The Evolving Role of Marked Lymph Node Biopsy (MLNB) and Targeted Axillary Dissection (TAD) after Neoadjuvant Chemotherapy (NACT) for Node Positive Breast Cancer: Systematic Review and Pooled Analysis

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Research Article

Keywords: Breast Cancer, Node Positive, Systematic-Review, Targeted Axillary Dissection

DOI: https://doi.org/10.21203/rs.3.rs-199729/v1

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Abstract

Background: Targeted axillary dissection (TAD) is a new axillary staging technique that consists of the surgical removal of biopsy-proven positive axillary nodes marked (marked lymph node biopsy: MLNB) prior to neoadjuvant chemotherapy (NACT) in addition to the sentinel lymph node biopsy (SLNB). In a meta-analysis of more than 3000 patients, we previously reported a false negative rate (FNR) of 13% using the SLNB alone in this setting. The aim of this systematic review and pooled analysis is to determine FNR of MLNB alone and TAD (MLNB plus SLNB) compared with the gold standard of complete axillary lymph node dissection (cALND).

Methods: The PubMed, Cochrane and Google Scholar databases were searched using Mesh relevant terms and free words.

Results: A total of 9 studies of 366 patients that met the inclusion criteria evaluating the FNR of MLNB alone were included in the pooled analysis yielding a pooled FNR of 6.28% (95% CI: 3.98-9.43). In 13 studies spanning 521 patients, the addition of SLNB to MLNB (TAD) was associated with a FNR of 5.18% (95% CI: 3.41-7.54) which was not significantly different from that of MLNB alone (p=0.48). Data regarding oncological safety of this approach were lacking. In a separate analysis of all published studies reporting successful identification and surgical retrieval of the MLN, we calculated a pooled success rate of 90.0% (95% CI = 85.1-95.1).

Conclusion: The present pooled analysis demonstrates that the FNR associated with MLNB alone or combined with SLNB is acceptably low and both approaches are highly accurate in staging the axilla in patients with node-positive breast cancer after NACT. The SLNB adds minimal new information and therefore it can be safely omitted from TAD. Further research to confirm the oncological safety of this de-escalation approach of axillary surgery is required.

Core Tip: MLNB alone and TAD are associated with acceptably low FNRs and represent valid alternatives to cALND in patients with node-positive breast cancer after excellent response to NACT.

Introduction

Due to the significant associated morbidity, complete ALND has been largely replaced by the less invasive SLNB as the gold standard for regional axillary staging in clinically node negative breast cancer patients undergoing upfront surgery1. Furthermore, a recent meta-analysis of 16 studies including approximately 1,500 patients, confirmed that the SLNB was technically feasible and sufficiently accurate for staging the axilla in initially clinically node-negative (cN0) breast cancer after NACT with an overall identification rate of 96% and a FNR of 5.9% which is well below the target limit of 10%2,3. Furthermore, retrospective studies provided evidence that the SLNB is oncologically safe in this setting. In a retrospective analysis of cN0, T1-T3 patients who underwent SLNB after NACT (n=575) or first-line surgery (n=3,171), axillary recurrence was 1.2% in the NACT group, with no difference in disease-free or overall survival between both groups. The incidence of axillary recurrence following a negative SLNB after NACT was reported to
be as low as 0.24% in patients with cN0 disease4.

Women diagnosed with biopsy proven node positive breast cancer are usually considered for NACT which has been shown to be beneficial in reducing tumor burden and increasing the success rate of breast conserving therapy (BCS) 5. Furthermore, this approach provides critical information regarding the tumor responsiveness to systemic therapy and the potential need for a new class of drugs in the adjuvant setting when pathological complete response (pCR) is not attained 2. Complete ALND has been the gold standard surgical management of the axilla in patients with node positive breast cancer receiving NACT. The growing body of evidence that de-escalation of axillary surgery towards SLNB in patients with clinically node negative breast cancer (cN0) after NACT is feasible and safe in addition to the recent level 1 evidence that most breast cancer patients with 1-2 positive sentinel nodes can safely avoid complete ALND when eligibility criteria from the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial are met has stimulated interest in extending de-escalation of axillary surgery to patients with initially node positive breast cancer responding well to NACT3.

However, in biopsy proven node positive patients undergoing NACT, SLNB studies have reported inconsistent false negative and identification rates6. Our recent meta-analysis of approximately more than 3000 patients with node positive breast cancer reported a FNR of 13% after NACT which is above the threshold target of 10%7. The studies included in our meta-analysis were heterogeneous, retrospective and non-standardized in nature. The variation in FNRs in this setting has been attributed to anatomical changes resulting in aberrant lymphatic drainage, consequential NACT-associated fibrosis, fat necrosis and/or granulation tissue formation or the tumor itself 8.

