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Sentinel lymph node biopsy: role in advance breast cancer

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Abstract

Prognosis in patients with breast cancer depends mainly on the extent of lymph node involvement, size of the tumor, and the histological grade of the tumor. Among these factors, axillary lymph node status is regarded as the single best marker of prognosis. Sentinel lymph node biopsy has become a standard staging tool in the surgical management of breast cancer. The positive impact of sentinel lymph node biopsy on postoperative negative outcomes in breast cancer patients, without compromising the oncological outcomes, is its major advantage. It has evolved over the last few decades and has proven its utility beyond early breast cancer. Its applicability and efficacy in patients with clinically positive axilla who have had a complete clinical response after neoadjuvant chemotherapy is being aggressively evaluated at present. However, the accuracy of sentinel lymph node biopsy after neoadjuvant chemotherapy in patients with metastatic breast cancer is unclear. This review study discusses role of sentinel lymph node biopsy in role in advance breast cancer a useful tool in new clinical scenarios of metastatic breast cancer management.

Keywords: Sentinel lymph node biopsy; Metastatic breast cancer; Neoadjuvant chemotherapy

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Introduction

Over the past few years, most studies of sentinel lymph-node biopsy (SLNB) have been to validate the accuracy of the technique to predict whether axillary lymph nodes (ALN) will be positive or negative at ALN dissection (ALND) [1]. Although some of these studies have addressed the short-term morbidity of SLNB compared with standard ALND, formal, randomized controlled trials are needed to establish the long-term effect of not resecting further lymph nodes when the SLN is negative [2-5]. The effects of this procedure on locoregional control and overall survival need to be ascertained before this method can be accepted as standard of care, and the health economics need to be assessed before SLNB can be introduced into routine clinical practice. One of published study involved 516 patients with breast tumors of 2 cm or less in diameter who were randomly assigned to either SLNB followed by completion ALND (ALND group) or SLNB and completion ALND only if the SLN contained metastatic disease (SLN group), this study only included patients who had successful mapping (>95% of patients), and although the number of patients was modest compared with some multicenter studies, the methodologies and practice were consistent and done by a small group

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of experienced surgeons resulting in excellent quality control, which is a criticism of many multicenter studies [6]. This study analysis showed that 9% (95% CI 4–17) of patients had false-negative disease, and the negative predictive value was 95% (95% CI 91–98), with a mean number of SLNs per person of 1·66 in the ALND group and 1·63 in the SLNB group. No axillary recurrences were reported at a mean follow up of only 46 months and short-term survival was not compromised in the SLN group [7].

Other study showed that the presence of peritumoral vascular invasion in three of the five patients who died of their disease is consistent with early hematogenous dissemination and with the Fisherian paradigm of nodal metastases being indicators and not determinants of risk of distant relapse, this finding does not relate directly to any differences in overall survival and, because of the low number of patients with axillary recurrences, the study is unlikely to have the power to make definitive conclusions about any effect of SLNB on overall survival; it is possible that no randomized controlled trial will ever show any statistical difference in this endpoint [8]. While other studies have confirmed that few patients (about 2% at 3 years' follow-up) will have axillary recurrence [9].

Moreover, omission of axillary surgery in patients with tumor stage (T) 1–2 tumors was associated with unexpectedly low rates of axillary relapse at 5 years (7%) [10]. Other study surmise that two types of cancer cells might exist stem cells and non-stem cells, supporting ideas that metastatic cells within lymph nodes might not always have the capacity to establish viable metastatic foci at distant sites [11]. Presumably, such foci do not contain cancer stem cells and, thus, (as in the case of axillary lymph nodes) cannot progress and become a source for distant dissemination [12].

The unusually high number of patients with positive SLNs was quite high in both groups of this trial (36% in the SLNB group and 32% in the ALND group), especially given the small size of the tumors (most studies cite rates of 25–30%), possibly as a result of the intense pathological scrutiny of the SLNB, which tends to upstage disease status [13]. One of the main drawbacks of SLNB is the need for almost a quarter of patients to return for further axillary surgery [14].

