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RESEARCH ARTICLE

Assessment of the Impact of Chemotherapeutic 'Treatment Effect' on Oncological Outcomes in Initially Node-Positive Breast Cancer Patients Undergoing Sentinel Lymph Node Biopsy Only After Neoadjuvant Chemotherapy

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ABSTRACT

Background: Sentinel lymph node biopsy (SLNB) is acceptable for patients who were initially node-positive (cN+) and who achieve a complete radiological response after neoadjuvant chemotherapy (NACT). The impact of identifying chemotherapeutic 'treatment effect' (TE) in resected nodes on reducing false-negative rates and oncological outcomes remains unclear. The aim of this study was to assess the impact of TE seen on SLNB and to determine oncological outcomes in this patient cohort.

Methods: cN+ breast cancer patients who received NACT and achieved nodal pathological complete response after SLNB only between 2014 and 2023 were assessed. Patients with negative SLNB (ypN0) were divided into two groups: (1) with TE and (2) without TE. Crude axillary recurrence rates were compared using the log-rank test. Median disease-free (DFS) and overall survival (OS) were compared using Kaplan–Meier curves.

Results: One hundred and fourteen patients were ypN0 after SLNB: 84 (73.7%) with TE and 30 (26.3%) without TE. Axillary recurrence trended towards a lower rate in those with TE (2.38% vs. 3.33%, $p = 0.77$). All patients with axillary recurrence had residual triple-negative disease within the breast. There were no differences in median DFS (47.5 vs. 43.5 months, $p = 0.91$) and OS (53.5 vs. 44.5 months, $p = 0.68$) between the two groups, respectively.

Conclusion: Absence of TE in patients undergoing SLNB only does not appear to affect DFS and OS, but may increase the risk of axillary recurrence. Larger studies are needed to further determine the impact of TE on oncologic outcomes in these patients.

1 | Introduction

Management of the axilla in node-positive breast cancer patients receiving neoadjuvant chemotherapy (NACT) continues to evolve. Prospective multicentre studies have shown that sentinel lymph node biopsy (SLNB) is feasible, with an acceptably low false-negative rate (FNR), in patients with initially node-positive disease who achieve a radiological complete response

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after NACT, when dual tracer mapping is used and when three or more sentinel lymph nodes (SLNs) are excised [1–3]. The alternative is a targeted axillary dissection (TAD), which involves clipping the metastatic node at the time of biopsy and retrieving the clipped node in combination with an SLNB [4]. There remains ongoing debate as to which technique is superior, with TAD being associated with a lower FNR and being used increasingly, as demonstrated by a recent survey of breast surgeons in Europe [5, 6]. Studies that have evaluated the accuracy of TAD have shown that the clipped node is not a sentinel node in up to 35% of cases [4, 7], indicating that performing a SLNB may miss the originally abnormal node. However, those who favour using an SLNB argue that the histological presence of chemotherapeutic 'treatment effect' (TE) in the SLNs accounts for this. In addition, there remains a paucity of evidence to suggest that oncological outcomes are better in patients undergoing a TAD versus SLNB only [8], with recent data showing that the latter was comparable to TAD, with no difference in 3-year rates of axillary recurrence [9].

The presence of chemotherapeutic TE within excised axillary nodes without residual disease after NACT in initially node-positive patients is associated with an improved prognosis [10]. Previous evidence has also indicated that the majority of patients who undergo SLNB will have TE identified [11, 12]. However, it remains unclear if the absence of TE in this setting is associated with a higher FNR or poorer oncological outcomes, such as increased axillary recurrence rates. Many of the original studies, such as ACOSOG Z0171 [1], SENTINA [2] and SN FNAC [3] did not examine TE as a factor affecting FNR, and, therefore, it is also unclear if such patients who did not have TE identified within the SLNs should proceed to an axillary lymph node dissection (ALND). ALND remains the current standard of care for patients with residual disease after NACT. For patients undergoing TAD or SLNB only with no residual disease after NACT, axillary radiotherapy (RT) remains the standard of care [13]. The omission of RT in this setting is being evaluated in the NSABP B51 [14] and ATNEC [15] studies. As the move towards de-escalation of axillary treatment continues, accurate axillary staging of those with residual disease becomes more critical. The aim of this study, therefore, was to assess the frequency of TE reported after SLNB only, and to compare oncological outcomes in ypN0 patients with TE and those with no TE in this cohort.

