean 2.2 vs 3.5, p=< 0.001) and a lower proportion with a positive SLN (p=< 0.0001). When ≥3 SLNs were excised, this was significantly associated with the clipped node being a SLN, though this was not always the case. [Table 1] On multivariate analysis, >3 suspicious nodes on US at presentation (OR 2.5, p=0.001) and the excision of fewer SLNs (1-2 vs ≥3 excised, OR 0.3, p=<0.0001) were significantly associated with the clipped node as a non-SLN. [Table 2]

In the cohort of 22 patients in whom the clipped node was a non-SLN and was the only positive node on TAD, 11 patients had macrometastases, 9 had micrometastases, and 2 patients had ITCs in the clipped node. 6 of these patients did not undergo completion ALND. All of these patients received adjuvant systemic therapy and radiation therapy. Six patients had a breast pCR. Fifteen (68%) patients had hormone-receptor-positive tumors, 4 (18%) were HER2-positive, and 5 (23%) were triple-negative. 21 patients (95%) underwent TAD using dual-tracer mapping technique. All patients received neoadjuvant taxane-based therapy, 18 (82%) anthracycline-based therapy, and all patients with HER2-positive disease (18%) received HER2-targeted therapy. All patients received adjuvant radiation therapy and all but 1 patient received adjuvant systemic therapy. [Table 3] In that same cohort of 22 patients, the 21 patients who had dual-tracer mapping all received isosulfan blue dye in addition to technetium labeled sulfur colloid. The majority had between 3-5cc of blue dye injected. The average number of TAD nodes (SLNs and clipped node) excised in this population was 2.7 (range 1-6 nodes excised). [Table 4]

Discussion

In this highly selected group of breast cancer patients with cN1 disease with a low burden of clinically node-positive disease at diagnosis undergoing TAD after NAC, the clipped node was a non-SLN in approximately 10%. We found that higher nodal disease burden (>3 suspicious nodes by axillary US) is associated with the likelihood of the clipped node being a non-SLN. This has implications for axillary staging as de-escalation strategies are extrapolated to a broader patient population with a higher disease burden at diagnosis. There is a possibility in this population that the clipped node will be even less likely to be a

SLN, suggesting that selective excision of the clipped node is even more important for the accuracy of axillary staging.

Our data also emphasize the importance of preoperatively marking the previously biopsy-proven metastatic node given that this node can be the only identifiable residual disease which would be missed with a SLN dissection alone. Previous studies have demonstrated that the clipped node is a non-SLN about 25% of the time.^{11,12} The majority of patients in this study (94.6%) underwent dual-tracer mapping technique which is the accepted standard of care for SLND after NAC given its low FNR. The lower rate identified in our study may reflect advancements in detection of nodal disease by imaging, intraoperative technique, response to systemic therapy, or patient selection for TAD. This lower rate of non-SLN identification is supported by data from a recent international analysis of patients with cN+ disease treated with TAD or SLN biopsy who converted to ypN0 describing that a clip was retrieved as a SLN in 85% of the patients in the SLN arm in whom a clip was placed but not selectively excised.¹⁵

Although the rate of the clipped node being a non-SLN was relatively low at 10%, in half of those patients the clipped node was the only identified residual nodal disease on TAD after NAC. In contemporary practice, as multidisciplinary decision making is increasingly based on the presence or absence of residual disease after NAC, precise axillary staging becomes even more important. Randomized trials in patients with residual disease have demonstrated improved outcomes with the addition of adjuvant systemic therapy in HER2-positive disease,⁷ triple negative breast cancer,¹⁶ high-risk ER-positive/HER2-negative disease,^{9,17} and BRCA-associated breast cancer.⁸ Furthermore, in the context of recently reported data from NSABP B-51 (San Antonio Breast Cancer Symposium 2023) suggesting oncologic safety of omission of regional nodal radiation in cN1 breast cancer which converts to ypN0 after NAC,¹⁰ incorrect axillary staging as a pathologic complete response may result in omission of adjuvant regional nodal irradiation despite the presence of residual disease. The majority of the 22 patients in our population in which the clipped node was the only identifiable residual disease on TAD had hormone receptor-positive disease, which is expected given the lower rates of pCR in this population.¹ Therefore, these patients are at highest risk of missing residual disease without selective identification of the clipped node, with implications for adjuvant therapy.