Targeted axillary dissection (TAD) is a new axillary staging technique whereby the lymph node positive for metastatic disease at initial diagnosis is marked using different methods such as carbon tattooing, radio-iodine, metallic clips, ferromagnetic seeds etc. prior to NACT so that this marked lymph node (MLN) can be removed during breast cancer surgery9. Intuitively the MLN biopsy (MLNB) should reflect the status of residual axillary disease more accurately than the SLNB alone in this setting. The MLN is usually identified, biopsied and marked using ultrasonography of the axilla for guidance. If the MLN cannot be identified or remains positive for metastatic disease after NACT, ALND is usually carried out.

There have been numerous studies, with varying results, that have investigated the role of MLNB and TAD in this context. The aim of this study was to evaluate the FNR of MLNB alone and combined with SLNB (TAD) by pooling the data from the relevant studies.

**Materials And Methods**

**Data sources and searches**

Comprehensive searches of PubMed, Google Scholar and Cochrane Library databases were performed to identify and extract publications and records relevant to this study. Depending on the database, the
search terms varied. The search strategy of the databases included key words such as: targeted axillary dissection, axillary lymph node clearance, neoadjuvant chemotherapy, node positive breast cancer and false negative rate. A further advanced search was conducted using the combination of words or phrases and abbreviations, using Boolean operators ('AND', 'OR', 'NOT'). The PubMed and Cochrane Library databases were searched on two separate occasions: November 8th 2020 and November 17th 2020. A final literature search was conducted on the 23rd of January 2021. Furthermore, bibliography from the included reviews and articles were manually screened for additional relevant publications.

Inclusion and Exclusion Criteria

This analysis included both retrospective and prospective cohort studies. All publications were required to have summarized findings in the abstract regarding the effect of MLNB alone or combined with SLNB on the FNR in post-NACT patients with biopsy proven node positive breast cancer who underwent ALNC. Of the studies that met these requirements, the full texts (where available) were reviewed and the following raw data were required to be included:

- Total number of patients undergoing MLNB
- Total number of patients undergoing TAD
- Number of false negative events/patients with false negative results
- FNR (%)

Abstracts not evaluating the FNR of MLNB or TAD in post-NACT biopsy proven node positive breast cancer patients were excluded. In addition, studies were excluded in which the data were unclear or unavailable. This analysis excluded studies that were published in languages other than English and those with non-human subjects. Publications comparing MLNB or TAD to other axillary staging techniques were included in this analysis - data regarding these methods were ignored for the purposes of our calculations, except where relevant to the smaller pooled analysis. In addition, both full texts and abstracts were included in this review.

Data Management.

Data extracted from eligible studies include the first author, FNR, absolute false negative number and total patient number. We extracted and combined the FNRs of the included studies to calculate the overall rates of false negative for MLNB and TAD from the datasets. By combining data sets from all included studies, the mean values were calculated to provide the overall FNR of MLNB (+/- SLNB) in post-NACT for biopsy proven node positive breast cancer. Furthermore, the confidence intervals were calculated using SciStat® and testing for statistical significance (5%) in the difference between FNRs was calculated using the Chi-squared test.
Results

Literature search results and characteristics of the included studies

In the preliminary search, a total of 174 records were identified (157 from Google Scholar; 16 from PubMed; 1 from the Cochrane Library). Following the removal of duplicates, 147 publications were reviewed for inclusion. Once these studies were screened for eligibility, 138 were immediately excluded. The full texts (where available) were examined for the remaining studies and relevant abstracts and/or full text from the respective bibliographies.

Results of pooled analysis

Through analysis of the 9 included studies (Table 1), a total of 366 post NACT patients with biopsy proven node positive breast cancer underwent MLNB in addition to cALND 10–18. Of these, 23 false negative results were recorded yielding a FNR of 6.28% (95% CI = 0.03.984 to 0.09429). In 12 studies (Table 2) spanning 521 patients that evaluated the addition of MLNB to SLNB (TAD), we calculated an overall FNR of 5.18% (95% CI = 0.0341 to 0.0754) 10,12,13,15,18–26.

Statistical analysis showed that the difference in FNR between MLNB and TAD was not statistically significant (p-value = 0.484, Chi-squared statistic=0.489)

Analysis of studies (Table 3) 19,10–18,20,22,23,25–28 reporting the technical success of localizing and retrieving the marked lymph-node revealed a summative successful retrieval rate of 90.0% (95% CI = 0.8515 to 0.9505).

Our search did not reveal any prospective studies reporting long term survival data in patients with ypN0 undergoing MLNB or TAD.

Discussion

We have systematically reviewed the feasibility of MLNB alone and in combination with SLNB in patients with biopsy proven node positive breast cancer who received NACT and quantified an overall FNR of 6.28% for MLNB alone and 5.16% for TAD. These FNRs are significantly below our reported FNR for SLNB alone of 13% in the same setting 7. Furthermore, the FNRs observed in our pooled analysis are below the accepted target of 10% for clinically node negative breast cancer 2,3. This pooled analysis has confirmed that MLNB is an accurate technique in axillary staging after systemic therapy, and is associated with a high technical success rate and an acceptably low FNR. Although the addition of SLNB to the MLNB was found to be associated with a lower FNR, however the difference of 1.12% was not statistically significant. On the contrary, most studies demonstrated that the added evaluation of MLNB significantly decreased the FNR of SLNB alone 10,19,26.

