

# The sentinel lymph node biopsy for breast cancer over the years

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## Summary

The sentinel lymph node biopsy (SLNB) has progressively substituted complete axillary lymph node dissection (CALND), and has dramatically changed breast surgery impact on women's psychophysical wellness, reducing surgical morbidity while granting an adequate nodal staging. The present authors have seen a gradual improvement in the technique in order to reduce both surgical time and the number of interventions required, in particular with the intraoperative histological examination of sentinel node. Anyway, there is still great debate about the predictability of axillary nodal status in case of negative SLNB, as well as in case of positive one. Therefore, the authors reviewed the SLNB history and discussed its controversial points.

*Key words:* Sentinel lymph node biopsy; Complete axillary lymph node dissection; Breast cancer.

## Introduction

As initially breast cancer was considered as a local disease, complete axillary lymph node dissection (CALND) in association with mastectomy aimed first to completely remove cancer and second to stage the disease. Breast cancer staging according to TNM, that considers axillary lymph node status, was introduced during the first half of the twentieth century [1]. Over the years, nodal staging has proven to be a fundamental prognostic factor for breast cancer patients, while systematic CALND has not proved to be equally important. From this perspective, axillary lymph node investigation became an exclusively staging method to better tailor patient's follow up and following treatment, and CALND lost its curative intent.

## Evolution of sentinel lymph node biopsy

About two decades ago, a new technique was introduced by Veronesi *et al.* in order to spare CALND to axillary node-negative patients, called sentinel lymph node biopsy (SLNB) [2], which consisted in the radio-guided identification of the first lymph node which drains the primary breast tumor, and consequently the probable first lymph node involved by neoplastic cells in case of tumor lymphatic dissemination. SLNB principal advantage is its proven accuracy in staging the axilla while preventing the high morbidity correlated to CALND [3], including ipsilateral arm edema or paresthesia, which in the past were very frequent and very disabling for many breast cancer survivors.

Since its first introduction in the authors' Department of Surgery in 2002, SLNB experienced two growth spurts, one during the first years of its application due to the in-

creasing confidence of surgeons with the new technique and its increasing indications, and the other after the introduction of a systematic, mammographic screening in their region in 2005 [4, 5]. In fact, the screening resulted in an overall increased incidence of breast cancers diagnosed, and especially of early stage ones, which are more likely to undergo SLNB. Unfortunately, the evident decrease of advanced breast cancers relative percentage not always corresponded to their overall number decrease, due to exclusion from the screening because of age or compliance, or to screening ineffectiveness as for women with cancer of unknown primary (CUP syndrome) who have their breast cancer diagnosed through the sole axillary node involvement [6].

With the progressive spread of SLNB, some controversies emerged about this technique, for example about its possible intraoperative failure. Despite the low prevalence of intraoperative sentinel node identification failure in the present population (2%), in a recent study it resulted independently predicted by the early lack of radiotracer uptake on the lymphoscintiscan, the late lack of uptake by intraoperative sentinel node research, and the low preoperative sentinel node uptake related to a higher breast lesion radiotracer uptake [7]. However, in the literature a great number of risk factors for SLNB failure have been described, including elderly, elevated BMI, breast size, regional lymph node metastasis, number of positive lymph nodes, tumor location other than the upper-outer quadrant, type of injected radiocolloid, site of injection, injection volume, radiocolloid dose, time between injection of radiocolloid and surgery, tumor size, prior breast surgery or biopsy, and low level of institutional experience [7]. As a consequence, the authors assisted to a pro-

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gressive evolution of SLNB technique to optimize sentinel node identification, both for what concerns the used tracers (radioisotope, blue dye, indocyanine green, or combinations) [8] and their injection site (peri-tumoral, intra-tumoral, or peri-areolar) [9].

Another topic many authors questioned about is the predictability of non-sentinel lymph node status by SLNB negativity or positivity for neoplastic infiltration. In the first case, an argument of great debate is represented by nodal recurrence after negative SLNB. Many different hypotheses have been purposed to explain this adverse event, including the “skip metastasis” theory [10], the wrong node excision because of limited surgeon experience [11], or a false negative histological examination resulting from the small size of micro-metastases, which may not be included in any microscopical section [12]. Concerning the predictability of axillary, non-sentinel, metastatic nodes in case of SLNB positivity, many nomograms have been designed in order to predict axillary status, and eventually spare CALND, with different grade of success [13].