In contrast, several studies have suggested that clip placement and removal is not necessary given low rates of local-regional recurrence in patients who convert to ypN0, though follow-up was at only 3 years.^{18,19} An analysis of patients with cN+ disease treated with TAD and SLN after NAC and determined to have axillary pCR (ypN0) showed no difference in local regional, regional or distant recurrence between the procedures.¹⁵ While TAD may not improve local-regional outcomes over SLN dissection alone, residual disease remains a critical factor in determining adjuvant treatment and its role in most accurately defining the extent of residual disease remains relevant.

Limitations of this study include that it is a single-institution, retrospective study and represents a very specific patient population as 90% of the patients in our population had less than 3 suspicious axillary nodes on US at presentation. Likely in large part due to this

narrow population with lower disease burden, the clipped node was a non-sentinel node only 10% of the time as compared with prior studies reporting a rate closer to 25%. This study also includes patients treated over a 10 year timespan during which time systemic therapy regimens were rapidly evolving and patients were treated according to the standard of care at any given time. Further studies evaluating outcomes in this population to determine the clinical impact of identification of residual disease as well as to understand the association with the clipped node being a non-sentinel node in patients with a higher nodal disease burden prior to neoadjuvant chemotherapy are needed given that this study was limited to patients with more limited nodal disease burden at presentation.

In conclusion, the clipped node was a non-SLN in approximately 10% of patients undergoing TAD after NAC. Furthermore, when the clipped node was a non-SLN and positive for malignancy, half of the time it was the only positive node on TAD. In these patients, the clipped node is the only identifiable residual disease in the axilla and not detected by SLN dissection alone. Given implications for adjuvant multidisciplinary decision-making in current practice, selective excision of the clipped node facilitates precise identification of residual nodal disease after NAC.

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Synopsis

In 10.3% of patients, the clipped node was a non-SLN. 60% of clipped non-SLNs contained metastases and were the only positive node in 52%. Selective clipped node excision is recommended for precise identification of residual nodal disease after neoadjuvant chemotherapy.

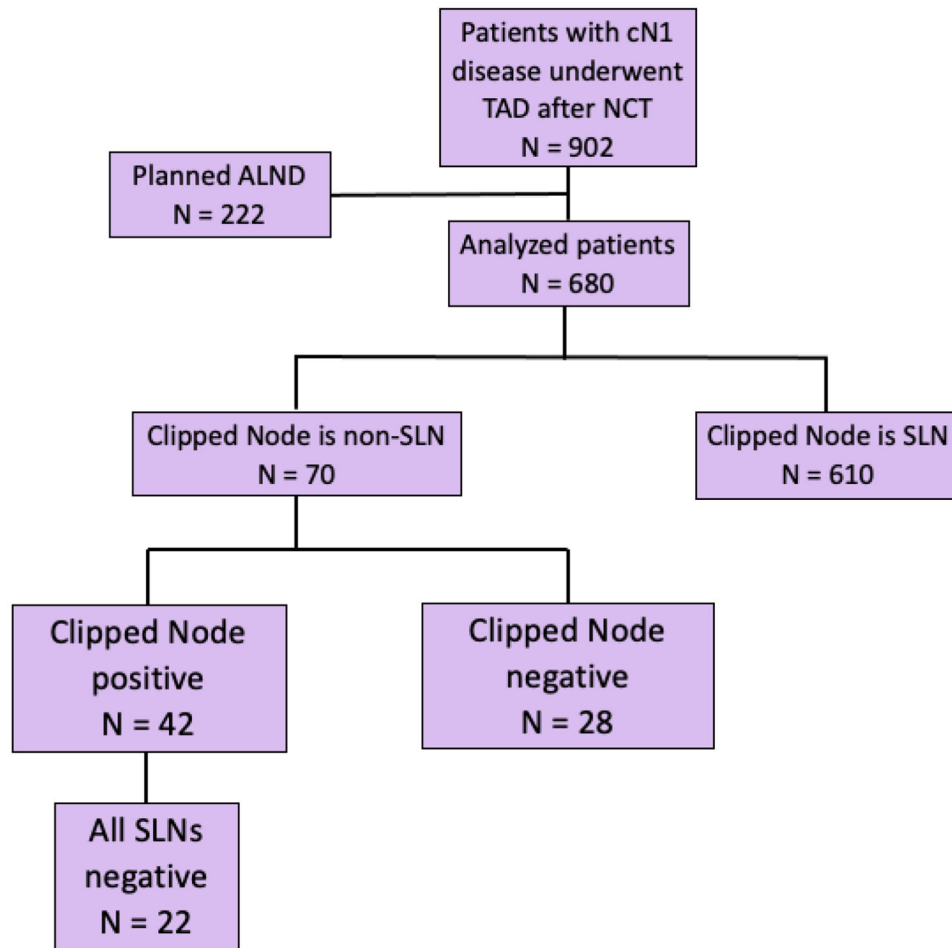


Figure 1:
Consort diagram of patients included in the study.