As the authors of other resulted data point out, this incurs psychological morbidity and attempts are being made to do accurate intraoperative assessment of the SLN [15]. The pathological methods they used would be too labor intense (more than 60 sections per node) for most managed healthcare systems in the developed world [16], this is an important issue that is frequently referred to by some institutions in the context of SLNB [17]. Intraoperative assessment can be reliably undertaken with touch imprint cytology and immunohistochemistry without sacrificing nodal tissue [18].

Tumor-infiltrating mononuclear cells and immunohistochemistry might off er a method of reliably assessing the SLN intraoperatively, but this is by no means certain and some groups have cited accuracy of only 40%. Even if nodal status can be accurately assessed intraoperatively, the downside is that patients wake up to find out (in node positive cases) that they have had an ALND from the presence of a drain [19]. This can be psychologically

damaging if no proper counselling is immediately available [20]. Other study report, a third of patients with tumor-infiltrated SLNs had micrometastases only and only a few of these patients had a subsequent breast-cancer event (ie, death or locoregional or distant recurrence) [21]. Some of these patients will not have clinically relevant disease and do not need further axillary surgery either for local control or determination of systemic treatments, which would have little measurable effect on clinical outcomes [11]. Whether a 17% incidence of non-SLN metastases is acceptable remains a matter of judgment. Other authors propose a trial of similar design to the ACOSOG Z0011 trial to address the question of completion ALND for micrometastatic disease [19].

However, this trial has stopped recruiting as a result of poor accrual, and it is unlikely we will ever obtain a statistically robust answer from a randomized trial [22]. The report reinforces previous validation studies and strengthens the role of SLNB as a staging procedure in patients with early-stage breast cancer, convincing evidence is presented that SLNB reduces overall hospital costs; indeed, the few data on health economic assessment suggests that, at best, the technique is cost neutral as a result of the additional expenses incurred by the technique, eg, gamma probe; radioisotope; serial sections and immunohistochemistry coupled with early discharge after ALND with drains in situ [23]. That no detrimental effects from omission of completion ALND in patients with negative SLNs have emerged in terms of locoregional control and survival at a mean follow up of over 6 years is reassuring [24].

Patients underwent SLNB using different methodologies (patent blue dye and nuclear medicine) [25]. In the intraoperative period, all of the patients underwent intraoperative frozen sectioning, and in the presence of lymph node metastasis these patients underwent ALND [26]. Upon examination of the SLNB paraffin-embedded sections, only patients with macrometastasis underwent ALND as in Figure 1.

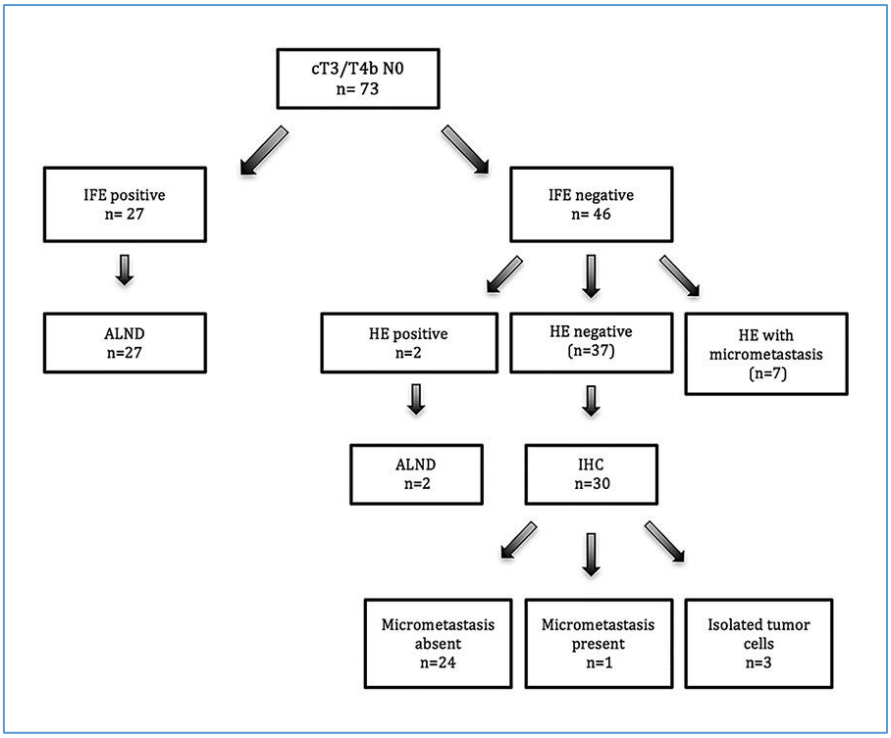

Figure 1.

