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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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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 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 complications27.
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 sites28.
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
Koolen 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
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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.

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Figures

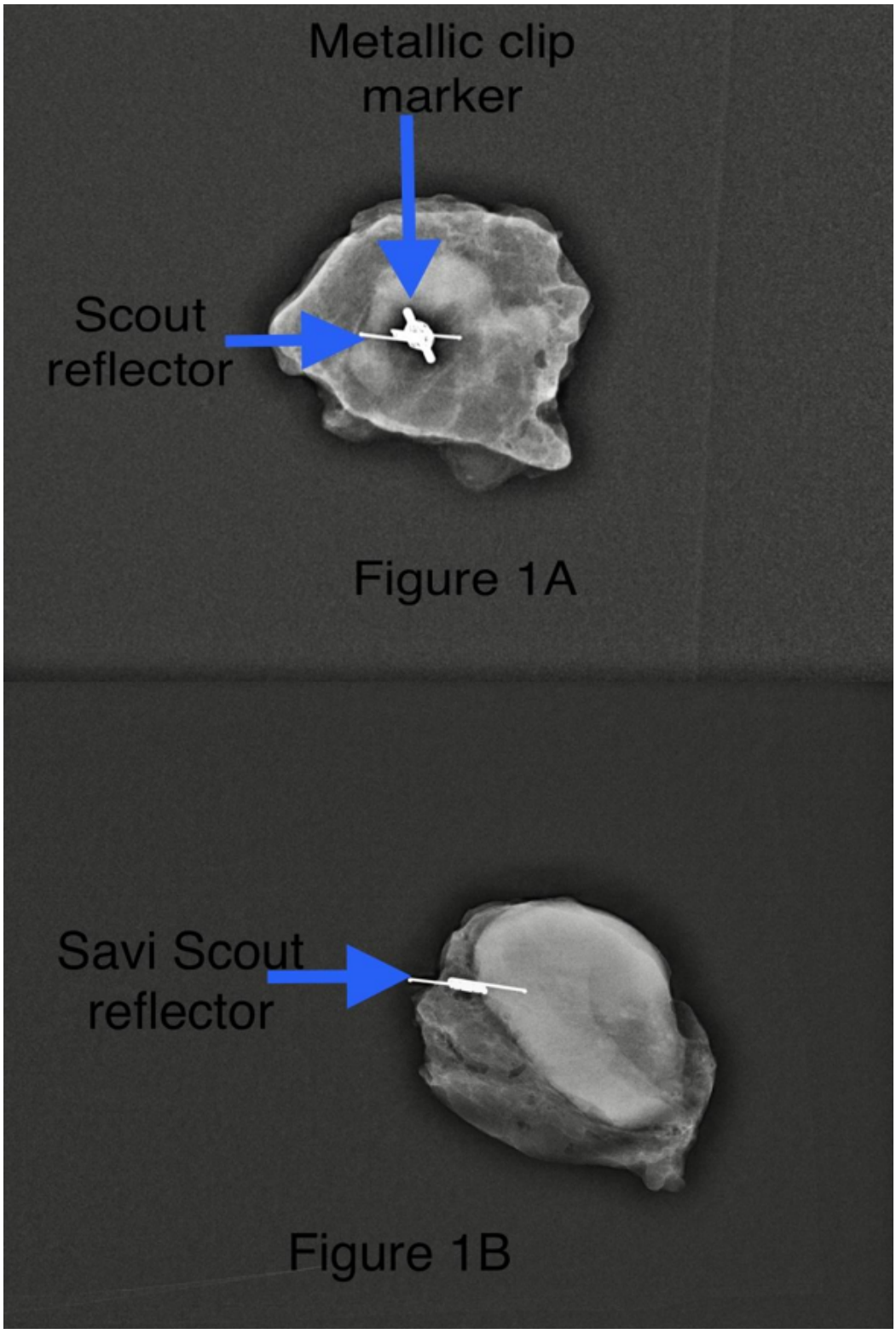

Figure 1

In figure 1A the patient had a metallic marker clip deployed within the pathological lymph node at the time of biopsy before NACT and a second localization procedure using Savi Scout prior to surgery. In figure 1B, the patient had the Savi Scout reflector at the time of biopsy prior to NACT thus avoiding a second procedure. There were no MRI artefacts related to the Savi Scout reflector in 1B. The surgical procedure of identification and retrieval of the Savi Scout reflector took 15 minutes.