Table 1.

Univariate analysis of factors associated with clipped node status (SLN or non-SLN) on TAD for patients with cN1 breast cancer treated with NAC.

Variable	Total (N=680)	Clipped node as a non-SLN (N=70)	Clipped node as a SLN (N=610)	p-value
Demographic information				
Age, years				0.8
Median	52	52.5	52	
Mean (range)	52.6 (25-85)	52.4 (29-79)	52.6 (25-85)	
Gender				1.0
Male	5 (0.7)	0 (0)	5 (0.8)	
Female	675 (99.3)	70 (100)	605 (99.2)	
Race				1.0
White	421 (61.9)	43 (61.4)	378 (62)	
Black, Hispanic, Asian	259 (38.1)	27 (38.6)	232 (38)	
Clinical factors				
Histology				0.06
Ductal	647 (95.4)	69 (100)	578 (94.9)	
Lobular with/without ductal	31 (4.6)	0 (0)	31 (5.1)	
Clinical T stage				0.2
Tis	5 (0.7)	1 (1.4)	4 (0.7)	
T1	111 (16.3)	14 (20)	97 (15.9)	
T2	400 (58.8)	45 (64.3)	355 (58.2)	
T3	150 (22.1)	9 (12.9)	141 (23.1)	
T4	14 (2.1)	1 (1.4)	13 (2.1)	
Tumor subtype				0.4
HR+/HER2+	128 (18.8)	10 (14.3)	118 (19.3)	
HR+/HER2-	359 (52.8)	35 (50)	324 (53.1)	
HR-/HER2+	60 (8.8)	6 (8.6)	54 (8.9)	
HR-/HER2-	133 (19.6)	19 (27.1)	114 (18.7)	
Grade				0.2
G1	36 (5.3)	1 (1.5)	35 (5.8)	
G2	269 (39.9)	25 (36.2)	244 (40.3)	
G3	369 (54.8)	43 (62.3)	326 (53.9)	
Ki67 (%)				0.5
Median	40	40	40	
Mean (range)	43.1 (1-100)	45.4 (10-99)	42.8 (1-100)	
Size of tumor at diagnosis (cm)				0.1
Median	3.3	3	3.4	
Mean (range)	4.0 (0-18)	3.4 (0-9.3)	4.1 (0-18)	

Variable	Total (N=680)	Clipped node as a non-SLN (N=70)	Clipped node as a SLN (N=610)	p-value
# Suspicious clinical nodes on US at presentation				0.003*
1-3	611 (89.9)	55 (78.6)	556 (91.2)	
>3	69 (10.2)	15 (21.4)	54 (8.9)	
Intraoperative and pathologic factors				
Tracer for intraoperative mapping				0.8
Isotope only	37 (5.4)	4 (5.7)	33 (5.4)	
Dual tracer	643 (94.6)	66 (94.3)	577 (94.6)	
SLN retrieved				0.001
No	3 (0.4)	3 (4.3)	0 (0)	
Yes	677 (99.6)	67 (95.7)	610 (100)	
# SLNs excised, continuous				<0.0001
Median	3	2	3	
Mean (range)	3.4 (0-11)	2.2 (0-7)	3.5 (0-11)	
# SLNs excised, categorical				<0.0001
0-2	341 (37.8)	83 (70.3)	534 (68.1)	
≥3	561 (62.2)	35 (29.7)	250 (31.9)	
Positive SLN				<0.0001
No	300 (44.1)	48 (68.6)	252 (41.3)	
Yes	380 (55.9)	22 (31.4)	358 (58.7)	
Clipped node positive for malignancy				0.8
No	286 (42.1)	28 (40)	258 (42.3)	
Yes	394 (57.9)	42 (60)	352 (57.7)	
Size of residual primary tumor on pathology (cm)				0.3
Median	1.1	1	1.1	
Mean (range)	1.8 (0-15)	1.6 (0-9.8)	1.9 (0-15)	
Size of residual metastases in positive clipped nodes (mm)				0.4
Median	4.3	3	4.5	
Mean (range)	5.9 (0-35)	5.2 (0-30)	6 (0-35)	
pCR axilla				0.4
No	404 (59.4)	45 (64.3)	359 (58.9)	
Yes	276 (40.6)	25 (35.7)	251 (41.2)	
pCR breast				0.8
No	438 (65.7)	43 (64.2)	395 (65.8)	
Yes	229 (34.3)	24 (35.8)	205 (34.2)	