Diagnostic flowchart for axillary evaluation. IFE, intraoperative freezing evaluation.

New technique in SLNB

In recent years new techniques for SLNB have been successfully developed. They use innovative tracers such as indocyanine green (ICG), superparamagnetic iron oxide (SPIO), and microbubbles [27]. Whilst each technique has its own advantages/disadvantages, they have shown promising but variable results between studies, small patient numbers and short patient follow-up [28]. So, they have to be considered still investigational until there is final evidence that they are accurate in SLNB with a low FN rate [29].

Discussion

De-escalation of surgery in breast cancer has been associated with a significant reduction of morbidity. Measurement of this impact should consider the disease's epidemiological profile, which corresponds to the most frequent cancer in women, representing approximately 25% of cancers in women, with an increasing incidence and prevalence [30]. Thus, small changes in practices, even in restricted subgroups, determine actions in larger numbers of patients, making it important to individualize treatment scenarios [31].

Regarding tumor size, axillary lymph node involvement is more likely in tumors larger than 5 cm and with skin involvement, although the benefit of not performing ALND is unavailable to this population [32]. However, the initial contraindications for SLNB have become debatable and relative over time, mainly because of the current association of the method with

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neoadjuvant chemotherapy and because prognostic/molecular staging has become as important as tumor TNM staging (tumor-node-metastasis) for defining treatment [33].

Regarding tumor size for determining axillary treatment, the staging may be clinical, radiological, or pathological, which may influence selecting patients for SLNB [34]. Disagreement is often observed between clinical and pathological examinations as well as for imaging tests [35]. Such variations in clinical/radiological sensitivity for determining tumor size may interfere with the indication for SLNB, which can have clinical repercussions since initial clinical decisions are based on the clinical-radiological evaluation but can be modified via the anatomopathological evaluation [36].

Thus, in the published study, patients initially considered to have T3 tumors were shown to have T2 tumors [37], thus if the initial option had been ALND, most (6 out of 9 patients) would have undergone an unnecessary procedure [38]. One study evaluated surgeons' behaviors regarding axillary preservation in different settings and found that surgeons who had treated more breast cancer patients and participated in multidisciplinary teams had a greater tendency for axillary preservation [39].

Further, many patients were overtreated with ALND, especially due to a lack of updating or training the surgeons [40]. The service is located in an oncologic hospital that treats approximately 2% of the women with breast cancer in Brazil [41]. For pathologically confirmed tumors larger than 5 cm, the negative SN rate was 55.3% [42]; however, the systematic review yielded a rate of 28.7%, with a range of 13.3–65.0%, although no articles described the patient selection process [43], the presence of an axillary ultrasound evaluation, or the tumor size considered, whether clinical, radiological, or pathological [44].

In the other study, multiple criteria were used to select patients, such as axillary ultrasounds, FNAB, and intraoperative frozen sections, which was the reason for the high absence rate of axillary metastatic disease (46.8%). Ultrasonography elevates the axillary evaluation accuracy [45]. Likewise, ALND currently has no benefit in the presence of micrometastasis [46], and, as such, ALND can be avoided in 55.3% of patients, which we consider a very high number [47].

Larger tumor sizes yield higher rates of axillary involvement, and discussions are ongoing regarding the acceptable and tolerable size for considering SLNB [48].

A previous study of patients with clinically negative axilla who had undergone ALND considered up to 8 cm to be an acceptable size limit, with a negativity rate of 25% [49]. In evaluating this case series, the negativity rate decreased as the tumor size increased, being 26 out of 38 (68.4%) in tumors of 5.1–6.0 cm, 8 out of 12 (66.7%) in tumors of 6.1–7.0 cm, 4 out of 8 (50.0%) in tumors of 7.1–8.0 cm, and 1 out of 6 (16.7%) and 1 out of 4 (25.0%) in tumors larger than 8 cm [50].

The literature on tumor size is scarce; thus, measuring tumor size is suggested in later studies, but in this study the use of SLNB in tumors up to 8.0 cm seems acceptable, since the only case without metastatic disease in tumors >8.0 cm was from the cT2pT3 group [51].

