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TARGETED AXILLARY DISSECTION AMONG PATIENTS WITH NODE-POSITIVE BREAST CANCER TREATED WITH NEOADJUVANT CHEMOTHERAPY

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Artigo de Revisão Narrativa

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ABSTRACT

Invasive breast cancer with axillary lymph node invasion is a recurrent problem worldwide. The morbidity associated with axillary lymph node dissection along with the high rate of nodal downstaging after neoadjuvant chemotherapy made the standard treatment shift towards less invasive surgery. Sentinel Lymph Node Biopsy (SLNB) after Neoadjuvant Chemotherapy (NACT) is associated with high false negative rates. To overcome this problem, it was concluded that the positive nodes should first be indicated with image-detectable markers and then removed together with SLNB: Targeted Axillary Dissection (TAD).

This review aims to describe and evaluate the different marking techniques for TAD in patients with node-positive breast cancer treated with NACT, namely:

- Clip placement and guidewire localization;
- Clip placement and 125I-labeled radioactive seed localization;
- Clip placement and skin mark clipped axillary nodes;
- Clip placement and intraoperative ultrasound;
- Tattooing of biopsied axillary lymph nodes with a sterile black carbon suspension;
- Marking lymph nodes metastasis with magnetic seeds;
- Radar and infrared light technology localization.

The main objective is to assess false negative rates and identification rates of the different techniques.

An online search was conducted in Pubmed with the search equation: "Breast Neoplasms" [Mesh] AND neoadjuvant AND axilla*. Research was restricted to articles written in English, published in the period from 2010 to 2020. All types of articles were selected to be reviewed. The studies considered relevant from the bibliographic references of the selected articles were also analyzed. Even though some techniques have been tested in small number of patients to make definitive conclusions, they demonstrated great potential of being implemented in our everyday worklife and replace the current standard of health care not only due to their accuracy but also because of their manageability and capability to provide patient comfort.

Keywords: Breast Neoplasms; Lymphatic Metastasis; Neoadjuvant Therapy; Targetted Axilllary Dissection

Targeted axillary dissection among patients with node-positive breast cancer treated with neoadjuvant chemotherapy

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ABBREVIATIONS AND ACRONYMS

ACOSOG = American College of Surgeons Oncology Group

ALND = Axillary Lymph Node Dissection

CT = Computer Tomography

FNR = False Negative Rate

LN= Lymphatic Node

MRI = Magnetic Resonance Imaging

NACT = Neoadjuvant Chemotherapy

NPV = Negative Predictive Value

SMART = Skin Marked Clipped Axillary Nodes Removal Technique

SLNB = Sentinel Lymph Node Biopsy

TAD = Targeted Axillary Dissection

US = Ultrasound

1. INTRODUCTION

Over the last century, surgical procedures in breast cancer patients have evolved from being disfiguring to relatively non-invasive. (1) As this is one of the most common types of cancer worldwide the relevance of this progress is notorious. (2)

The management of invasive breast cancer involves the effort of a multidisciplinary team to establish a correct diagnosis and staging of the primary tumor. (3) Not only the type of systemic therapy and radiation is decided according to the lymph node (LN) status, but also the prognostic depends on the presence of nodal metastases. (4–9)

In patients with breast cancer and axillary metastasis, neoadjuvant chemotherapy (NACT) results in a complete pathological response in a still growing number of patients, which is due to improvements in the available treatments over the last decades. (5)

The high rate of nodal downstaging has led to the acceptance of sentinel lymph node biopsy (SLNB) to stage the axilla after NACT in patients who had a clinical and radiological complete response (40-75%). (5,10) Such paradigm shift allowed the avoiding of the majority of axillary lymph node dissections after NACT and its morbidity effects such as pain, paraesthesia, shoulder disfunction and more significantly, lymphoedema. (11,12) Therefore, management of the axilla in breast cancer patients has shifted into a less radical and less invasive approach. Furthermore, in line with the ACOSOG Z0011 and AMAROS clinical trials, which showed no benefit of the completion axillary lymph node dissection (ALND) in selected patients with positive sentinel LN(s), current guidelines state that SLNB is sufficient, even in the case of nodal involvement, in most patients with small tumors who are receiving adjuvant therapies. (13–15)

