

Indications for the sentinel node: multicentric, size of tumor, prior surgery

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Abstract Sentinel lymph node biopsy (SLNB) has been adopted as an applicable alternative to the standard axillary lymph node dissection (ALND) level I and II. It makes possible a less extensive axillary surgery in patients with early breast cancer with negative lymph node, who would not benefit from further dissection, in order to prevent unnecessary morbidity. On the other hand, SLNB is not appropriate in every clinical circumstance. In some clinical situations like tumor size T1 and T2, SLNB is, meanwhile, regarded as a standard procedure. In other settings like increased age and body mass index, pregnancy, ductal carcinoma in situ (DCIS), neoadjuvant chemotherapy, advanced disease (T3 and T4), prior surgery and multifocal/multicentric disease, there is a controversial debate about the importance of SLNB. This article reviews the absolute and relative contraindications of this procedure in respect to the latter three clinical situations.

For the advanced breast cancers T3 and T4, there seems to be an increasing evidence of an acceptable accuracy, although it should be further evaluated in randomized clinical trials (RCT). The indication of SLNB in previously operated patients depends on the type of prior surgery. A diagnostic biopsy does not represent a contraindication, whereas the sentinel node biopsy should not be used after an extensive breast surgery neither in the context of oncologic nor non-oncologic purposes. In the context of multicentric disease, there is growing evidence that SLNB is suitable, but actually it should be restricted to RCT. However, the multifocal disease is only a relative contraindication, that is it could be applied in well-selected patients.

Keywords: Axillary dissection; Multicentric disease; Sentinel node

Introduction

Axillary lymph node dissection (ALND) is a standard procedure for the surgical treatment of early breast cancer. It is not only important for the treatment of this disease, that is reducing the local recurrence rate by removing metastatic lymph nodes, but also for the diagnostic procedure. The degree of the

axillary lymph node invasion is important for the accurate staging and choice of the adequate adjuvant therapy.

The procedure of sentinel lymph node biopsy (SLNB) has become a widely accepted alternative to the ALND and helps to identify patients with negative axillary lymph nodes in order to prevent an unnecessary axillary dissection which represents no benefit for these women, but is additionally associated with morbidity from this procedure, that is increased risk of infection, decreased range of motion and lymphedema [1].

SLNB is regarded as a standard surgical procedure by the most experts and panels for women with T1- and T2-tumors, usually less than 3 cm in

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diameter [2]. In addition, a clinically negative axilla c(N0) is required, that is there should not be any suspicious palpable axillary lymph nodes. Apart from these clear indications and contraindications, there are some special clinical conditions in which it is not clear whether SLNB represents a relative/absolute contraindication or not.

Patients with increased age, increased body mass index, pregnancy, ductal carcinoma in situ (DCIS), neoadjuvant chemotherapy, advanced disease (T3 and T4), prior surgery and multifocal/multicentric disease delineate special circumstances for which indications and limitations of SLNB are not clearly defined. In this review, the indications for the latter three are further evaluated.

Multicentric/multifocal breast cancer

The role of SLNB in multicentric and multifocal disease in breast cancer is not yet clearly defined. Multicentricity is described as the presence of more than one cancer spots in the breast, occurring in separate quadrants or at a distance of more than 2–5 cm from each other [3]. In contrast to that definition, the multifocal disease is referred to the presence of several foci in the same quadrant of the breast.

It occurs in approximately 10–63% [3,4] of the cases and may result in inaccurate lymph node staging and high false-negative rates after an SLNB [5,6]. The most trials addressing SLNB have excluded women with multicentric or multifocal lesions. Therefore, this topic is not clearly evaluated and a recommendation is difficult to give. Most experts and panelists have been considered multicentricity/multifocality as a relative contraindication because of the suspicion that several tumor spots might drain to more than one dominant lymphatic pathway and sentinel lymph node (SLN). However, this point of view begins to change. At the beginning of SLNB era, this biopsy technique was used by injecting either radiolabeled colloid or blue dye peritumorally, that is directly near the tumor lesion [7,8]. Recently some trials have evaluated different sites of injection like intradermal [9,10], subdermal [5] or subareolar [11,12]. It has been shown that these injection sites were associated even with greater success and a comparable false negative rate to that associated with the standard injection site [13]. These results support the theory that all quadrants of the breast drain into the same lymph node. Assuming the idea that the whole breast drains to the same SLN, one could suggest that SLNB can even be performed in multicentric and multifocal cancer. This theory is supported by several authors [12,14–16]. Additionally, some