Therefore the SLNB can be safely omitted in the context of successful MLNB thus reducing costs and additional complications. Optimizing the FNR in patients receiving NACT for a biopsy-proven node positive breast is important since under-staging the residual axillary disease can potentially result in
adjuvant systemic therapy under-treatment and compromise of oncological outcome in patients particularly with HER2 positive and triple negative breast cancer (TNBC) where residual disease is used to guide the use of further adjuvant systemic therapy, such as capecitabine for TNBC and TD-M1 for HER2 positive disease 2.

The initial techniques of marking the target lymph node included deployment of clips made of various materials such as stainless steel, titanium or polyglycolic acid 12 and carbon or black ink tattooing 29. The majority of the studies included in the current analysis were based on TAD implementing the use of clips deployed within the pathological lymph node in a procedure following initial percutaneous ultrasonography guided biopsy. It is recommended that the marker is deployed at the time of biopsy to obviate the need for a second procedure 19. Tattooed target lymph nodes can be visualized directly during surgery however the marker clips require a second localization procedure prior to surgery and accurate identification with ultrasonography can be challenging when the pathological lymph nodes revert to normal after NACT. Displacement of the marker clip into the surrounding perinodal fat and fibrous tissue (secondary to node shrinkage post-NACT) can be also a contributing factor to difficulty localization by ultrasonography 13. HydroMark (Devicor Medical Products) that consists of a metal clip made of titanium or stainless steel embedded in a hydrogel made primarily of collagen has the highest degree of visibility on ultrasonography up to 12 months however some authors cautioned that ultrasound visibility after 6 months can be significantly reduced due to collagen resorption 26. Displacement of the wire used for the localization of the clip-containing target lymph node represents another limitation to the use of clips 13. These limitations stimulated interest into developing new methods that do not require a second localization procedure and wire insertion 23,30–32

Marking axillary lymph nodes with radioactive iodine (125I) (MARI) seeds that can be localized using a gamma probe was used in three publications included in this analysis 11,14,18. This technique stems from the success in localizing residual breast disease having implanted radioactive iodine seeds prior to NACT in the center of the primary tumor 18,33. The MARI technique is straightforward and easy to learn and perform by surgeons experienced in SLNB dissection. Furthermore it obviates the need for wire insertion. From a surgical prospective, another advantage is the long half-life of the iodine seed - around 60 days – allowing adequate time for NACT and bypassing scheduling conflicts associated with the much shorter half-life (around 8 hours) of radio-colloids used in dual-tracer SLNB. Radioactive iodine seeds are associated with a decreased displacement risk in the time between insertion and surgery, and therefore a decreased risk of injury to vascular structures in the surrounding area 14,34. However, the use of radioactive materials is complicated by complex regulatory requirements. Moreover the time that the seed can stay within the human body is limited to 5-7 days in certain jurisdictions thus prohibiting deployment of the seed at the time of biopsy prior to NACT.

Carbon tattooing of the metastatic node was implemented in three publications 17,22,25 included in this analysis; all tattooing was performed under ultrasound guidance. Reported advantages of this technique include the ease of intraoperative identification, no requirement of an invasive localization procedure thus reducing burden for the patient and avoiding the use of radioactive materials 17,25. A previous study
described a ‘dual-localization’ technique whereby a metastatic lymph node is marked with a clip (prior to NACT) and tattooed with activated charcoal (after NACT); this was performed to circumvent a second localization procedure and unavailability of radioactive seeds in many countries 35. Furthermore, the black ink used by Park et al was found to be detectable for up to 197 days post-tattooing, thereby allowing appropriate time for NACT. Potential tattoo pigment migration to other lymph-nodes in addition to the need for a wider surgical dissection to visualize the tattooed nodes represent limitations to using this technique.

The limitations discussed above have inspired the evolution of novel radiation free wireless technologies have emerged including magnetic seeds 23(Magseed®; Endomagnetics Inc., Cambridge, UK); infrared reflectors 27(Savi Scout; Merit Medical Inc., Aliso Viejo, CA, USA) and radiofrequency identification 28(RFID) tags (LOCalizer; Hologic, Santa Carla, CA, USA). Radiation-free wireless methods, 3 of which are listed above, bypass scheduling conflicts by facilitating localisation a day prior to the surgical excision. Magseed uses a 5mm paramagnetic seed; this is deployed through a sterile 18-gauge needle and is detected via a handheld probe from the skin surface - up to a reliable depth of 4 cm. Nonetheless, in the context of MLNB and TAD, scope for improvement in Magseed exists. This primarily focuses on the ease of use, and includes possibly reducing the relatively large size of the detection probe and, during probe use, circumventing the necessity of removing all metal instruments from the surgical field 36. Savi Scout involves the insertion of a 12x1.6 mm electromagnetic wave reflector into the target lymph node using a sterile 16-gauge introducer needle delivery system. The reflector can be detected by a radar up to 6 cm depth from the skin. Electrocautery should be used with caution when performing MLNB or TAD using the Savi Scout system. Unlike Magseed and RFID tags, the reflector of Savi Scout does not generate significant MRI artefacts and this is important if MRI is used to monitor response to therapy (Figure 1) 32. The radar reflection localization (RRL) of Savi Scout enhances identification of the reflector by an audible sound and digital display of distance from the probe. Sun et al reported recovery of all reflectors and no complications 27.