SLN = sentinel lymph node, NAC = neoadjuvant chemotherapy, TAD = targeted axillary dissection, pCR = pathologic complete response

Table 2.

Multivariate analysis of factors associated with clipped node as a non-SLN.

Variable	Odds Ratio	p-value	95% Confidence Interval	
# SLNs excised				
1-2 nodes				
≥3 nodes	0.3	<0.0001	0.2	0.5
# Suspicious clinical nodes on original US				
>3	2.5	0.01	1.2	5.1

SLN = sentinel lymph node, NAC = neoadjuvant chemotherapy, TAD = targeted axillary dissection

Table 3:

Tumor and treatment characteristics of 22 patients where the clipped node was a non-SLN and the only positive node on TAD.

	ER	PR	HER2	Axillary Surgery	Breast pCR	NAC Taxane	NAC AC	NAC HER2	Adj RT	Adj ET	Adj Pembro	Adj HER2
1	+	+	-	TAD	+	+	+	-	+	+	-	-
2	+	+	-	ALND	-	+	+	-	+	+	-	-
3	+	-	+	TAD	+	+	-	+	+	+	-	+
4	+	+	-	TAD	+	+	+	-	+	+	-	-
5	+	+	+	TAD	-	+	+	+	+	+	-	+
6	+	+	-	TAD	-	+	+	-	+	+	-	-
7	-	-	+	TAD	+	+	-	+	+	-	-	+
8	-	-	-	ALND	-	+	+	-	+	-	-	-
9	+	+	-	ALND	-	+	+	-	+	+	-	-
10	+	+	-	ALND	-	+	+	-	+	+	-	-
11	-	-	-	ALND	+	+	+	-	+	-	-	-
12	+	-	-	ALND	-	+	+	-	+	+	-	-
13	-	-	-	ALND	-	+	+	-	+	-	-	-
14	+	-	-	ALND	-	+	+	-	+	+	-	-
15	+	+	-	ALND	-	+	+	-	+	+	-	-
16	-	-	+	ALND	-	+	-	+	+	-	-	+
17	+	+	-	ALND	-	+	+	-	+	+	-	-
18	+	+	-	ALND	-	+	+	-	+	+	-	-
19	+	+	-	ALND	-	+	+	-	+	+	-	-
20	-	-	-	ALND	+	+	-	-	+	-	+	-
21	-	-	-	ALND	-	+	+	-	+	-	+	-
22	+	+	-	ALND	-	+	+	-	+	+	-	-

ER = estrogen receptor, PR = progesterone receptor, ALND = axillary lymph node dissection, SLN = sentinel lymph node, TAD = targeted axillary dissection, pCR = pathologic complete response, NAC = neoadjuvant chemotherapy, AC = anthracycline-based therapy, NAC HER2 = Neoadjuvant HER2-targeted therapy, Adj = adjuvant, ET = endocrine therapy, Pembro = pembrolizumab, Adj HER2 = Adjuvant HER2-targeted therapy

Table 4:

TAD technique utilized in 22 patients in whom the clipped node was a non-SLN and the only positive node on TAD.

	Type Blue Dye	Volume of Blue Dye	Isotope	# TAD Nodes
1	Iso	5	+	2
2	Iso	1	+	3
3	Iso	5	+	2
4	Iso	5	+	3
5	Iso	5	+	2
6	–	–	+	2
7	Iso	4	+	3
8	Iso	No data	+	3
9	Iso	4	+	1
10	Iso	5	+	2
11	Iso	5	+	3
12	Iso	5	+	2
13	Iso	5	+	3
14	Iso	3	+	6
15	Iso	5	+	2
16	Iso	3	+	3
17	Iso	5	+	1
18	Iso	5	+	3
19	Iso	5	+	3
20	Iso	5	+	3
21	Iso	3	+	3
22	Iso	5	+	4

TAD = targeted axillary dissection, Iso = isosulfan blue dye