investigators were able to show that the test performance of SLNB in multicentric and multifocal disease is nearly equivalent to that for unifocal breast cancer [17–19]. Identification rates ranged from 90% to 97% [20] and false negative rates from 0% to 8% [19]. Knauer *et al.* [20] reported on a multi-institutional trial in which the SNB-feasibility and accuracy was evaluated in 142 patients with multicentric breast cancer. Compared to patients with unicentric cancer it has been shown a higher rate of SN metastases, whereas there was no difference in sensitivity (96.0%), negative predictive value (93.3%) and overall accuracy (97.3%) [20].

Nevertheless, it should be pointed out that the above-mentioned studies were only small and non-randomized series, so that further evaluations of this procedure have to be done. Therefore, we finally conclude with the German Society of Senology and point out that there is not sufficient evidence to recommend the procedure of SLNB in multicentric disease outside of randomized trials for routine clinical practice [21]. However, the multifocal breast cancer should not represent a contraindication according to the leading professional societies and published trials [2,21,22].

Prior surgery – previous biopsy

The impact of prior surgery of the breast and the axilla on accurate lymphatic mapping has not been evaluated very well either. On one hand, there are the oncologic biopsy procedures like incisional, excisional or core biopsy, which seem not to affect the success of SLNB according to some limited data [23]. On the other hand, there are the non-oncologic and oncologic procedures like reduction and augmentation mammoplasty or breast reduction that are not sufficiently examined. Neither the breast surgery nor the axillary surgery (i.e. mammoplasty through an axillary incision) is fully evaluated.

Concerning the prior breast surgery with the aim of a diagnostic biopsy, growing data suggest that the success of SLNB is not affected [23–27]. Nevertheless, it has to be emphasized that many previous trials on SLNB have excluded women with excisional biopsy [28] and/or previous axillary surgery [29]. Additionally, some authors reported on a higher failure rate after an excisional biopsy [29–31], whereas others found promising results. Miner *et al.* [32] were able to clarify that the type of previously performed diagnostic biopsy or the location of the primary lesion did not influence the localization of the SLN. In another study it has been shown that excision done before SLNB did not interfere with the subsequent identification rate of the SLN [33]. It could be shown that neither the excision volume

nor the time interval between the diagnostic biopsy and the lymph node mapping did play a role in affecting the success of SLNB [23]. So, taking into account the available data, a prior biopsy seems not to influence the successful lymphatic mapping.

The other group of prior breast surgery with non-oncologic and oncologic aims has been less examined. The effect on the identification rates of the SLN in women who have undergone a non-oncologic breast surgery, for example reduction mammoplasty, is not clearly known. Probably, the most important point for the correct identification of the SLN is the presence of an intact lymphatic pathway between the tumor and the axilla. If the tumor is situated in the upper quadrant, it is likely that, for example a reduction procedure does not affect the lymphatic drainage. Therefore, a sentinel procedure could be done, especially when prior surgery was performed more than 6–12 month previously. In the re-operative oncologic setting, it could be speculated that the intact lymphatic pathway seems to be as essential as in the non-oncologic setting for a successful identification of the sentinel node. Up to date, there are no randomized clinical trials (RCT) concerning this special situation.