Currently, the evident trend in quantitatively reducing the impact of breast surgical and non-surgical treatments on breast cancer patients resulted in the advent of quadrantectomy in order to spare the majority of breast gland [14, 15], in the numeric limitation of excised nodes with SLNB for the axilla [16], and in the introduction of intraoperative radiotherapy (IORT) in order to avoid the many sessions of postoperative external breast radiotherapy (EBRT) [17]. Along with the reduction of surgery extension, breast surgeons aimed also to decrease the overall number of surgical interventions themselves and this is why the intraoperative sentinel node histological examination has been introduced, in order to allow surgeons to perform CALND in the same operative time, when appropriate [16, 18–21]. In particular, the immediate intraoperative SLNB evaluation resulted superior than its delayed scheduled evaluation after surgery, as in about 14–38% allowed the prevention of a second operation in patients candidated to CALND for sentinel node positivity, with some evident consequent advantages, such as an economic saving, its favourable impact on patient’s psycho-physical wellness, and the prevention of possible surgical difficulties, while reoperating recently surgical injured axillary tissues [16, 20, 22].

As expected, with the passing of time, the present authors assisted in a technical evolution also in the intraoperative examination procedure for SLNB. In fact, from the traditional morphological evaluation by hematoxylin-eosin staining, a new biomolecular quantitative system has been developed, the so called one-step nucleic acid amplification (OSNA) method, which consists in a short homogenization step followed by amplification of cytokeratin (CK) 19 mRNA directly from the lysate [19, 23]. This interesting technique significantly accelerated sentinel node

analysis, with a consequent reduction of operative time and anaesthesiaologic risk, a cost-benefit gain, and a high accuracy in the result [21, 24, 25].

The classification of nodal metastases also underwent dramatical changes during the last decades, and the presence of neoplastic cells into the sentinel node was then quantitatively divided into the following entities, based on the size of metastatic foci: macrometastases (> 2 mm), micrometastases (0.2 - 2 mm), and ITCs (< 0.2 mm) [26, 27]. In a recent study the present authors suggested that the quantitative sentinel node involvement directly correlates with the non-sentinel node axillary staging [16], and then they agree with most studies which conclude that patients with sentinel node macrometastasis have a worse prognosis than those with micrometastasis or node-negative patients.

Taking a look at the challenging future of axillary surgery, some authors have attempted to identify patients at low-risk of axillary recurrence and then eligible for omitting CALND after positive SLNB [28, 29]. The ACOSOG Z0011 and IBCSG 23-01 trials, which compared patients with positive sentinel node with or without consequent CALND, demonstrated no significant differences between the two groups in terms of both disease-free and overall survival [30, 31]. In addition, the NSABBP B-04 trial demonstrated that metachronous CALND by axillary recurrence after SLNB did not compromise overall survival in comparison with synchronous CALND by non-sentinel node involvement suspicion [32]. Other studies concluded that both whole-breast irradiation and systemic adjuvant treatment result comparable with CALND in case of small-volume lymph node metastasis [33, 34]. However, still many points need to be clarified before adopting as standard management to omit CALND in presence of positive sentinel nodes [35, 36]. For example some criticisms were raised regarding the safety of omitting CALND in presence of positive sentinel nodes in young women or in women treated by radical mastectomy in presence of sentinel nodes micro-metastases [35, 36]. Furthermore, more encouraging results, from studies that attempt to reduce the prevalence of CALND, will probably allow us to move forward to a minimally invasive approach to the future axillary management until we would eventually, perhaps, even relegate the SLNB to the pages of history [37].

Also SLNB contraindications have been widely criticized during the last years, and nowadays some of them have been radically abandoned. For example, SLNB is now routinely performed during pregnancy, a condition in which it has been demonstrated to be safe and effective [38]. Yet, it is possible to offer SLNB to women who have already had a previous SLNB performed [39], as well as to those who are going to receive neoadjuvant chemotherapy [40]. Finally, SLNB results an indispensable technique in modern breast surgery as highlighted by the more recent EUSOMA guide lines [41].

## Conclusion

Based on the present data, independent from the axillary surgical approach and by eventual non-surgical treatments, the present authors can conclude that cancer biological behavior represents the most important predictive factor for both SLNB positivity and for axillary recurrence by SLNB negativity, and that an accurate biological cancer assessment may help in identifying a group of women at high risk for axillary recurrence and in better planning their follow-up. However, even in the case of recurrence, they observed no cancer-related mortality, suggesting no significant impact of loco-regional lymph node involvement on the quality of life of women with breast cancer, and what is most important on their overall survival [42].

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