However, SLNB alone after NACT has a high false negative rate (12.6-14.2%) and, when the initially metastatic LN is marked, the sentinel LNs did not correspond to it in 23%. (10,16) As the sentinel LN is the hypothetical first LN (or group of nodes) to which a cancer can drain to, this means that other nodes in the axilla can have residual disease, reinforcing the idea that SLNB is not enough to achieve the desired detection results. This also suggests that chemotherapy can alter axillary lymphatic drainage pathways, leading to high false negative rate (FNR). (17)

To overcome these issues, the positive nodes should be marked before NACT, with an image-detectable marker, and then removed together with SLNB after NACT – targeted axillary dissection (TAD). After Caudle et al. showed that adding the excision of the clipped node to the SLNB was able to reduce the FNR from 10.1 to 1.4%, this strategy has been endorsed by some guidelines. (4,13,16,18,19) In fact, with a FNR of 2%, oncological compromise would only affect approximately 1 in 10 000 patients, which does not justify the need for a more invasive strategy therefore preserving the quality of life of patients. (16)

However, the best technique for TAD in patients with initially node-positive breast cancer who are clinically negative after NACT is still unclear.

This review aims to describe and evaluate the different marking techniques for TAD in patients with node-positive breast cancer treated with NACT, namely:

- Clip placement and guidewire localization;

- Clip placement and 125i-labeled radioactive seed localization;

- Clip placement and skin mark clipped axillary nodes;

- Clip placement and intraoperative ultrasound;

- Tattooing of biopsied axillary lymph nodes with a sterile black carbon suspension;

- Marking lymph nodes metastasis with magnetic seeds;

- Radar and infrared light technology localization.

These techniques will be compared in terms of feasibility, advantages and disadvantages, specific side effects, identification rates and false-negative rates.

Additionally, it will be briefly discussed in which sense these techniques can improve the treatment and quality of life of these patients.

2. MATERIALS AND METHODS

An online search was conducted at Pubmed with the search equation: "Breast Neoplasms"[Mesh] AND neoadjuvant AND axilla*.

The search was restricted to articles written in English, published in the period from 2010 to 2020. All types of articles were selected for review.

The studies considered relevant from the bibliographic references of the selected articles were also analysed

3. COMPARISON OF TECHNOLOGIES

3.1. Clip placement and guidewire localization

This technique, which has been used to localise non-palpable lesions in the breast for decades, could be adapted to use in the preoperative image-guided localization of axillary LNs. (5)

The wire is usually packaged with a 19-gauge hollow delivery needle which is used as a sheath in which the flexible fixed wires must be placed and then anchored to the tissue. To correctly allocate the wire, either adjacent or through the targeted LN, mammography, ultrasound (US), Magnetic Resonance Imaging (MRI) and rarely Computer Tomography-guidance can help localizing the nodes. (5)

The low price point and the familiar, yet complex, surgeons and radiologists' workflow may seem the primary benefits of this technology. Due to the risk of migration this procedure can be described as complex since the placement and removal must be performed on the same day. (5,20,21) However, the wire is easily visualized protruding from the skin and can be followed by the surgeon to reach the targeted LN. (5)

There has been some hesitation both from radiologists and surgeons to use these wires as a localization method mainly due to its known complications such as pain, hematoma, and adjacent tissue injury particularly of the sensitive structures like arteries, veins and brachial plexus that exist in the axilla. (5)

Although it was not reported in two trials using wire localization in the axilla, there is evidence in the literature for wire migration in the breast, sometimes of a great distance. (3,5) There is always the possibility of the clip being dislocated and/or removed with irrigation and suction. (22) It is also uncomfortable and stressful for the patient. (20)

In one study described by Balabsumarian, it was demonstrated a good concordance between the retrieval of the clipped node and the SLN (86%) associated with an accurate retrieval of the clipped node (92%) (12)