2 | Materials and Methods

2.1 | Patient Inclusion and Treatment Pathway

A retrospective review of a prospectively maintained database within a single institution was performed. The study was approved by the Clinical Audit Committee of St Vincent's University Hospital (No. 4267). The requirement for informed consent was waived owing to the retrospective nature of the study. Data were collected from patients with confirmed invasive breast cancer who had cytologically proven metastatic axillary lymph nodes at diagnosis and received NACT followed by SLNB only between January 2014 and December 2023. Patients with inflammatory breast cancer, occult breast cancer, a previous history of breast cancer, stage IV disease at presentation, residual nodal metastases after SLNB or those who underwent ALND were excluded. All patients underwent bilateral mammography as well as breast and axillary ultrasonography at diagnosis. Pre- and post-treatment magnetic resonance imaging (MRI) of the breast were also performed to monitor response to NACT.

Patients found to have indeterminate or abnormal axillary lymph nodes at diagnosis underwent fine-needle aspiration (FNA) cytology. Criteria for performing FNA included cortical thickness ≥ 3 mm, focal or eccentric cortical thickening and a replaced, abnormal or absent fatty hilum. Only FNA-confirmed nodal metastases were considered node-positive. Chemotherapy regimens were prescribed at the discretion of the treating medical oncology team. After NACT, axillary status was re-evaluated by clinical examination as well as ultrasonography and MRI. Patients within this cohort who had normal axillary imaging (ultrasound or MRI) after NACT were considered for SLNB.

2.2 | Surgical Technique

The technique for performing SLNB after NACT in patients who were initially node-positive was standardised. All patients received dual nodal tracers that consisted of (i) subareolar injection of 20 MBq technetium-99m performed preoperatively on the morning of surgery and (ii) periareolar injection of patent blue dye after induction of anaesthesia followed by 5 min of manual massage. SLNs were retrieved using hand-held gamma probe guidance and visual inspection for blue dye. All surgeons aimed to excise a minimum of three sentinel nodes. Completion ALND was indicated if residual nodal metastases, determined by standardised pathological assessment outlined below, were identified. If less than three lymph nodes were identified after SLNB, further individualised axillary treatment was discussed at the multidisciplinary team (MDT) meeting.

2.3 | Pathological Assessment

Histopathological assessment of SLNs involved serial slicing of each lymph node at 2 mm intervals prior to paraffin embedding and preparation of standard H&E sections. Further investigation, such as deeper level sections or cytokeratin immunohistochemistry were performed on selected cases at the discretion of the reporting pathologist. Consultant pathologists with expertise in breast pathology documented the presence or absence of TE in the final pathology report. TE in lymph nodes was evidenced by the presence of some or all of the following findings: parenchymal fibrosis/scarring, aggregated foamy macrophages, myxoid change and increased vascularity, akin to tumour bed changes in the breast. Information regarding the presence or absence of TE was obtained from the original pathology report, where available. Selected cases were re-reviewed by two dedicated breast pathologists (A.M. and C.Q.). SLN slides were reviewed in cases where there was no mention of TE in the SLNs on the original pathology report. In addition, all cases reported as showing no evidence of TE were also reviewed to identify subtle TE, which may not have been recognised in earlier years of post-NACT reporting and have been described in more recent publications [11]. Cases considered to

be 'indeterminate' on initial review by pathologist 1 (A.M.) were also reviewed by the second pathologist (C.Q.), and the classification reached by consensus. If TE was not identified after SLNB, further axillary treatment was discussed at the MDT on a case-by-case basis.

2.4 | Data Collection and Outcomes

Patient demographics, clinical as well as pathological characteristics of tumours, receptor status, type of breast surgery performed, number of sentinel nodes retrieved and presence or absence of breast pCR were recorded for each patient. Patients were divided into two groups based on the pathology report: (1) ypN0 with TE and (2) ypN0 with no TE.

Axillary recurrence was defined as histologically confirmed nodal metastasis in the ipsilateral axilla. Local recurrence was defined as ipsilateral breast or chest wall recurrence. Distant recurrence was defined as radiological and pathological confirmation of breast cancer recurrence beyond the ipsilateral breast, chest wall or regional lymph node basin. The time of recurrence, death and last follow-up were recorded. Time to event was calculated from the date of surgery to determine median disease-free survival (DFS) and overall survival (OS).