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Patients with T4b tumors are candidates for neoadjuvant chemotherapy, but some patients with localized skin invasion, limited clinical conditions, or no conditions suitable for neoadjuvant chemotherapy are candidates for primary surgery [52]. In these cases, SLNB was considered in the absence of axillary disease. Thus, combining the studies, and even with a restricted number of patients (*n* = 41) [53], the study showed the importance of axillary preservation in this patient group, where the rate of absence of metastatic disease was 61.0% [54].

Key New Recommendation

A major change from the 2005 guideline is the additional recommendation that axillary lymph node dissection can be omitted for some sentinel lymph node–positive patients. The impetus for this recommendation was a careful evaluation of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, which randomly assigned clinically node-negative patients who had clinical T1 or T2 tumors and only one or two positive sentinel lymph nodes to either completion of axillary lymph node dissection or sentinel lymph node biopsy only. All patients underwent whole-breast irradiation with opposing tangential fields. Prone irradiation accelerated partial-breast irradiation, and third-field nodal irradiation were prohibited. Nearly all patients in both arms received adjuvant chemotherapy or endocrine therapy [55].

At a median follow-up of 6.3 years, 0.9% of the sentinel lymph node biopsy only group developed axillary recurrence compared to 0.5% of the group receiving sentinel lymph node biopsy followed by axillary lymph node dissection. There was no significant difference in overall survival or disease-free survival between the two groups [56]. This trial illustrated that completion of axillary lymph node dissection may be omitted in a select group of patients with sentinel lymph node metastases and led to this significant change in the 2014 ASCO guideline. In the opinion of the ASCO expert panel, axillary lymph node dissection can be avoided in patients with one or two nodes involved with metastatic cancer but only when conventionally fractionated whole-breast irradiation is planned, and adjuvant systemic therapy is given. This recommendation applies to patients with either sentinel lymph node micrometastases or macrometastases [57].

This single important change will affect most women with early breast cancer and nodal metastasis since most women with tumor-involved sentinel nodes have only one or two involved nodes. The recommendation does not apply to patients treated with accelerated partial-breast irradiation or irradiation in the prone position. Those whose axillary nodal disease is documented by fine-needle aspiration may still undergo sentinel lymph node biopsy if the abnormal lymph node is removed. The panel still advises completion of axillary lymph node dissection for women with early-stage breast cancer undergoing mastectomy [58].

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Limitations of sentinel lymph node biopsy

During pregnancy, treatment of breast cancer has to be carefully managed because recommendations for therapy need to take into account the gestational age at the time of diagnosis, the stage of the tumor, and patient preference; limited data are available regarding long-term outcomes on toxicity from adjuvant therapy. The various treatment options available need to be extensively discussed with patients and their families [59].

Breast conservation with radiation can only be offered to women in their third trimester of pregnancy, with radiation or adjuvant therapy administered after delivery. Thus far, SLN biopsy with blue dye is contraindicated during pregnancy because the effects of the dye and its ability to enter the fetal circulation are not fully understood [60].

The use of radiolabeled colloids has been considered safe in some studies that demonstrate the exposure of radiation to the fetus to be minimal. Although some centers do offer lymphoscintigraphy and SLN dissection for axillary staging based on the studies of the low prenatal exposure when the procedure is performed by an experienced radiologist, most surgeons routinely offer ALND during pregnancy [61].

Conclusion

Sentinel node biopsy is the current paradigm in the management of regional basin in breast cancer. With continuous improvement in cure rates over the last few decades, limiting surgery and maintaining QOL have become important concepts in the management of breast cancer. SLNB has proven to be an efficacious and cost-effective tool in breast cancer. Its application has expanded beyond early breast cancer, and it has been established in areas where it was previously considered inapplicable. For instance, SLNB is gradually incorporated in the management of patients with cN+ axilla who are rendered cN0 after NACT.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

This study has been approved by the Ethical Review Committee of the Mayo Clinic Rochester. The publication of any potentially identifiable images or data contained in the article requires personal written informed consent.

All subjects or their guardians will sign informed consent. Authors tend to submit research results to peer-reviewed journals or academic conferences for publication.

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Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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