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Sentinel node biopsy for personalized breast cancer management; advances and controversies

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ABSTRACT

Sentinel lymph node biopsy (SLNB) has become the gold standard for axillary lymph node staging, providing valuable prognostic information while minimizing complications compared to axillary lymph node dissection. However, there are ongoing debates and controversies surrounding SLNB in specific cases. Studies have explored the use of SLNB in neoadjuvant chemotherapy, emphasizing the need for customized therapy decisions. Factors such as age, tumor characteristics, and treatment response influence the selection of SLNB or axillary lymph node dissection. Additionally, the presence of extranodal extension, micrometastases, and isolated tumor cells has been evaluated to determine the need for lymphadenectomy. The importance of accurate oncological staging by thorough pathological evaluation has been highlighted, particularly with regards to invasion depth and lympho-vascular invasion. The significance of biological tumor status, such as hormone receptor and HER2 status, in axillary management decisions has been emphasized. Moreover, discussions have emerged regarding SLNB in the context of local recurrence, with differing perspectives on its utility. Future extensive studies are needed to refine protocols and incorporate these concepts related to SLNB into breast cancer management guidelines.

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Introduction

The surgical management of the axilla has always been a topic of controversy. Previously, it was believed that achieving effective control in the surrounding area required a complete removal of axillary lymph nodes, which was considered the gold standard at that time. However, in recent years, due to increased complications and reduced quality of life for patients undergoing this procedure, it has been abandoned in favor of sentinel lymph node biopsy [1,2]. This technique involves identifying the sentinel node, which is the first lymph node that receives drainage from the tumor site based on the theory of cancer spreading through the lymphatic system. With advancements in modern medicine, such as mammography screening, less toxic systemic treatments, improved radiotherapy techniques, and the introduction of conservative surgery and sentinel lymph node biopsy, the overall outcomes for breast cancer treatment have improved [3,4].

Complications arising from axillary lymph node dissection affect around 40% of patients and include paresthesia (22%), seroma (15.6%), lymphedema (9.4%), persistent inflammation or local infection (9%), chronic pain, and limited limb mobility disorders (less than 5%) [2-4]. To avoid unnecessary removal of axillary nodes and to accurately stage patients with clinically negative lymph nodes (cN0) using minimally invasive methods, identifying the sentinel node is crucial.

A comprehensive search was conducted across the databases PubMed, Scopus, and Web of Science. The search query was designed to incorporate relevant keywords related to our topic. Specifically, the query included terms such as "axillary approach in breast cancer" or "SLNB in breast cancer" along with "sentinel lymph node identification" or "indication for SLNB." The selected keywords were chosen based on their relevance to our research area and their potential to yield the most relevant and applicable articles for our review.

In our study we only included free full-text articles published mostly in the past 10 years to ensure the quality and relevance of our research. Following the completion of the search and a meticulous evaluation based on article

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relevance, research quality, and data reliability, a total of 38 articles were deemed suitable for inclusion. These selected articles offer a comprehensive and up-to-date understanding of axillary management in breast cancer, thus contributing significantly to the final analysis.

Discussions

The techniques of identifying the sentinel lymph node

There are numerous techniques for identifying SLN, the most common being the use of a radioactive tracer, Technetium-99m (99mTc), but also colorimetric techniques that use vital dyes (isosulfan blue, patent blue, methylene blue).

Radioactive tracer method: Technetium-99m (99mTc) is the isotope used, which together with the colloidal human albumin used due to its ability to be quickly taken up by the lymphatic system, are transported to the potentially invaded ganglion. 99mTc has a long half-life and therefore must be administered 6-24 hours preoperatively. For a better orientation of the surgeon, 3-5 hours preoperatively, a gamma-camera lymphoscintigraphy can be performed [2].