2.5 | Statistical Analysis

Clinical and pathological characteristics were reported as medians and ranges for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics were compared using the Chi-square or Fisher's exact test. Crude axillary recurrence, local recurrence and distant recurrence rates were compared between both groups using the log-rank test. Kaplan–Meier curves were performed to estimate median DFS and OS. Statistical analyses were done using IBM SPSS Statistics Version 26.0 (Armonk, NY), and p values less than 0.05 were considered statistically significant.

3 | Results

3.1 | Baseline Demographics and Clinical Characteristics

From January 2014 to December 2023, 114 patients who were ypN0 after SLNB were identified. Of these, 113 (99.1%) patients were female, and one (0.9%) patient was male. The median age of the study population was 50 years (range 32–83). Approximately two-thirds (67.5%) of tumours were larger than 2 cm (cT2–3) in size on baseline breast imaging. Only 14 patients (12.3%) had multifocal or multicentric tumours. HER2-positive tumours accounted for 58 (50.9%) patients. Breast-conserving surgery (BCS) was performed in 73 (64%) cases.

3.2 | Pathological Characteristics

Of the 114 patients who met the inclusion criteria and were included in the analysis, 84 (73.7%) had TE and 30 (26.3%) had no TE, broadly similar to rates of TE identification in published studies [11, 12]. All patients had a positive pre-treatment FNA showing metastatic carcinoma. The majority of patients (95.6%) had invasive breast carcinoma, no special type (ductal). Seventy-eight (68.4%) tumours were reported to be grade 3. Lymphovascular invasion was present in only three (2.1%) cases. Breast pCR, defined as the absence of invasive disease, occurred in 53 (46.5%) patients after surgery. The median number of SLNs retrieved was 3 (range 1–7). In 44 (38.6%) patients, only one or two SLNs were removed.

3.3 | Predictive Factors of TE

Clinical and pathological characteristics of the entire cohort are summarised in Table 1. We compared the two subgroups of patients to identify predictors of TE. There was no difference in the number of nodes removed in patients with no TE (25% vs. 26.8%, $p = 0.83$), suggesting that the absence of TE was not related to retrieval of a smaller number of nodes. Patients with

TABLE 1 | Clinical and pathological characteristics of ypN0 patients undergoing SLNB only.

	TE $N = 84$ (73.7%)	No TE $N = 30$ (26.3%)	p value
Age			
≤ 50	40 (71.4%)	16 (28.6%)	$p = 0.67$
> 50	44 (75.9%)	14 (24.1%)	
Tumour type			
Ductal	81 (74.3%)	28 (25.7%)	$p = 0.47$
Lobular	3 (60%)	2 (40%)	
Multifocal or multicentric			$p = 0.27$
Yes	12 (85.7%)	2 (14.3%)	
No	72 (72%)	28 (28%)	
Tumour size			$p = 0.57$
cT1	29 (78.4%)	8 (21.6%)	
cT2	50 (70.4%)	21 (29.6%)	
cT3	5 (83.3%)	1 (16.7%)	
Tumour grade			
2	26 (72.2%)	10 (27.8%)	$p = 0.82$
3	58 (74.4%)	20 (25.6%)	
Tumour biology			
HR+/HER2−	18 (75%)	6 (25%)	
HER2+	40 (69%)	18 (31%)	$p = 0.44$
HR−/HER2−	26 (81.2%)	6 (18.8%)	
Number of SLNs			
< 3	33 (75%)	11 (25%)	$p = 0.83$
≥ 3	51 (73.2%)	19 (26.8%)	
Breast surgery			
BCS	51 (69.9%)	22 (30.1%)	$p = 0.27$
Mastectomy	33 (80.5%)	8 (19.5%)	
Breast pCR			
Yes	44 (83%)	9 (17%)	$p = 0.03$
No	40 (65.6%)	21 (34.4%)	

triple-negative breast cancer (TNBC) were more likely to have TE in the nodes compared to patients with luminal or HER2-positive breast cancers, although the difference did not reach statistical significance (81.2% vs. 75% vs. 69%, respectively; $p = 0.44$). TE was more common in patients with a breast pCR compared to patients without a breast pCR (83% vs. 65.6%, respectively; $p = 0.03$). Otherwise, there were no differences between the two groups in terms of age of diagnosis, tumour size, histological type, tumour grade and type of breast surgery performed.