The LOCalizer utilizes a 10 X2 mm tag with glass casing that is deployed using a 12 gauge introducer needle. The detection probe is both user-friendly and site-specific. A unique five-digit number associated with each RFID tag enables both site-specific and user-friendly identification and this is of particular benefit in patients with multiple tag-deployment sites 28. However the size of the tag and the width of the introduced needle represent limitations particularly in patients with small pathological logical lymph-nodes. These novel wire-free radiation-free techniques were used only in a small number of patients included in this analysis. Further research is required to determine their clinical performance in larger series and establish which one of these technologies will achieve optimal marking and localization of pathological lymph nodes in addition to analysis of cost effectiveness 37.

We have observed a pooled successful localization and retrieval rate of the MLN of 90% and this means that the MLN is not received in 10% of cases. In such cases, complete ALND should be performed to ensure accurate staging. If the MLNB is performed as part of TAD, then the SLNB can be considered as an
alternative to ALND in patients with complete radiological response provided that a minimal of 3 sentinel
nodes are harvested using the dual localization technique 2,19 since the FNR will be below 10% in this
setting. In the ACOSOG Z1071 (Alliance) study, the MLN was found to be within the SLNB in 78% of cases
when the dual localization technique was used 19.

There is currently no consensus regarding the applicability of MLNB or TAD to patients with multiple
pathological lymph nodes. Lim et al raised concerns regarding differential axillary nodal response to
NACT. To determine the false negative rate, the Skin Mark clipped Axillary nodes Removal Technique
(SMART) clips were removed and followed by ALND16. This study implemented clipping multiple nodes;
results showed a false negative rate of 7.1% by prediction of the first clipped node. This was reduced to
0% with the addition of another second clipped node.

Conservative National Comprehensive Cancer Network (NCCN) guidelines determine the implementation
of TAD in patients. The procedure is currently permitted in patients presenting with biopsy proven node
positive disease, contingent upon the following factors: imaging suggests only 1 or 2 suspicious nodes,
that these positive nodes are not palpable upon clinical examination and that all eligibility criteria
outlined in the Z0011 study are met 38.

The conservative National Comprehensive Cancer Network (NCCN) guidelines permit the use of TAD in
patients who present with biopsy proven node positive disease if only 1 or 2 suspicious nodes are found
on imaging, these positive nodes are not palpable clinically, and the other eligibility criteria from the
Z0011 study are otherwise met 38.

Their main barrier to routine implementation of TAD and MLNB as part of standard clinical practice is the
paucity of data regarding the oncological safety. Although ALND may not be needed for patients with
limited residual nodal burden and biologically favorable tumors, SLNB alone was reported to be inferior to
ALND in patients with ypN1 disease following NACT in terms of 5 year survival in a recent retrospective
study 39. Although there are currently no prospective studies reporting long term survival data in patients
with ypN0 undergoing MLNB or TAD, we have estimated that the probability of compromising overall
survival (OS) or disease-free survival (DFS) would be approximately 1 in 2,000 for a FNR of 10% and 1 in
10,000 for a FNR of 2% if ALND is omitted 2,3. Therefore the benefit risk balance would favor TAD to
ALND in this patient population.

Further evidence regarding the oncological safety of axillary surgery de-escalation in patients render
SLNB negative after NACT for cN1 breast cancer has been provided by data analysis of a large European
study 40.

The main limitations of our study include the heterogeneous nature of studies included in the analysis
and lack of standardized inclusion criteria, methods of marking and localization and definition of
response to NACT and selection criteria for MLNB or TAD. Furthermore, pathological examination of the
MLN was not standardized 15. Caudle et al suggested that the FNR of TAD could be lower if
immunohistochemistry was to become a routine part of pathological evaluation 10. Moreover most
studies had a small sample size (less than 100) and selection and publication bias could not be excluded.

Ongoing prospective trials aim to provide important data regarding the optical technique and the long-term oncological safety. Van Nijnatten and colleagues commenced a prospective multicenter validation study in 2017; expected completion of the trial was in 2020 and the results are awaited 41. The study aims to test the feasibility of MARI and SLNB. Another prospective multicenter trial, led by Huenke et al, aims to publish data regarding DFS in patients who have undergone TAD and axillary radiotherapy, and establish this procedure as a valid alternative to cALND 42.