Identification technique using vital dyes: after injecting the substance, it is taken up by the lymphatic system; an incision at the base of the axilla, followed by exploration of the region will lead to the identification of the ganglion, colored blue. The advantages of the method are the low cost and the simplicity of the identification technique. As disadvantages we can list the possible allergic reactions to the injected substance, but with low incidence rates (< 2%) and the short time from injection to complete drainage of the dye, which is about 30 minutes [2,3].

These techniques can be complementary, thus increasing the accuracy of the method. Numerous studies have demonstrated a 100% identification rate, with false negative results below 5% [4,5].

Another method used for identifying the sentinel lymph node (SLN) is the use of fluorescent substances. Indocyanine green (ICG), compared to the radioisotope technique, has shown similar results in SLN identification, but at a lower cost and greater practicality in services where specialized nuclear medicine laboratories are not available [5]. When compared to the results obtained through the complementary technique of radiotracer + colorimetry or simple colorimetry, indocyanine green has demonstrated its superiority [6].

A new method for SLN identification has recently been introduced into practice, showing promising results. This method utilizes superparamagnetic iron oxide nanoparticles (SPIO), which facilitate easier SLN biopsy. The technique has become a standard in some centers reporting encouraging results comparable to those obtained using 99mTc [7]. The technique is based on the principles of magnetic resonance. The compound accumulates at the SLN level and is detected by a handheld magnetometer. The disadvantages of this technique include radiation exposure, the need for a specialized nuclear medicine laboratory, and a steep learning curve for the technique [4].

Contrast-enhanced ultrasound (CEUS) is a newly introduced method for real-time identification of the sentinel lymph node (SLN). Similar to previous methods, CEUS involves percutaneous injection of a contrast agent. This technique categorizes lymph nodes into three types:

- Type I: Uniform accumulation of the contrast agent
- Type II: Incomplete diffusion of the contrast agent
- Type III: Absence of the contrast agent in the examinated lymph nodes

Type I indicates the absence of metastases in the SLN, while Type II and III indicate the presence of secondary lymph node involvement. Although the technique has an identification accuracy of approximately 96%, current studies have shown the superiority of colorimetric methods (such as indocyanine green + methylene blue) compared to CEUS [8]. The cumulative sensitivity of CEUS guidance has been demonstrated to be around 55% with a specificity of 100% in certain studies. Therefore, it remains a useful tool for preoperative, real-time selection of patients who require extensive axillary dissection, but further extensive studies are needed to demonstrate the validity of this method [9].

Furthermore, there are controversies regarding the site of contrast agent injection for SLN identification. Different regions, such as subareolar, intratumoral, or peritumoral have been described in the literature. However, the studies do not provide conclusive results regarding the causative relationship between the injection site of the localization marker and potential false-negative outcomes [10].

Indications for sentinel node biopsy

Sentinel lymph node biopsy (SLNB) is considered the standard method for staging axillary lymph nodes in early breast cancer patients with newly diagnosed, clinically negative axillary nodes (cN0). The outcome of SLNB itself serves as a crucial prognostic factor, guiding personalized surgical and oncological management.

Extensive randomized clinical trials have supported SLNB in patients with cT1-T2cN0 status. The NSABP B-32 (National Surgical Adjuvant Breast and Bowel Project) study reported comparable 8-year survival rates between SLNB followed by axillary lymph node dissection and SLNB alone, with rates of 90.3% and 91.8%, respectively [11]. However, SLNB demonstrated minimal or no adverse effects. Similar findings were observed in the ALMANAC (Axillary Lymphatic Mapping Against Nodal Axillary Clearance) study, which reported a severe post-SLNB edema frequency of approximately 1% [12].

Recent literature data indicate that SLNB is also recommended for early breast cancer cases with isolated

tumor cells or micrometastases in 1-2 sentinel lymph nodes following limited mastectomy and radiotherapy. The ACOSOG Z0011 (American College of Surgeons Oncology Group) and IBCSG 23-01 (International Breast Cancer Study Group) studies found no statistically significant differences in survival or mortality when comparing SLN biopsy with lymph node dissection versus SLNB alone [13,14].