In the ACOSOG Z1071 study, 338 eligible patients underwent both SLNB and ALND after chemotherapy. In 12.6% of the population, cancer was not identified in the SLNs but was found in LNs obtained with ALND (FNR of 12.6%). (23) Plecha et al. reported that the clipped node identification rate was of 97% when wire localization was used. (12,14,24)

3.2. Clip placement and 125i-labeled radioactive seed localization

The use of labelled radioactive seeds as a localization technique was initially designed for nonpalpable lesions in the breast. However it is currently being adapted for the axilla. (5)

The radioactivity level within the seed ranges from 0.1 to 0.3 millicuries, with a half-life of 60 days, which makes the scheduling of surgery easier besides being considered safe for human exposure. (5,22)

After NACT and 1 to 5 days prior to the surgery, the clipped node is localized with the help of mammogram or US guidance and afterwards using a gamma probe to detect the 125i-seed. (5)

This technique's advantages include decreased risk of displacement, better patient comfort and lower potential of injuries to the surrounding vascular structures during surgery. (22)

Concerning the drawbacks, the most obvious is the exposure to radiation. It is not only expensive and a complicated procedure, but it also faces legal problems for retrieval and disposal of radioactive materials. (5,21,25,26) It also requires the involvement of a nuclear physician and does not provide real-time visual guidance. (27) Nevertheless, the dose of radiation is small and there is no significant exposure to people who may come into contact with the patient before or after surgery. (5) Seed loss, the need for special instruments to identify the seeds and seed migration are other potential disadvantages of this technique. (12,26)

A study conducted by Straver describes the experience of six radiologists conducting this procedure who didn't find any complication and had no significant difficulties. (28)

Applying a marker clip to LNs under US guidance and then marking these LNs post-NACT with radioactive I125 seeds achieved an identification rate (IR) of 96.7% and concordance among clipped LNs and SLNs reached 91% (25,26). The clipped node was associated with FNR of 4.2%, and specifically localizing and removing the clipped node in addition to removal of SLNs resulted in an FNR of 2.0%. (22)

3.3. Clip placement and skin mark clipped axillary nodes

Preoperatively, the clip localization was marked on the skin with the ipsilateral arm abducted at 90º. This aims to mimic the arm position during surgery, with an US probe placed perpendicularly to the skin to perform the skin marking. Then, a 21G needle is inserted perpendicularly into the skin to place the clip. Identification of the clip was based on its perpendicular distance from the skin and morphology and position were determined relatively to surrounding structures based on pre-NACT diagnostic US. If the clip is no longer visible, prior axillary US images and chest cross-sectional imaging studies can be reviewed to assist locating the clip. (10)

In the SMART trial, with a total of 25 clipped nodes in 14 patients, Lim et al. reported that there were no complications with the clip placement. Despite its different types the one which had the highest rate of identification was the UltraCor Twirl (18). It showed a 100% removal rate whilst others had less than 80%. The UltraCord Twirl's success rate is mainly due to the improvements in its US visibility. (10)

When comparing to the visibility of other US clips these are still suboptimal, with reported rates of only 72%-83.3%. This is mainly due to the NACT which causes shrinkage and fibrosis of the LNs, making them less hypoechogenic upon US and harder to identify against a background of echogenic fat. (10)

The advantages of this technique include it being non-invasive, wireless and radiation-free due to its preoperative location. It is also less expensive than other localizing devices and more accessible to health centres. (10) No complications of this technique were reported. Limitations of SMART trial included a small sample size of only 14 patients and, as all patients underwent ALND, it was not possible to assess the compatibility with SLNB and to evaluate the FNR. (10)

3.4. Clip placement and intraoperative ultrasound

Size, morphology, internal echogenicity, disproportionate enlargement, presence of eccentric or uneven cortical thickening and abnormal "rounding" shape are sonographic features which characterise malignant LNs. (22) (Figure 1)