**Conclusions**

The present pooled analysis demonstrates that MLNB and TAD are feasible with a high technical success rate and an acceptably low FNR in patients responding well to primary chemotherapy for node positive breast cancer. Successful implementation of the technique requires careful multidisciplinary collaboration between breast radiologists, breast surgeons, and breast pathologists. Further research to determine the optimal technique, standardize selection criteria and confirm oncological safety is required.

**Tables**

Table 1: MLNB studies and FNR
| Study               | Year | Number of False Negatives | Total Patients | Method of marking Targeted Lymph Node (TLN) | Localization Method |
|---------------------|------|---------------------------|----------------|---------------------------------------------|---------------------|
| Caudle et al 10     | 2016 | 5                         | 120            | Metallic Clip                              | Iodine-125 seed     |
| Donker et al 11     | 2015 | 5                         | 70             | Radio-iodine seed                          | Gamma probe         |
| Flores-Funes et al 12 | 2019 | 0                         | 23             | Metallic Clip                              | Wire guided         |
| Hartmann et al 13   | 2018 | 0                         | 3              | Metallic clip                              | Wire guided         |
| Koolen et al 14     | 2017 | 5                         | 32             | Radio-iodine seed                          | Gamma probe         |
| Kuemmel et al 15    | 2020 | 4                         | 46             | Metallic Clip                              | Wire guided         |
| Lim et al 16        | 2020 | 1                         | 1              | Metallic Clip                              | NR                  |
| Spautz et al 17     | 2020 | 3                         | 43             | Carbon Tattooing                           | N/A (visualized)    |
| Straver et al 18    | 2010 | 0                         | 15             | Radio-iodine seed                          | Gamma probe         |
| **Total**           |      | **22**                    | **366**        |                                             |                     |

NR - Not Reported

N/A - Not Applicable

Table 2: TAD (MLNB + SLN) studies and FNR
| Study                          | Year | Number of False Negatives | Total Patients | Method of marking Target Lymph Node (TLN) | Localization Method        |
|-------------------------------|------|---------------------------|----------------|----------------------------------------|---------------------------|
| Boughey et al 19              | 2017 | 7                         | 107            | Metallic Clip                          | NR                       |
| Cabioglu et al 20             | 2018 | 1                         | 24             | Metallic Clip                          | NR                       |
| Caudle et al 10               | 2016 | 1                         | 74             | Metallic Clip                          | Iodine-125 seed          |
| Coufal et al 21               | 2018 | 0                         | 35             | Metallic Clip                          | Full abstract unavailable - Not determined |
| Flores-Funes et al 12         | 2019 | 0                         | 23             | Metallic Clip                          | Wire guided              |
| Gatek et al 22                | 2020 | 0                         | 8              | Carbon Tattooing                       | N/A (visualized)         |
| Hartmann et al 13             | 2018 | 0                         | 3              | Metallic clip                          | Wire guided              |
| Kuemmel et al 15              | 2020 | 2                         | 46             | Metallic Clip                          | Wire guided              |
| Martinez et al 23             | 2020 | 1                         | 17             | Metallic Clip                          | Magseed                  |
| Mittendorf et al 9            | 2014 | 7                         | 96             | Metallic Clip                          | NR                       |
| Park S et al 25               | 2018 | 1                         | 24             | Carbon Tattooing                       | N/A (visualized)         |
| Siso et al 26                 | 2018 | 1                         | 24             | Metallic Clip                          | Intraoperative ultrasound |
| Straver et al 18              | 2010 | 0                         | 15             | Radio-iodine seed                      | Gamma probe              |
| **Total**                     |      | **27**                    | **521**        |                                        |                          |

NR - Not Reported

N/A - Not Applicable
Table 3: Successful Retrieval Rate
| Study                  | Year | Number of retrieved MLNs | Total number of marked lymph nodes | Method of marking Target Lymph Node (TLN) | Localization Method |
|------------------------|------|--------------------------|------------------------------------|------------------------------------------|---------------------|
| Boughey et al 19       | 2017 | 141                      | 170                                | Metallic Clip                           | NR                  |
| Cabioglu et al 20      | 2018 | 83                       | 86                                 | Metallic Clip                           | NR                  |
| Caudle et al 10        | 2016 | 208                      | 208                                | Metallic Clip                           | Iodine-125 seed     |
| Donker et al 11        | 2015 | 97                       | 100                                | Radio-iodine seed                        | Gamma probe         |
| Flores-Funes et al 12  | 2019 | 22                       | 23                                 | Metallic Clip                           | Wire guided         |
| Gatek et al 22         | 2020 | 8                        | 8                                  | Carbon Tattooing                        | N/A (visualized)    |
| Hartmann et al 13      | 2018 | 17                       | 24                                 | Metallic clip                           | Wire guided         |
| Kooien et al 14        | 2017 | 93                       | 93                                 | Radio-iodine seed                        | Gamma probe         |
| Kuemmel et al 15       | 2020 | 329                      | 423                                | Metallic Clip                           | Wire guided         |
| Lim et al 16           | 2020 | 18                       | 21                                 | Metallic Clip                           | NR                  |
| Lowes et al 28         | 2020 | 6                        | 6                                  | Radiofrequency Identification (RFID) tags| RFID probe          |
| Martinez et al 23      | 2020 | 29                       | 30                                 | Metallic Clip                           | Magseed             |
| Park S, et al 25       | 2018 | 20                       | 20                                 | Carbon Tattooing                        | N/A (visualized)    |
| Siso et al 26          | 2018 | 35                       | 35                                 | Metallic Clip                           | Intraoperative ultrasound |
| Spautz et al 17        | 2020 | 121                      | 123                                | Carbon Tattooing                        | N/A (visualized)    |
| Straver et al. 18 | 2010 | 15 | 15 | Radio-iodine seed | Gamma probe |
|------------------|------|----|----|------------------|-------------|
| Sun et al. 27    | 2020 | 45 | 45 | Metallic Clip    | Savi Scout System |
| **Total**        | 1287 | 1430 | | |