Controversies surround SLNB in specific situations. It may be performed even in cases of resectable multifocal breast tumors, as the risk of axillary recurrence appears to be similar to that of single tumors, despite a higher likelihood of false negative results [15].

In patients diagnosed with ductal carcinoma in situ (DCIS) through breast puncture-biopsy, axillary metastases only occur in the presence of an invasive component. Metastases in the sentinel lymph nodes were identified in only 2.7% of DCIS patients who underwent total mastectomy [16]. Therefore, the indication for SLNB in DCIS is limited to cases proposed for total mastectomy or those with a high suspicion of an invasive component [17].

Another contentious topic is the indication of SLNB after neoadjuvant chemotherapy. Although it can be performed, SLNB has a lower identification rate of 77.6% compared to 97% in patients without preoperative neoadjuvant therapy [18].

Post-SLNB approach

The negative outcome of sentinel lymph node biopsy (SLNB) warrants a conservative approach in the management of patients with breast carcinoma. The therapeutic control achieved through this minimally invasive approach is comparable to extensive axillary lymph node dissection but without the associated complications of lymphadenectomy, thereby improving patients' quality of life.

The 10-year follow-up results of patients from the ACOSOG Z0011 study confirm that conservative treatment and adjuvant therapy following SLNB with 1-2 micrometastatic positive nodes are preferable, without axillary lymph node dissection [13]. Similar findings were observed in the IBCSG 23-01 study, where the 10-year survival rate was approximately 75% in the group undergoing axillary dissection compared to approximately 77% in the SLNB group with positive results and smaller metastases (2 mm) without extracapsular extension [14].

A large prospective study conducted between 2015 and 2020, involving 889 patients with T1-T2 breast carcinoma and 1-2 macrometastases in the sentinel lymph node, aimed to evaluate whether SLNB is associated with a poorer prognosis compared to axillary lymph node dissection. The study analyzed overall survival and recurrence rates and concluded that SLNB with appropriate biopsy and adjuvant treatment does not yield inferior results to axillary lymph node dissection [19]. Furthermore, the ongoing international randomized prospective clinical trial POSNOC-Positive Sentinel Node aims to demonstrate that adjuvant therapy following a positive SLNB result with 1-2 macrometastases is non-inferior to the protocol of adjuvant therapy combined with axillary approach in terms of axillary recurrence at 5 years [20]. These results have the potential to shift the established paradigm in managing this patient population.

A meta-analysis published in 2021, involving 8,864 patients, further supports the aforementioned conclusions, indicating that lymph node dissection can be avoided in patients with early breast cancer and metastases in 1-2 sentinel lymph nodes [21].

Axillary lymph node dissection remains the target of radical treatment in several situations:

1. cN2 – N3 + positive biopsy result
2. cN0 + > 2 SLN positive on biopsy
3. cN0 in the patient proposed for total mastectomy + > 3 SLN positive on biopsy
4. cN1 – N2 + positive biopsy resulted in patients who do not receive neoadjuvant therapy
5. cN1 – N2 after neoadjuvant treatment
6. cN0 + SLN positive on biopsy after neoadjuvant treatment
7. carcinomatous mastitis
8. local recurrence + cN1 – N2 + positive biopsy result
9. axillary metastases with unknown breast starting point

Minimal nodal invasion

Thorough pathological evaluation using serial sections and immunohistochemistry techniques of the sentinel lymph node (SLN) enables the identification of invasion at the smallest level. Isolated tumor cells, classified as pN0(i+), are characterized by clusters of tumor cells measuring ≤ 0.2 mm. Micrometastases, classified as pN1mi, are deposits with dimensions larger than 0.2 mm but ≤ 2 mm, while macrometastases refer to deposits over 2 mm [22].