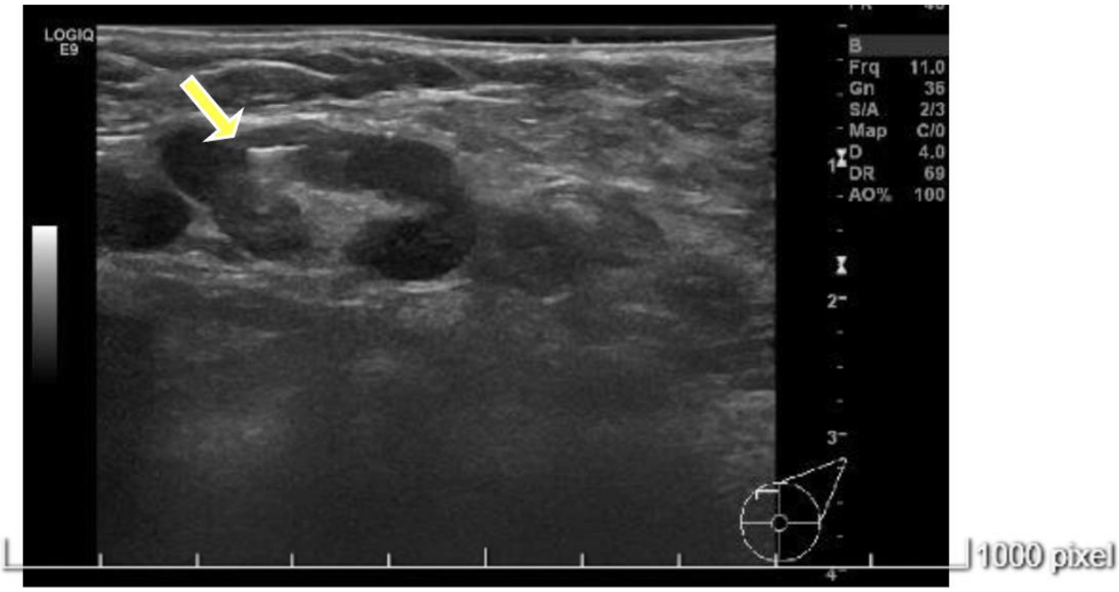

Figure 1 Metastatic LN marked with a clip (yellow arrow), before NAC

Nevertheless, the Z1071 trial exposed evidence demonstrating that US is not a precise method for identifying normalized axillary nodes following NACT as more than 50% of cases are still pathologically positive. (12) It also concluded that TAD is a more accurate procedure for staging the LNs after NACT. (3,12) This led to the use of marker clips to be identified by US.

These can be divided in two categories: a metallic clip typically made of stainless steel or titanium and a sonographically-visible metallic clip with an associated bioresorbable material typically made of collagen, polylactic acid, or polyglycolic acid, which absorbs water over time. (5)

Whilst some studies refer this technique to not have any problems regarding clip migration or complications related to the clip insertion or patient distress (20,29), others are worried about the possibility of migration and extrusion. This is a situation that can happen in 50% of procedures using sonographically-visible water-absorbing clips (5). On the other hand there is also the advantage of the time that a clip can remain visible, making the scheduling of surgeries and clip placement much easier. (5,20) It is also a very cost-effective technique and in terms of re-excision rates it can be superior to wire localization in some cases. (30)

The technique is very safe in experienced hands, with close to a 100% success rate. (10,20)

In one study described by Woods, 44 out of 46 (95.7%) marker clips were identified preoperatively and successfully removed using intraoperative US; in the two remaining patients the Hydro-MARK clip was successfully removed after ALND. This suggests that sonographically-visible hygroscopic or metallic clips could be a reasonable choice for use in intraoperative US axillary localizations. (5)

3.5. Tattooing of biopsied axillary lymph nodes with a sterile black carbon suspension

For tattooing, 1 ml of CharcotraceTM black ink (Phebra, Lane Cove West, Australia) was injected adjacent to the soft tissue and into the cortex of the node after local anaesthesia through US guidance. This procedure usually takes approximately 5 to 20 minutes per patient. The radiologist marked the location of the LN on the skin with an oil-based pen to guide the surgical incision. (31,32)

Tattooing with activated charcoal has been reported to yield high identification rates in preceding studies of 95-100%, (25,31–33) two of these studies focused on tattooing after NACT, in which one had 28 patients and the other 20 patients (32,33) whilst another, which involved tattooing before NACT, involved 49 patients. (31)

