

The Management of Sentinel Lymph Node Biopsy in Breast Cancer

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Abstract

Breast cancer is a public health issue due to its high incidence and mortality in advanced stages. As breast cancer is lymphophilic (the disease is spread mainly through the lymphatic system), axillary surgery remains essential in the treatment and staging of this condition. Sentinel lymph node biopsy has become the gold standard for axillary nodal staging, successfully replacing total axillary lymphadenectomy. This procedure has evolved significantly in the last 30 years and represents a topic of great relevance and interest. Certain issues related to the sentinel lymph node (identification techniques, indications and contraindications, the role of adjuvant therapy), will be highlighted in this paper.

Keywords: Breast Cancer; Sentinel Lymph Node Biopsy; Techniques of Sentinel Lymph Node Biopsy; Total Axillary Lymphadenectomy

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Introduction

Breast cancer is the second leading cause of death worldwide in recent years [1]. Recently, the screening and therapeutic techniques performed for breast cancer have led to early detection of the disease, reduced complications and increased survival rates at 5 years [2]. Assessment of regional lymph node status in patients with this condition is particularly important for therapeutic and prognostic decisions [3]. Neoplastic dissemination is performed mainly by the lymphatic system at the level of the first lymph node (sentinel node) which drains the lymph from the tumour [4].

The term "sentinel node" was first introduced in 1951 by Gould during a parotidectomy [5]. In 1977, Cabanas adopted it for penile neoplasm [6]. In 1992, Donald Morton demonstrated the veracity of lymphatic dissemination of cutaneous malignant melanoma [7]. The identification of the sentinel node in breast cancer was performed in 1993 by Kreg, who used a radioactive tracer with a gamma camera [8], and in 1994, Giuliano did the same research using blue dyes at the John Wayne Oncology Institute [9].

The article aims to highlight the importance of the sentinel node in breast cancer.

Materials and Methods

Sentinel node versus total axillary lymphadenectomy

The sentinel nodes are defined as the first node or nodes that

drains lymph from the breast and implicitly from the tumour, while also representing a prognostic marker (by the possibility of specifying the nature of regional nodes) for the 5-year survival rate and a factor in establishing the local and systemic therapeutic attitudes [2].

It is essential that patients receive an adequate pre-therapeutic assessment of the axillary lymphatic region. At the time of surgery, there are patients with positive sentinel lymph node who require completion axillary lymphadenectomy and those with a negative result for whom axillary lymphadenectomy is not required [10].

Sentinel lymph node biopsy was accepted as a less invasive axillary staging alternative than total axillary lymphadenectomy for those patients diagnosed in the early stages of the disease (pN0). The morbidity in these cases decreased significantly [2].

The results of the ACOSOGZ0011 study showed that completion axillary lymphadenectomy in situations where there are only 1-2 positive axillary sentinel nodes can be avoided in patients with less advanced breast cancer, with no significant differences in 10-year survival [11].

In the management of breast cancer, axillary lymphadenectomy was the gold standard for staging, but unwanted effects such as arm lymphedema accompanied by limited movement, skin

sensitivity disorders and seroma formation led to its successful replacement by sentinel lymph node biopsy [2] (Table 1).

Indications	Contraindications	Special circumstances
Early stage breast cancer (T1, T2) and clinically negative axilla [12] or T3 and clinically negative axilla [13]	The 2014 American Society of Clinical Oncology and 2010 International Expert Panel Guidelines recommended that sentinel lymph node biopsy not be performed in patients with inflammatory breast cancer (T4d) [14] or breast cancer with dissemination to the skin and chest wall; in these conditions axillary lymphadenectomy is performed [10]	Neoadjuvant chemotherapy
<3 invaded lymph nodes on sentinel lymph node biopsy in patients with lumpectomy followed by irradiation of the whole breast [10]		
Mastectomy performed for extensive (ductal carcinoma in situ) DCIS		Multicenter disorders
DCIS with clinical suspicion of an invasive condition, including tumor size > 5 cm [4]		
DCIS with lumpectomy, with subsequent identification of an invasive form of the disease [10]		History of breast and axillary surgery [14]
Negative axillary lymph nodes after neoadjuvant therapy (cNO) [10]		
In case of conversion of positive N1 tumours to NO, neoadjuvant post-therapy [10]	Pregnancy: the only dye accepted as safe for the foetus in sentinel lymph node biopsy is methylene blue [15]	

Table 1: Indications and contraindications for performing sentinel lymph node biopsy.