Dosani et al. address the management controversy surrounding minimal invasion, specifically isolated tumor cells or micrometastases. The study concludes that patients with pN0(i+) breast carcinoma have a prognosis similar to those with stage pN0, and patients with stage pN1mi have an intermediate prognosis between pN0 and stage pN1a. The authors suggest that SLNB and monitoring are sufficient as a therapeutic option without the need for axillary lymph node dissection. However, further extensive studies are necessary to determine the necessity of radiotherapy in cases of pN0(i+) and pN1mi, with each case requiring a multidisciplinary approach tailored to the patient's specific characteristics [23].

A unique situation arises when isolated tumor cells are associated with primary lobulated tumors, as their

evolutionary pattern is inconsistent. In such cases, axillary lymph node dissection is indicated [24].

Takada et al. demonstrated an association between the number of intratumoral lymphocytes (tumor-infiltrating lymphocytes - TILs) and the extent of lymph node invasion, showing an inverse correlation. Furthermore, the study concluded that the presence of macrometastases identified by SLNB in patients with cN0 does not warrant axillary lymph node dissection. This procedure can be avoided after neoadjuvant chemotherapy in cases where a sufficient presence of TILs is demonstrated at the site of the primary tumor formation [25].

Management of extranodal extension

Overcoming the barrier of the lymph node capsule by tumor cells and their migration into adjacent tissue is an independent prognostic factor. Previously, it was believed that extranodal extension in patients with stage T1-2 and 1-2 positive nodes on SLNB required extensive axillary lymph node dissection. However, recent studies have shown that extracapsular invasion $\leq$ 2 mm does not necessitate axillary lymphadenectomy, as overall survival and recurrence rates are comparable to those of patients without extranodal extension [26].

Including the evaluation of extranodal extension in the staging protocol is crucial for accurate oncological staging. Attempts have been made to establish cut-off values based on the circumferential and perpendicular diameter of the invasion extension, but significant predictive values have not been obtained. Therefore, further extensive studies are necessary to determine specific dimensions of invasion that can predict the metastatic load in axillary nodes, thus guiding appropriate therapeutic approaches [27,28].

Another independent prognostic factor recently analyzed in the literature for patients with breast carcinoma is the degree of lympho-vascular invasion, which impacts disease-free survival (DFS) [29]. Lympho-vascular invasion is also associated with a higher incidence of secondary axillary nodal involvement [30]. However, larger studies are needed to precisely determine the degree of invasion and establish a cut-off value that indicates the need for SLNB or axillary lymphadenectomy as an intervention.

Controversies

1. Age

In cases where axillary nodes (cN+) are present at the initial presentation, the appropriate surgical intervention or neoadjuvant chemotherapy is determined based on individual considerations. A recent study revealed that aggressive primary lymphadenectomy, involving the removal of more than 12 lymph nodes, does not confer a survival benefit for patients aged 70 and above. Similarly, in the cohort receiving neoadjuvant treatment, no correlation was found between the number of excised nodes and overall survival [31,32]. The Society of Oncological Surgery strongly advocates against routine use of sentinel lymph node biopsy (SLNB) in patients aged 70 and above with early breast carcinoma, HR+, HER2-, and cN0. Future prospective studies are required to incorporate these concepts into the management protocols for breast carcinoma [33,34].

2. SLNB after chemotherapy

The decision regarding sentinel lymph node biopsy (SLNB) following neoadjuvant chemotherapy should be individualized based on the specific case. Current recommendations support post-chemotherapy SLNB in patients initially diagnosed as cN0. For patients who remain positive after neoadjuvant therapy upon initial axillary evaluation, axillary lymph node dissection is recommended. However, for patients who respond to treatment and become N0, SLNB is preferable prior to deciding on axillary lymphadenectomy. Nevertheless, post-chemotherapy SLNB has high rates of false-negative results, even when complementary identification techniques (such as dual tracer) are employed [35,36].