Black ink has the advantage of being identified up to an average of 130 days (25,32,33) as well as being an affordable alternative to the already existing methods (25). It is also unnecessary to verify the removal of a clip or radioactive seed during surgery. (32)

There is also some clinically negligible risk of charcoal absorption or migration and the long-term complications of tattooing should be further validated using cohort studies. (32)

The diagnostic performance of TAD using sterile black carbon suspension showed values as follows: FNR 8.3%; accuracy 95%; NPV 90.8%; and sensitivity 91.7%. Concordance among tattooed LNs and SLNs is not absolute, indicating an improvement in the accuracy of post-NACT SLNB with the help of TAD as this technique selects to remove marked LNs not supposed to be SLNs (25). These findings appear to be associated with fibrosis in the lymphatic channel associated with NACT, which would result in altered lymphatic drainage. (34)

Moreover, because patients undergoing NACT often have more than one suspicious axillary node on US at initial staging, marking or locating one metastatic node for subsequent removal may be limited. (31) Therefore, localization of axillary nodes based on restaging US may be more useful for patients with multiple suspicious nodes at initial staging. (31,35,36)

3.6. Marking lymph nodes metastasis with magnetic seeds

The magnetic seed is a new technology that uses a 1×5mm surgical stainless-steel marker. (5,37) It can be detected using a magnetometer (Sentimag, Endomag, Cambridge, UK), which provides information about how far away it is and its direction to the marker. (26) This means the marked node can be located similarly as how the radioactive iodine seed would be detected but without the regulatory problems associated with the use of radioactive materials. (38)

Seed placement performed under US guidance is similar to sonographically guided clip placement. The seed is localized in the operating room using the Sentimag (Endomag) magnetometer. Sentimag creates an alternating magnetic field that transiently magnetizes the seed. (5,26)

Magseed® appears to be an accurate, safe and nonradioactive method for precisely localizing axillary lymph nodes preoperatively, with 97% of target nodes being successfully removed in surgery. (26)

On a trial including 35 patients, seed loss was reported in only one patient. However, the surgeon believed the seed was suctioned or dropped during surgery and therefore removed. Besides the single case of seed misplacement that occurred at the time of deployment, no documented complications occurred during Magseed® placement. (26)

Major disadvantages of using magnetic seeds are the cost of each seed which can restrict the routine use of this technology, depth limitation and substantial artefact obscuring underlying tissue. (12,26,39). This MRI artefact can complicate the assessment of treatment response in tumors located within 3 cm of the axillary cavity. As such, we do not recommend implanting the magnetic seed before NACT on any tumors in this area. (38)

According to the retrospective study made by Greenwood et al., the Magseed® was visualized in the axillary LN on 31 out of 32 of these mammograms (97%), and for one patient (3%) with an implant, the Magseed ® and axillary lymph node was not visualized in the field of view. Successful retrieval was documented for 37 out of 38 Magseed ® (97%). (26)

Both Price et al. and Lamb et al. documented a 100% successful retrieval rate in their initial experience of breast lesion localization with Magseed ®. (26,40,41)

3.7. Radar and infrared light technology localization

Nonradioactive infrared (NIR) activated electromagnetic wave reflector is implanted under imaging guidance. The reflector is typically placed under US or mammographic guidance, and an audible signal from the implanted reflector is then detected percutaneously using the manufacturer's handpiece-and-console system. (5,21,42)

The use of NIR fluorescence for SLN mapping has several advantages over conventional modalities such as real-time visual guidance, superior depth penetration when compared to blue dyes, as well as broader availability compared to radioactive tracers. (27) Also, the reflector is approved for long term placement so it could be placed before the NACT. Cox et al. conducted a study reporting better patient overall experience. In fact, due to its scheduling benefits, lower levels of anxiety, better comfort and improved clinical management were achieved. (36)

No cases of reflector migration were reported in a cohort study involving 20 patients and 22 reflectors. (5,21).