The indications for total axillary lymphadenectomy are:

- ≥ 3 lymph nodes invaded at sentinel node biopsy
- 1, 2 lymph nodes metastasized to sentinel node biopsy, but without irradiation of the entire breast [10].

Research conducted by the Yale School of Public Health shows that elderly patients diagnosed with early breast cancer (ductal carcinoma in situ) do not benefit from excision sentinel lymph node biopsy, because it reduces neither the risk of mortality from the disease nor the development of a more aggressive form thereof [16]. A prospective study presented at a virtual symposium in December 2020 (San Antonio Breast Cancer) showed that patients over the age of 70, who were estrogen-receptor positive and HER 2 negative, and who were being administered hormone therapy, showed a significantly increased survival rate [17]. NICE guidelines recommend that sentinel lymph node biopsy should not be routinely performed in patients diagnosed with ductal

carcinoma in situ or candidates for lumpectomy. It should only be proposed if they are considered to be at increased risk of developing an invasive form of the disease [18] or when they require radical mastectomy [19].

The NICE guidelines recommend the following:

1. Do not perform adjuvant axillary radiotherapy after complete axillary lymphadenectomy.
2. Do not perform axillary or supraclavicular radiotherapy in patients with early breast cancer with a negative sentinel lymph node.
3. Do not administer Paclitaxel as adjuvant therapy to patients with positive sentinel lymph node breast cancer.
4. Patients whose sentinel lymph node has isolated malignant cells (ITC) should be considered to have a negative sentinel lymph node (Table 2).

Before	After
The most accurate way to assess the status of the axillary lymph nodes, allowing the practice of selective axillary surgery [20]	Decreased sentinel lymph node accuracy by inadequate response (primary tumour and metastatic lymph nodes responding to chemotherapy produce reactive fibrosis-like changes that influence lymph drainage pattern [21])
May show an increased rate of false-negative results after neoadjuvant chemotherapy according to The SENTINEL NeoAdjuvant Study [2]	It can be performed in patients with proven axillary lymph node metastases before starting neoadjuvant therapy [22] In cases of extensive breast cancer [23]

Table 2: Conditions for sentinel lymph node biopsy before and after neoadjuvant therapy.

Techniques used in sentinel lymph node biopsy

Sentinel lymph node biopsy is performed by injecting 1 or 2 tracers (recommended technique) at the breast parenchyma or subareolar plexus. These tracers enter the lymphatic system and are transported to the sentinel lymph node that takes the lymph from the tumour [24].

The sentinel lymph ganglion can be identified using several techniques and different substances, such as: vital dyes, radioactive tracers or the combination of the 2 methods.

When sentinel node is identified with vital dyes, the most commonly used are Isosulfan Blue, Fluorescein and Patent Bleu V [25], which is injected at the periphery of the tumour or in the subareolar plexus. Chagpar has shown that injection at the subareolar and periareolar regions leads to better sentinel lymph node identification than by peritumoral injection [26]. It is important not to inject directly into the tumour, the procedure involves injecting the substance and massaging the area in order to promote faster drainage [27]. Isosulfan blue is associated with anaphylactic-type side effects [24] and can be replaced by methylene blue, which also produces certain (milder) adverse reaction, such as induration and local pain-associated erythema [28].

Discussion

The radioactive tracer consists of a radioactive isotope that is attached to a colloidal substance and is injected preoperatively at the periphery of the tumour, intradermally or in the subareolar plexus [29]. ⁹⁹mTc is the most used radioactive isotope in the sentinel lymph node biopsy technique, being efficient and safe. In the USA, sulphur colloid marked with ⁹⁹mTc is used, and in Europe nanocolloid human serum albumin marked with ⁹⁹mTc is used, the latter having a rapid resorption and migration from the injection site into the lymphatic network and a high degree of retention in the sentinel lymph node [29]. In recent years, new radiocolloids, which are much more efficient than the current ones, have occurred:

- ⁹⁹mTc tilmanocept has a high degree of localisation, rapid migration into the lymphatic network and no contraindications or significant adverse reactions [30,31].
- ⁹⁹mTc rituximab provides very clear images with high accuracy, sensitivity and specificity [25].