NR - Not Reported

N/A - Not Applicable

**Declarations**

Ethics Approval and Consent to Participate
Not Applicable

Consent for Publication
Not Applicable

Figures provided taken from within the London Breast Institute

Availability of data and materials
The data for this manuscript are taken from published article, available online (references given in bibliography)

Competing Interests
The authors declare that they have no competing interests

Funding
The authors declare there are no sources of funding involved at any stage of writing this manuscript

Authors’ contributions
PS and KM carried out the data search and analyses, and wrote the article. ST and MM reviewed and gave constructive feedback to further add to the article.

Acknowledgements
Not Applicable

Authors’ Information (Optional)
Not Applicable

**Bibliography**

1. Charalampoudis P, Markopoulos C, Kovacs T. Controversies and recommendations regarding sentinel lymph node biopsy in primary breast cancer: A comprehensive review of current data. Eur J Surg Oncol.
1. 2018 Jan;44(1):5–14.
2. Wazir U, Mokbel K. De-escalation of Axillary Surgery in the Neoadjuvant Chemotherapy (NACT) Setting for Breast Cancer: Is it Oncologically Safe? Anticancer Res. 2020 Oct;40(10):5351–4.
3. Geng C, Chen X, Pan X, Li J. The Feasibility and Accuracy of Sentinel Lymph Node Biopsy in Initially Clinically Node-Negative Breast Cancer after Neoadjuvant Chemotherapy: A Systematic Review and Meta-Analysis. PLoS One. 2016 Sep;11(9):e0162605.
4. Classe J-M, Loaec C, Gimbergues P, Alran S, de Lara CT, Dupre PF, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019 Jan;173(2):343–52.
5. Kim HS, Shin MS, Kim CJ, Yoo SH, Yoo TK, Eom YH, et al. Improved Model for Predicting Axillary Response to Neoadjuvant Chemotherapy in Patients with Clinically Node-Positive Breast Cancer. J Breast Cancer. 2017 Dec;20(4):378.
6. Fu JF, Chen HL, Yang J, Yi CH, Zheng S. Feasibility and accuracy of sentinel lymph node biopsy in clinically node-positive breast cancer after neoadjuvant chemotherapy: a meta-analysis. PLoS One [Internet]. 2014 Sep 11 [cited 2020 Dec 5];9(9). Available from: https://pubmed.ncbi.nlm.nih.gov/25210779/
7. El Hage Chehade H, Headon H, El Tokhy O, Heeney J, Kasem A, Mokbel K. Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients. Am J Surg. 2016 Nov;212(5):969–81.
8. Sutton TL, Johnson N, Garreau JR. Adequate sentinel node harvest is associated with low false negative rate in breast cancer managed with neoadjuvant chemotherapy and targeted axillary dissection. Am J Surg. 2020 May;219(5):851-854. doi: 10.1016/j.amjsurg.2020.03.012. Epub 2020 Mar 10. PMID: 32245609.
9. Mittendorf EA, Caudle AS, Yang W, Krishnamurthy S, Shaitelman S, Chavez-MacGregor M, et al. Implementation of the American College of Surgeons Oncology Group Z1071 Trial Data in Clinical Practice: Is There a Way Forward for Sentinel Lymph Node Dissection in Clinically Node-Positive Breast Cancer Patients Treated with Neoadjuvant Chemotherapy? [Internet]. Vol. 21, Annals of Surgical Oncology. 2014. p. 2468–73. Available from: http://dx.doi.org/10.1245/s10434-014-3775-6
10. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved Axillary Evaluation Following Neoadjuvant Therapy for Patients With Node-Positive Breast Cancer Using Selective Evaluation of Clipped Nodes: Implementation of Targeted Axillary Dissection [Internet]. Vol. 34, Journal of Clinical Oncology. 2016. p. 1072–8. Available from: http://dx.doi.org/10.1200/jco.2015.64.0094
11. Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. Ann Surg. 2015 Feb;261(2):378–82.
12. Flores-Funes D, Aguilar-Jiménez J, Martínez-Gálvez M, Ibáñez-Ibáñez MJ, Carrasco-González L, Gil-Izquierdo JI, et al. The problem of axillary staging in breast cancer after neoadjuvant chemotherapy. Role of targeted axillary dissection and types of lymph node markers. Cir Esp. 2020 Nov;98(9):510–5.
