Is Axillary Sentinel Lymph Node Biopsy Required in Patients Who Undergo Primary Breast Surgery?

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Summary

Local treatment of the axilla in clinically node-negative (cN0) early breast cancer patients with routine sentinel lymph node biopsy (SLNB) is debated for various reasons: i) pN staging information may not be necessary for the postoperative treatment decision regarding adjuvant systemic therapy in the great majority of patients; ii) the SLNB-positive rate is declining below 20% in specialized breast centers; iii) albeit being a minimally invasive procedure, SLNB causes a significant reduction in quality of life in 23% of patients; and iv) previous randomized trials from the pre-SLNB era did not show a disadvantage for patients without axillary surgery with regard to overall survival. These data support the hypothesis that avoiding axillary treatment in patients with clinically and sonographically unsuspicious lymph nodes seems to be a safe option, although omitting axillary surgery may increase the risk of locoregional recurrence. Currently, the information regarding node-positive status is essential to guide postoperative treatment such as systemic or radiation therapies in a non-negligible minority of patients. Three ongoing prospective European trials (SOUND, INSEMA, BOOG 2013-08) with axillary observation alone versus SLNB in cN0 patients and primary breast-conserving surgery have the objective to evaluate oncologic safety when omitting SLNB.

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From the View of the Epidemiologist

Jutta Engel

The Munich Cancer Registry (MCR) is the population-based clinical cancer registry of Upper Bavaria and, partly, of Lower Bavaria (Southern Germany) [1]. Its epidemiologic catchment area currently comprises approximately 4.8 million inhabitants. Figure 1 shows trends in axillary lymph node dissection (ALND) and sentinel lymph node (SLN) biopsy (SLNB) over 15 years in the MCR for 43,435 patients with invasive breast cancer (M0 at diagnosis, without neoadjuvant therapy). According to this, more than 80% of this population-based collective received an SLNB, either exclusively (66.1%) or followed by an ALND (15.5%). Further, in women without clinical evidence of positive lymph nodes, SLNB is performed in over 85% [1].

In Principle, SLNB Could Be Necessary for Two Reasons

Firstly, SLNB could be needed as a diagnostic tool to support decisions regarding further adjuvant systemic therapy and predict response to therapy. However, this exclusive diagnostic function of the SLNB could be replaced by information from the primary tumor; the analysis of gene expression profiles has identified molecular (intrinsic) subtypes of breast cancer that differ significantly in their response to therapy [2–4]. Alternatively, a classification in which these subtypes are distinguished by an immunohistochemical algorithm is proposed as a surrogate [2]. Accordingly, the St. Gallen Consensus incorporated this biological model [2, 5, 6].

Secondly, SLNB could be needed as a therapeutic procedure to identify affected lymph nodes and remove them (possibly with subsequent ALND), since it is a commonly held belief that a meta-

Fig. 1. Trends for axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) over 15 years in the data of the Munich Cancer Registry for 43,435 patients with invasive breast cancer (M0 at diagnosis, without neoadjuvant therapy).

static risk could emanate from these affected lymph nodes. However, this therapeutic function of SLNB seems superfluous, because recent evidence demonstrates that no risk of metastasis emerges from positive lymph nodes [7].

Risk of metastasis arises from the primary tumor only (as long as it is not removed) which is amplified by the arguments below.

- The first argument is supported by evidence-based medicine. There are several randomized controlled trials (six for breast cancer only) in which ALND was omitted partly or completely. No single randomized study without regional lymph node removal showed any survival disadvantage [8–13]. An important question is whether this has to be proven repeatedly for each tumor or whether there is a common biologic principle.
- A second argument is provided by studies with neoadjuvant therapy, which show that the lymph node status is partly reversible, but no prognostic improvement is achieved [14].
- In addition, anatomy and physiology give no indication of a filter function of lymph nodes. Dissemination of tumor cells takes place from the primary tumor and propagates in parallel by both lymphogenous and hematogenous spread. The relationship between the two systems may be so intertwined that their separation, and therefore a cascade principle, is unrealistic [15–17].
- An independent argument provides a linear relationship between the diameter of the primary tumor, 10-year tumor-specific mortality, proportion of positive lymph node status, and number of positive lymph nodes. A non-linear relationship would be expected for a cascade principle, but the development shows a linear relationship. The regression line shows that with every millimeter-increase in tumor diameter, a further 1.2% of patients develop positive lymph nodes. That means, for large tumors, the SLN is the ‘oldest’ one, but not significantly larger than the ‘youngest’ lymph node itself. Thus, the primary tumor sequentially affects the lymph nodes, and there seems to be a growth limitation in the macroscopic sector [7].