The current gold standard for sentinel lymph node biopsy is the concomitant use of vital dyes and radioactive tracer to identify it, ensuring a higher identification rate and a much lower rate of false-negative results (according to the American Society of Clinical Oncology) [32].

Lymphoscintigraphy is performed using the gamma camera to identify the area with increased radioactivity "hot spots" [33] (Table 3).

	Advantages	Disadvantages
Indocyanine Green (ICG)	<ul style="list-style-type: none"> • Injected directly into the breast (subareolar) [33] • Real time visualisation • Can detect a large number of lymph nodes • Safe method • Does not require nuclear medicine department [25] • Without severe side effects • Reduced false-negative results [34] • At a concentration <5 mg / ml, increases sensitivity [25] 	<ul style="list-style-type: none"> • It cannot be used in patients with iodine allergy • It cannot detect lymph nodes located > 1 cm deep

SentiMag system with SPIO (Super Paramagnetic Iron Oxide nanoparticles)	<ul style="list-style-type: none"> • Avoid the use of radioisotopes • It is a much more efficient alternative to the radioactive tracer [25] • It is injected directly into the breast, providing an ultra-sensitive detection of the magnetic tracer • Non-invasive • Does not require a nuclear medicine department, so surgeons have control of the procedure in sentinel lymph node biopsy • No major allergic reactions [25] • In case of involvement of invaded node, SPIO are deposited only in the unaffected areas of the lymph node [35] 	<ul style="list-style-type: none"> • Possible interference of the surgical instrument with the ferromagnetic signal • Does not detect deep lymph nodes [36] • May not be used in patients with hypersensitivity to iron, dextran or peacemaker compounds and in those undergoing sentinel node biopsy prior to chemotherapy [37]
Contrast Enhanced Ultrasound (CEUS) with microbubbles	<ul style="list-style-type: none"> • "Real time" visualisation • Does not require a nuclear medicine department • Requires only an ultrasound and a contrast agent • No side effects • Non-invasive • The microbubbles are based on the method of dispersion with sulphur hexafluoride gas • Injected periareolarly • The lymphatic network of the breast is visualised by ultrasonography and then identified and biopsied the sentinel lymph node [39] 	<ul style="list-style-type: none"> • It is not a very fast method • Dependent on an operator • Some studies have shown that the combined technique (vital dyes and radiotracer) is more effective than ceus on sentinel lymph node identification rate [38]

Table 3: New techniques used in sentinel node biopsy.

Conclusion

The status of the axillary lymph nodes is one of the most important prognostic factors in breast cancer patients. In early stages of breast cancer (T1, T2) and clinically negative axilla, the current standard is the identification and biopsy of the sentinel lymph node, which, in case of a negative result, avoids the total axillary lymphadenectomy that is performed if the status of the sentinel

lymph node is positive (considering that it reflects the condition of the other axillary nodes), or if the stage of the disease is more advanced (T3, dimensions exceeding 5 cm).

In the case of Ductal Carcinoma In Situ (DCIS), sentinel lymph node biopsy is performed only if mastectomy is recommended. Special circumstances such as pregnancy, neoadjuvant chemotherapy, a history of surgery on the breast or axilla are not a contraindication for the identification and biopsy of the sentinel lymph node, while inflammatory breast cancer is an absolute contraindication.

In case of a recurrence of the breast neoplasm or a procedure performed at the axillary level in the background, it is recommended to perform lymphoscintigraphy with nanocolloid human serum albumin marked with Tc99 or sulphur colloid, which has proven very effective for the sentinel lymph node technique.

The identification of the sentinel lymph node can be done using vital dyes (isosulfan blue, fluorescein, patent blue V), radioactive tracers (radioactive isotope fixed on a colloidal substance) or the combination of the 2 methods. The new techniques used (green indocyanine, superparamagnetic iron oxide nanoparticles and contrast ultrasound using microbubble as a contrast agent) have proven to be safe and feasible, with high specificity and sensitivity, so that surgeons can perform the interventions, independent of nuclear medicine departments.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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