13. Hartmann S, Reimer T, Gerber B, Stubert J, Stengel B, Stachs A. Wire localization of clip-marked
axillary lymph nodes in breast cancer patients treated with primary systemic therapy. Eur J Surg Oncol. 2018 Sep;44(9):1307–11.
14. Koolen BB, Donker M, Straver ME, van der Noordaa MEM, Rutgers EJT, Valdés Olmos RA, et al. Combined PET-CT and axillary lymph node marking with radioactive iodine seeds (MARI procedure) for tailored axillary treatment in node-positive breast cancer after neoadjuvant therapy. Br J Surg. 2017 Aug;104(9):1188–96.
15. Kuemmel S, Heil J, Rueland A, Seiberling C, Harrach H, Schindowski D, et al. A Prospective, Multicenter Registry Study to Evaluate the Clinical Feasibility of Targeted Axillary Dissection (TAD) in Node-Positive Breast Cancer Patients. Ann Surg [Internet]. 2020 Nov 4; Available from: http://dx.doi.org/10.1097/SLA.0000000000004572
16. Lim GH, Gudi M, Teo SY, Ng RP, Yan Z, Lee YS, et al. Would Removal of All Ultrasound Abnormal Metastatic Lymph Nodes Without Sentinel Lymph Node Biopsy Be Accurate in Patients with Breast Cancer with Neoadjuvant Chemotherapy? Oncologist. 2020 Nov;25(11):e1621–7.
17. Spautz CC, Schunemann Junior E, Budel LR, Cavalcanti TCS, Louveira MH, Junior PG, et al. Marking axillary nodes with 4% carbon microparticle suspension before neoadjuvant chemotherapy improves sentinel node identification rate and axillary staging. J Surg Oncol. 2020 Aug;122(2):164–9.
18. Straver ME, Loo CE, Alderliesten T, Rutgers EJT, Vrancken Peeters MTFD. Marking the axilla with radioactive iodine seeds (MARI procedure) may reduce the need for axillary dissection after neoadjuvant chemotherapy for breast cancer. Br J Surg. 2010 Aug;97(8):1226–31.
19. Boughey JC, Ballman KV, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, et al. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). Ann Surg. 2016 Apr;263(4):802–7.
20. Cabioğlu N, Karanlık H, Kangal D, Özkurt E, Öner G, Sezen F, et al. Improved False-Negative Rates with Intraoperative Identification of Clipped Nodes in Patients Undergoing Sentinel Lymph Node Biopsy After Neoadjuvant Chemotherapy. Ann Surg Oncol. 2018 Oct;25(10):3030–6.
21. Coufal O, Zapletal O, Gabrielová L, Fabian P, Schneiderová M. Targeted axillary dissection and sentinel lymph node biopsy in breast cancer patients after neoadjuvant chemotherapy - a retrospective study. Rozhl Chir [Internet]. 2018 [cited 2021 Jan 25];97(12). Available from: https://pubmed.ncbi.nlm.nih.gov/30646734/
22. Gatek J, Petru V, Kosac P, Ratajsky M, Duben J, Dudesek B, et al. Targeted axillary dissection with preoperative tattooing of biopsied positive axillary lymph nodes in breast cancer. Neoplasma. 2020 Nov;67(6):1329–34.
23. Mariscal Martínez A, Vives Roselló I, Salazar Gómez A, Catanese A, Pérez Molina M, Solà Suarez M, et al. Advantages of preoperative localization and surgical resection of metastatic axillary lymph nodes using magnetic seeds after neoadjuvant chemotherapy in breast cancer. Surg Oncol. 2020 Nov 23;36:28–33.
24. Fong Y, Giulianotti PC, Lewis J, Koerkamp BG, Reiner T. Imaging and Visualization in The Modern Operating Room: A Comprehensive Guide for Physicians. Springer; 2015. 288 p.
25. Park S, Koo JS, Kim GM, Sohn J, Kim SI, Cho YU, et al. Feasibility of Charcoal Tattooing of Cytology-
Proven Metastatic Axillary Lymph Node at Diagnosis and Sentinel Lymph Node Biopsy after Neoadjuvant Chemotherapy in Breast Cancer Patients. Cancer Res Treat. 2018 Jul;50(3):801–12.

26. Siso C, de Torres J, Esgueva-Colmenarejo A, Espinosa-Bravo M, Rus N, Cordoba O, et al. Intraoperative Ultrasound-Guided Excision of Axillary Clip in Patients with Node-Positive Breast Cancer Treated with Neoadjuvant Therapy (ILINA Trial) : A New Tool to Guide the Excision of the Clipped Node After Neoadjuvant Treatment. Ann Surg Oncol. 2018 Mar;25(3):784–91.