3.4 | Clinical Outcomes

During a median follow-up of 48 months (range 6−119 months), three axillary recurrences were observed. This represents 2.63% of the total cohort. The observed axillary recurrence rate was 2.38% for TE and 3.33% for no TE ($p = 0.77$). When examining clinicopathological characteristics in patients with an axillary recurrence, all patients had TNBC and did not have a pCR in the breast on final pathology. Three patients had local recurrences, two of whom also had an axillary recurrence. The local recurrence rate was 2.38% for TE and 3.33% for no TE ($p = 0.77$). Twelve patients had isolated distant recurrences; however, no differences in the distant recurrence rate were seen between the two groups (13% for TE and 10% for no TE, $p = 0.65$). Overall, 14 (12.3%) patients died. One patient had an isolated local recurrence. Ten patients died due to metastatic disease, one of whom developed locoregional recurrence followed by distant metastasis. The remaining three patients who passed away died from other causes. The median DFS was 47.5 months for TE and 43.5 months for no TE ($p = 0.91$; Figure 1). There were no differences in median OS (53.5 months for TE vs. 44.5 months for no TE, $p = 0.68$) between the two groups (Figure 2).

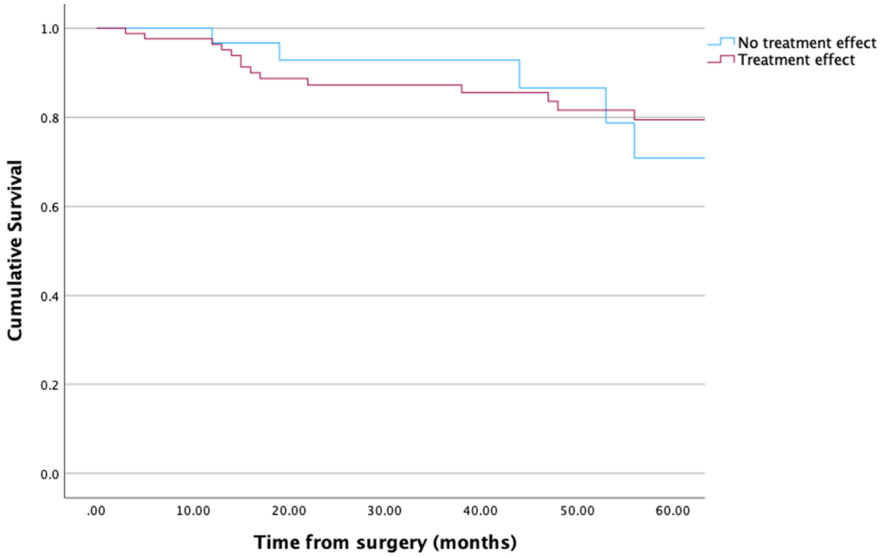

FIGURE 1 | Kaplan–Meier curve of DFS for ypN0 patients with and without TE after SLNB only.