Considering the greater scheduling flexibility, shorter operating times, lower re-excision rates and reduced deployment times it may be possible to make some indirect financial savings due to its effectiveness in spite of its initial higher and recurrent cost. (36)

The major disadvantage found was the hypothesis of it not being able to move the reflector or retrieve it once it was deployed. However one study stated that since SCOUT®, reflectors placement were reported to be successfully placed at the target site and so this factor could be eliminated (21,42)

Nevertheless, the reflectors cannot be placed in patients with a nickel allergy, and the retrieval of the reflector can be affected by cautery and by halogen operating room lights (5). One case of detection signal loss was described in a pilot study after the reflector came into contact with an electrocautery device. (21) Also, the clip is 12mm long which is relatively large compared to the normal-sized LNs. This may cause some uncertainty regarding the placement as it may need to be placed adjacent to an abnormal LN. (5,21)

Challenging cases often resulted from failure to obtain an audible signal from the reflector in the radiology suite, as demonstrated by the cases that include a faulty reflector, an axillary LN, or hematoma. (42)

Savi SCOUT®, which is an approved console to detect reflectors' localization, was successful in 97% [125/129; 95% confidence interval (CI) 92–99%] patients and 97% [148/152; 95%CI 93–99%] reflectors. Of the 4 unsuccessful cases, 3 were due to an inability to obtain an audible signal. (42). Nonetheless, this indicates that this technology is highly accurate and may help to successfully retrieve metastatic nodes and facilitate surgical planning in the axilla (5). It was reported a re-excision rate of 12.8%. (21)

4. CONCLUSION

Identifying metastatic nodes in the axilla after NACT is of the outmost importance in medical practice today. Therefore, there is an attempt to improve its current techniques. This is a necessity which arose from the limitations of the standard SLNB presenting a FNR above 10%, making it unsuitable for safely staging breast cancer patients.

On the other hand, targeted axillary dissection has presented FNR below 9% and IR above 95%. Even though it has been understood that it is more precise than SLNB alone, to better understand this procedure and maximize its potential, more studies need to be conducted, including larger number of patients.

At the present moment, the most studied technique is “Wire localization” as it is also the oldest one. However, according to data gathered from this review, some techniques have shown to be very promising due to their statistic results and management factors. For example, “Tattooing of biopsied axillary lymph nodes with a sterile black carbon suspension” or “Clip placement and skin mark clipped axillary nodes” could be a more practical option. They both performed equal or above the other techniques while only requiring the clip or the ink and ultrasound technology to place it correctly. The ultrasound component is a well-known technology which most health facilities have access to, besides being a more affordable option compared to others such as the ones using magnetic, radioactive seeds or even SCOUT® technology.

ANNEX I

Table 1 Comparison of targeted axillary dissection techniques

Techniques	Timing of device placement	Advantages	Disadvantages	FNR	IR
Guidewire	Immediately prior to surgery	Low price Familiar workflow Non-radioactive	Potential damage of adjacent structures Pain, hematoma	6.8%	97%
I-125 radioactive seed	5-7 days prior to surgery	Decreased risk of displacement Patient comfort Decreased risk of damaging adjacent structurers	Radiation Legal and regulatory complications Seed loss Special instruments Seed migration	4.2%	96.7%
Skin mark	Immediately prior to surgery	Low price Non-radioactive Wireless	Risk of migration and extrusion of the clip	N/A	100% (with UltraCor Twirl clip)
Intraoperative US	At time of biopsy	No patient distress Clip visible for long time Cost-effective Good re-excision rates Non-radioactive	Risk of migration and extrusion of the clip	7%	95.7%
Sterile black Carbon suspension	At time of biopsy	Average duration of 130 days Affordable Non-radioactive	Potential difficult visualization due to charcoal absorption or migration	8.3%	95-100%
Magnetic seed	At least up to 30 days prior to surgery	Accurate Safe Non-radioactive No restriction on duration	Cost Depth limitation MRI artifact	1.4%	97-100%
Radar and infrared light	At time of biopsy	Real-time visual guidance Superior depth Non-radioactive No restriction on duration	Contains nickel Structures may impede signal	N/A	97%

Abbreviation: FNR – False Negative Rate; IR – Identification Rate; MRI – Magnetic Ressonance Imaging; N/A – Not available; US – Ultrasound.

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