27. Sun J, Henry DA, Carr MJ, et al. Feasibility of Axillary Lymph Node Localization and Excision Using Radar Reflector Localization. Clinical Breast Cancer. 2020 Aug. DOI: 10.1016/j.clbc.2020.08.001.

28. Lowes S, Bell A, Milligan R, Amonkar S, Leaver A. Use of Hologic LOCalizer radiofrequency identification (RFID) tags to localise impalpable breast lesions and axillary nodes: experience of the first 150 cases in a UK breast unit. Clin Radiol. 2020 Dec;75(12):942-949. doi: 10.1016/j.crad.2020.08.014. Epub 2020 Sep 9. PMID: 32919756.

29. Choy N, Lipson J, Porter C, Ozawa M, Kieryn A, Pal S, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. Ann Surg Oncol. 2015 Feb;22(2):377–82.

30. Laws A, Dillon K, Kelly BN, Kantor O, Hughes KS, Gadd MA, et al. Node-Positive Patients Treated with Neoadjuvant Chemotherapy Can Be Spared Axillary Lymph Node Dissection with Wireless Non-Radioactive Localizers. Ann Surg Oncol. 2020 Nov;27(12):4819–27.

31. Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. AJCC Cancer Staging Atlas: A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook. Springer Science & Business Media; 2012. 637 p.

32. Kasem I, Mokbel K. Savi Scout® Radar Localisation of Non-palpable Breast Lesions: Systematic Review and Pooled Analysis of 842 Cases. Anticancer Res. 2020 Jul;40(7):3633–43.

33. García-Moreno JL, Benjumeda-Gonzalez AM, Amerigo-Góngora M, Landra-Dulanto PJ, Gonzalez-Corena Y, Gomez-Mencher J. Targeted axillary dissection in breast cancer by marking lymph node metastasis with a magnetic seed before starting neoadjuvant treatment. J Surg Case Rep. 2019 Nov;2019(11):rjz344.

34. Caudle AS, Yang WT, Mittendorf EA, Black DM, Hwang R, Hobbs B, et al. Selective surgical localization of axillary lymph nodes containing metastases in patients with breast cancer: a prospective feasibility trial. JAMA Surg. 2015 Feb;150(2):137–43.

35. Kim WH, Kim HJ, Kim SH, Jung JH, Park HY, Lee J, et al. Ultrasound-guided dual-localization for axillary nodes before and after neoadjuvant chemotherapy with clip and activated charcoal in breast cancer patients: a feasibility study. BMC Cancer. 2019 Aug 30;19(1):859.

36. Gera R, Tayeh S, Al-Reefy S, Mokbel K. Evolving Role of Magseed in Wireless Localization of Breast Lesions: Systematic Review and Pooled Analysis of 1,559 Procedures. Anticancer Res [Internet]. 2020 Apr [cited 2021 Jan 25];40(4). Available from: https://pubmed.ncbi.nlm.nih.gov/32234869/

37. Wazir U, Tayeh S, Perry N, Michell M, Malhotra A, Mokbel K. Wireless Breast Localization Using Radio-frequency Identification Tags: The First Reported European Experience in Breast Cancer. In Vivo [Internet]. 2020 [cited 2021 Jan 25];34(1). Available from: https://pubmed.ncbi.nlm.nih.gov/31882483/

38. Caretta-Weyer H, Greenberg CG, Wilke LG, Weiss J, LoConte NK, Decker M, et al. Impact of the
American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on clinical management of the axilla in older breast cancer patients: a SEER-medicare analysis. Ann Surg Oncol. 2013 Dec;20(13):4145–52.

39. Lee J, Jung JH, Kim WW, Lee RK, Kim HJ, Kim WH, et al. 5-year oncological outcomes of targeted axillary sampling in pT1-2N1 breast cancer. Asian J Surg. 2019 Jun;42(6):681–7.

40. Kahler-Ribeiro-Fontana S, Pagan E, Magnoni F, Vicini E, Morigi C, Corso G, et al. Long-term standard sentinel node biopsy after neoadjuvant treatment in breast cancer: a single institution ten-year follow-up. Eur J Surg Oncol [Internet]. 2020 Oct 15; Available from: http://dx.doi.org/10.1016/j.ejso.2020.10.014

41. van Nijnatten TJA, Simons JM, Smidt ML, van der Pol CC, van Diest PJ, Jager A, et al. A Novel Less-invasive Approach for Axillary Staging After Neoadjuvant Chemotherapy in Patients With Axillary Node-positive Breast Cancer by Combining Radioactive Iodine Seed Localization in the Axilla With the Sentinel Node Procedure (RISAS): A Dutch Prospective Multicenter Validation Study. Clin Breast Cancer. 2017 Aug;17(5):399–402.

42. Henke G, Knauer M, Ribi K, Hayoz S, Gérard M-A, Ruhstaller T, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials. 2018 Dec 4;19(1):667.