The impact of the axillary surgery also remains uncertain. In a retrospective trial it was pointed out that SLNB after prior axillary surgery, like ALND or SLNB, is associated with a higher rate of failure, of 25% [34]. Although there have been only 32 cases in this study that have had an attempted sentinel biopsy after prior axillary surgery, this result indicates a negative effect of repeated SLNB. On the other hand, Intra *et al.* [35] published data from a single institution trial that show feasibility and efficacy of SLNB in the re-operative setting. The authors demonstrated an identification rate of 87% in patients with 10 or less axillary lymph nodes previously removed [35]. However, in patients with more than 10 lymph nodes excised, the rate decreased to 44%. The recently published results of Port *et al.* [36] support these data. The authors were able to show in an unicenter trial that the success of re-operative SLNB was inversely related to the number of nodes removed previously and was more likely to be successful after a previous SLNB than a previous ALND (74% vs. 38%) [36].

Taken together, these results suggest that SLNB should not be performed after previous axillary surgery, neither in the oncologic setting nor in the non-oncologic setting. However, in a selected group of patients this procedure could be taken into account, especially after prior SLN procedure. SLNB can be performed in patients who have had a previous excisional biopsy and even in patients

after a limited non-oncologic breast surgery [22]. In summery, the application of SLNB after extensive previous breast surgery has a diminished identification rate and should therefore be contraindicated.

Large and locally advanced breast cancer

Most experts recommend the procedure of SLNB in T1 and T2 tumors [2]. Although there is only one randomized and controlled published trial in which SLNB was compared with ALND for the effects on long-term survival [37], there is a strong evidence for the high quality of test performance of SLNB in patients with early breast cancer, given by the numerous amount of test performance trials [2]. Nevertheless, it should be emphasized that most validation trials included only patients with T1 and T2 tumors. A recently published meta-analysis and three other additional systematic reviews have underlined the advantage and quality of this procedure in this special group of women [2,38–40]. As stated in another representative multicenter setting, the sensitivity of SLNB is about 90% and the false negative rate is about 10% [25,29] for early breast cancer. However, for the locally advanced and larger T3 and T4 tumors, there are also a few reports that describe SLNB in these patients. Some authors did reveal that the identification rate and the sensitivity of SLNB in patients with smaller tumors were equivalent to those with breast tumors larger than 4 cm [41]. Chung *et al.* [42] reported on an acceptable accuracy rate in patients with larger tumors (≥ 5 cm). In this trial, the SLN status accurately predicted the regional nodal status in 98% (40 of 41) of cases [42]. Wong *et al.* [43] published data of an analysis that was performed to determine whether tumor size affects the accuracy of SLNB. The SLN identification rate, false negative rate and overall accuracy of SLNB were not significantly different among tumor stages T1, T2 and T3 [43]. Another study did reveal similar results. The SLN was identified in 99% of cases. SLNB false-negative rate was 2% [44]. Although these data [41–44] seem to support the statement that tumor size does not harm the sensitivity, we conclude with the recommendation that SLNB should not be used routinely for this group of patients because of the small amount of RCT. In a selected group of patients with advanced breast cancer, SLNB has also been used after neoadjuvant chemotherapy [45]. It could be shown an identification rate between 85% and 94% [46–48] and a false negative rate of 12% [46]. These data seem to indicate a potent role for SLNB in this setting. Nevertheless, there have to be more trials including large numbers of patients to clarify this indication of SLNB [49]. In the meantime,

SLNB after neoadjuvant chemotherapy should be restricted to the hands of experts with adequate experience [50].

Conclusion

SLNB is not appropriate for every patient. In some conditions, as for example multicentric disease, it should not be used outside clinical trials. However, the multifocal disease is only a relative contra-indication, that is it could be applied in well-selected patients.

The indication of SLNB in previously operated patients depends on the kind of prior surgery. The biopsy techniques do not represent a contra-indication, whereas SLNB should not be applied after an extensive breast surgery neither in the context of oncologic nor non-oncologic purpose. It should neither be used after prior axillary surgery.

The adapted tumor size for the accurate SLNB should be restricted to T1 and T2. Within the limits of clinical trial this technique can be applicable in larger tumors like T3 and T4 and in the setting of preoperative chemotherapy.

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