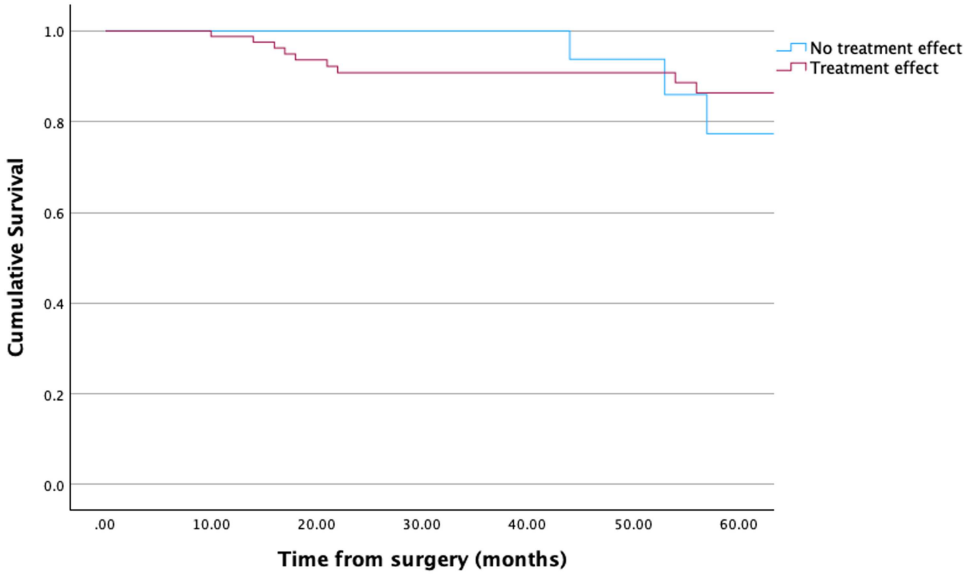

FIGURE 2 | Kaplan–Meier curve of OS for ypN0 patients with and without TE after SLNB only.

4 | Discussion

Axillary management of pathologically proven node-positive breast cancer patients who become radiologically node negative after NACT has evolved considerably over the last decade. Despite initial concerns over performing SLNB only in this setting, it is now deemed acceptable to do so provided a dual tracer technique is adopted and a minimum of three nodes are excised, as these factors have been demonstrated to lower the FNR below 10% [16]. Whilst it is clear that performing a TAD, with removal of the initially abnormal node that has been clipped at the time of diagnosis as well as SLNB, is associated with a lower FNR compared to SLNB alone [4], there remains ongoing debate regarding the impact of each technique on longer-term oncological outcomes [17, 18]. Recently, studies comparing oncological outcomes for patients treated with SLNB versus TAD have shown no differences in the incidence of axillary recurrence [9, 19]. As the premise of clipping the abnormal node and excising it after NACT is central to performing a TAD, it would seem equally important that for patients undergoing SLNB only, identification of chemotherapeutic TE in one or more of the sentinel nodes excised is achieved, indicating that an initially abnormal node has been removed. The absence of such a finding theoretically indicates that axillary staging is not as accurate, but it is unknown if this actually affects oncological outcomes. The findings of the current study would indicate that the finding of TE does not appear to affect outcomes including axillary recurrence, local recurrence and distant recurrence. Although axillary recurrence is slightly higher in the 'no TE' group, rates of axillary recurrence are low, consistent with the findings of previous studies [20, 21].

The idea of using TE within sentinel nodes as another method for documenting retrieval of an initially positive node after NACT, without needing to mark the node has been previously described [10]. However, in one study by Brown et al. [22], TE was present in only 50% of SLNs excised. In another study by Barrio et al. [11]. TE was identified in 88%, with at least three SLNs removed in all patients, in keeping with previous evidence indicating more accurate axillary staging with a lower FNR in patients where three or more nodes are removed. Interestingly, the current analysis did not demonstrate any difference in the number of nodes retrieved between patients with or without TE, with a median of three nodes excised in both groups, indicating that nodal yield may not be the driving factor in identifying such a finding.

The failure of identification of TE has several possible explanations. It is obviously possible that the initially metastatic lymph node may not have been removed surgically. This can occur due to fibrosis of afferent lymphatics by chemotherapy, which reduces the sensitivity of SLN mapping [23]. However, previous evidence from Pislar et al. [12] has also indicated that even when ALND is performed in this cohort, TE was not identified in 11% of patients who were initially node-positive. This suggests that even when a maximum number of nodes are retrieved, factors beyond the extent of axillary surgery, such as more aggressive tumour biology, influence the identification of TE in the nodes [11]. Previous evidence has clearly demonstrated that response rates to NACT in axillary lymph nodes vary according to different tumour subtypes, with triple-negative and HER2-positive tumours having higher axillary pCR rates (50% and 65%, respectively), compared to hormone receptor-positive patients (20%) [1]. It is possible that TE in the lymph nodes after NACT could also be affected by tumour subtype. Whilst the current analysis did not demonstrate a difference in receptor subtype between the two groups, patients in the TNBC cohort had the highest rate of TE in excised nodes (> 80%) yet all of the axillary recurrences occurred in patients with a TNBC subtype without breast pCR suggesting that the mechanism of recurrence in this small group of patients is not explained by the absence of TE but rather the biology of the disease [23]. However, the current study does demonstrate that for patients within the TNBC subtype who do not yield a breast pCR, care must be taken and significant consideration should be given to completion of ALND in the absence of TE, given the rate of axillary recurrences seen.