3. Tumor subtype

Neoadjuvant chemotherapy can have a de-escalating effect on the axillary stage, even in cases of aggressive, chemo-resistant (HR+HER2-) carcinomas. ER+HER2- tumors exhibit some of the highest rates of false-negative results in SLNB after neoadjuvant treatment. In these situations, axillary lymphadenectomy is recommended. Carcinomas with HER2+ status appear to have the best response to chemotherapy, further emphasizing the importance of incorporating the tumor's biological status into the axillary management decision [37,38].

4. Endocrine neoadjuvant therapy

It is well known that the beneficial effects of endocrine therapy in HR+ breast cancer increase the possibility of breast-conserving surgery [39,40]. However, there is limited data regarding its impact on axillary lymph nodes. Montagna et al. conducted a comparative analysis of the effects of endocrine therapy versus neoadjuvant chemotherapy on the complete response at the nodal level. A complete response was achieved in 11% of cases with endocrine therapy, which was similar to the response obtained with post-chemotherapy. Therefore, neoadjuvant endocrine therapy may be considered for patients with uncertain indications for neoadjuvant chemotherapy [41].

5. Recurrence

Patients with local, ipsilateral recurrence of breast carcinoma present a unique scenario that raises questions about the utility of sentinel lymph node biopsy (SLNB). Current studies are engaged in a debate regarding the role of SLNB in this specific patient population. One perspective, as advocated by Sávolt et al., suggests that SLNB should replace the traditional approach of performing axillary lymph node dissection for restaging in

cases of local recurrence [42]. Conversely, Ugras et al. propose a hypothesis that challenges the necessity of SLNB, deeming the technique unnecessary [43]. With the ongoing shift towards minimally invasive surgical interventions, it is imperative that extensive future studies are conducted to establish a therapeutic management strategy that minimizes side effects and potential complications associated with axillary lymph node assessment in cases of local recurrence.

Conclusions

The surgical management of the axilla has witnessed significant changes over the years. The traditional approach of extensive axillary lymph node dissection has been replaced by the less invasive and more efficient technique of sentinel lymph node biopsy (SLNB). SLNB, which involves identifying the sentinel node that receives drainage from the tumor site, has become the gold standard for staging axillary lymph nodes in early breast cancer patients with clinically negative nodes. Advancements in modern medicine, including less toxic systemic treatments, improved radiotherapy techniques, and the introduction of conservative surgery and SLNB, have contributed to improved overall outcomes in breast cancer treatment.

Various techniques for identifying the sentinel lymph node, such as radioactive tracers and vital dyes, have demonstrated high identification rates and low false-negative results. Additionally, the use of fluorescent substances and superparamagnetic iron oxide nanoparticles has shown promising results, offering practical alternatives to the radioisotope method. However, controversies persist regarding the best method for SLN identification and the site of contrast agent injection.

In the context of minimal nodal invasion, thorough pathological evaluation has revealed the significance of isolated tumor cells and micrometastases, indicating that SLNB with appropriate monitoring may be sufficient as a therapeutic option without axillary lymph node dissection. Extranodal extension and lympho-vascular invasion have emerged as independent prognostic factors, impacting disease-free survival and axillary management decisions. Further research is needed to establish specific dimensions of invasion that guide appropriate therapeutic approaches.

Age, tumor subtype, neoadjuvant therapy, and local recurrence present specific challenges and controversies in the context of SLNB. Individualized decision-making is crucial in determining the most suitable approach for each patient, considering factors such as age, tumor characteristics, treatment response, and biological tumor status.

In conclusion, SLNB has revolutionized the surgical management of the axilla in breast cancer patients, providing an effective and less invasive alternative to extensive axillary lymph node dissection. Ongoing research and prospective studies will continue to refine protocols and incorporate these concepts into breast cancer management guidelines, leading to improved patient outcomes and quality of life.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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