It also remains unclear if the mechanism yielding the absence of TE in the 'no TE' group of patients was driven by the response to chemotherapy, such as spontaneous nodal regression, as is often seen with the lower nodal yield after ALND in patients who have received NACT or by the underlying pathology [24]. Another consideration in a retrospective study is the pathology reporting recommendations used during that period. For example, currently the International Collaboration on Cancer Reporting (ICCR) strongly encourages reporting of TE in lymph nodes and gives helpful advice on it's recognition, but it is still a 'non-core' data item [25]. During the time of reporting the older cases in this study, this data point was sometimes omitted. It is likely that identification of more subtle histological evidence of TE improved as time progressed. To mitigate against this, the authors reviewed all SLN slides from patients with no comment on nodal TE and from the 'no TE' group, to determine the presence or absence of TE and identify subtle TE which may not have been appreciated at the time of reporting. After this review, 11 patients were re-classified as having subtle TE.

Although the rate of axillary recurrence between the TE and no TE groups was not statistically significant, it is likely that with a larger patient cohort and a longer follow-up period, a statistically significant difference may be seen. The axillary recurrence rate of 2.38% seen in the TE group is in keeping with recently published studies, such as the NEOSENTITURK MF-1803 study [26], which found an axillary recurrence rate of 0.3% within all patients in the SLNB arm at a median follow-up of 39 months. The rate of 3.33% seen within the no TE group in the current analysis is higher than the results published by Pilsar et al., [12] who experienced only one axillary recurrence across both groups at a median follow-up of 36 months, compared to 48 months in this study. The study by Pilsar et al. did, however, demonstrate a difference in recurrence-free survival (RFS) in favour of the TE group (91% vs. 86%), suggesting a possible benefit within the TE group, consistent with the rate of distant recurrences seen in this study, although both studies included relatively small patient cohorts.

Finally, de-escalation trials for breast cancer patients with axillary pCR after NACT continue to evolve. The NSABP B51 trial showed that among patients with nodal pCR, with or without breast pCR, omission of adjuvant regional nodal irradiation (RNI) led to equivalent oncological outcomes [27].

At a median follow-up of 5 years, there was no difference in RFS, DFS or OS between those randomised to RNI or no RNI. Therefore, in patients with initially node-positive disease who become ypN0 after NACT, RNI may be safely omitted without adversely affecting oncological outcomes. The ATNEC trial [15] is investigating whether omission of axillary treatment is non-inferior to ALND or axillary RT, and patients undergoing SLNB only are required to have histological evidence of nodal downstaging (fibrosis or scarring) to be considered eligible for inclusion. In this setting, the FNR of SLNB may matter in making RT decisions. If there is no TE and the initially abnormal node is missed, and if RNI is not given based on a falsely-negative axillary pCR, this may potentially lead to an increase in axillary recurrences. Therefore, the presence of TE, otherwise a TAD, with excision of the clipped node, may guide radiation oncologists in their decision for RT de-escalation. For patients with residual nodal metastases after NACT, Alliance 11202 [28] and TAXIS [29] trials will guide the decision for axillary RT as an alternative to ALND for local control.

The current limitations of this study include a small sample size and a retrospective nature. However, the retrospective nature accounts for any bias that may result in patients with no TE now proceeding to ALND, as this did not occur during the study period. One may argue that longer-term follow-up beyond the current median time is needed to fully assess oncological outcomes, especially in ER-positive patients. However, previous evidence has demonstrated that most axillary recurrences, especially in HER2-positive and TNBC patient cohorts, will be seen within the first 5 years [28]. Finally, our patient cohort is limited by changes in systemic therapy over time, as a proportion of our patients predate current treatment regimens, such as capecitabine, trastuzumab emtansine and pembrolizumab, that have improved patient outcomes [30–33]. It remains unclear whether axillary recurrences would have been lower if all patients, especially in the TNBC cohort, had received immunotherapy as the current standardised treatment.

5 | Conclusion

Whilst the current analysis adds to the growing body of evidence supporting limited axillary assessment in initially node-positive patients who achieve a complete radiological response after NACT, the absence of histopathological evidence of TE in patients undergoing SLNB only should be treated with caution. Whether or not a completion ALND is required in these patients is unclear, but the study demonstrates that excision of an initially abnormal node is of significant importance, and on this basis, TAD, with marking of the abnormal node at diagnosis, should be strongly considered.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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