- Relationships between tumor growth times, onset of metastasis, and death, as well as the long latency from the initiation of metastases to their diagnosis of about 7–8 years argue against a cascade theory and in favor of a parallel dissemination starting from the primary tumor [18].
- Meanwhile, there is also evidence from gene analyses that distant metastases arise from various clones of the primary tumor (and not from the lymph nodes). We know that a primary tumor will acquire gene mutations over time. Results of gene sequencing of various tumor foci of individual patients indicate that these gene mutations can be detected in the secondary foci, e.g., in two different liver foci or in patients with affected lymph nodes. Thus, both the chronologic order and the mutations of the primary tumor can be found in the metastases [19].
- A number of studies on gene analysis have shown that the site of metastasis can be seen in the gene signature of the primary tumor. For breast cancer, gene signatures were published in 2003 for bone metastatic colonization [20], in 2005 for the lung [21], and finally in 2009 for the central nervous system [22]. ‘Metastatic potential’ thus starts in the cells of the primary tumor, and these disseminated cells can then form metastases if the organ-specific properties match the gene signature they carry. The ‘seed and soil’ principle by Paget [23] seems to be valid.
- In the meantime, gene signatures are also determined by gene expression analyses, which allow a more accurate prognosis of survival in patients with both positive and negative lymph node status [24]. Gene expression analyses of the primary tumor enable a prognosis independent of the lymph node status, weakening the benefit provided by the knowledge of lymph node status.
- The metastatic process is based on comparable biologic capabilities acquired during the multistep development of human tumors. The hallmarks of cancer constitute an organizing principle for rationalizing the complexities of neoplastic disease [25]. Therefore, plenty of genes are required which the cells of the primary tumor must have (or numerous driver mutations

which the primary tumor ‘acquires’ during growth [25, 26]) to be able to successfully metastasize at all. Also, a pre-metastatic niche, which can be formed only from the primary tumor, seems to be necessary [27]. The process of metastasis is complex and starts from the primary tumor, not from positive lymph nodes [7, 28, 29].

In summary, from our point of view, SLNB is not required, neither as a diagnostic nor as a therapeutic intervention in routine care [30].

Surgeon's View: Pros and Cons for SLNB

Oreste Gentilini, Toralf Reimer, Marjolein L. Smidt

Previous randomized trials comparing ALND versus no axillary surgery in clinically node-negative patients (cN0) showed no benefit regarding overall survival for the ALND arm, even with long-term follow-up [31]. Currently, SLNB is accepted as staging procedure in cN0 patients with a false-negative rate of 6–8% [32]. Historically, pN status as an important prognostic factor was an indicator for (neo-)adjuvant systemic treatment and postoperative radiotherapy (RT). Today, systemic treatment is planned mostly according to tumor biology like intrinsic tumor subtypes, tumor grade, and Ki-67 rather than nodal status. Chemotherapy and/or targeted therapy is always indicated for triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors (stage pT1b and above) independently of SLNB results. In luminal-like breast cancer, the indication for chemotherapy is more and more based on the use of multi-gene assays in patients with pN1a [33]. In conclusion, the only indication for a SLNB in cN0 patients who undergo primary surgery is to identify 4 or more involved axillary lymph nodes in luminal-like breast carcinomas resulting in a clear indication for postoperative chemotherapy and RT. In the AMAROS trial and a Dutch population-based study, only 3 and 1.7%, respectively, of all luminal-like tumors in an SLNB cohort showed 4 or more involved axillary lymph nodes ($\geq$ stage pN2a) [34, 35]. Hence, even here, the chances of added value from the SLNB concerning treatment changes are low.

Initially in the NSABP B-32 trial, the SLN-positive rate was 29% [36]. Currently, in the era of mammographic screening, the reported SLN-positive rates in highly specialized centers are below 20%. A Memorial Sloan Kettering analysis revealed an SLN-positive rate of 17.6% in a breast-conserving surgery (BCS) cohort [37]. This finding is confirmed by a Mayo Clinic cohort in another unicentric evaluation of 1,140 patients (T1/T2) with an SLN-positive rate of 13% [38]. These cN0 patients were all preoperatively evaluated by axillary ultrasound (AUS) with or without fine-needle aspiration (FNA) biopsy.

As expected, postoperative morbidity (lymphedema, numbness or paresthesia, impairment of arm mobility) is significantly lower with SLNB compared to ALND [39]. However, SLNB is still an invasive staging procedure resulting in a significant reduction in quality of life in 23% of patients and lymphedema in over 8% of patients after only 3 years [40].

Omission of Axillary Surgery: Published Randomized Trials

Prior to the SLNB era, trials comparing ALND versus no axillary surgery and versus axillary RT were conducted to avoid the side effects of level I/II ALND [41]. 4 prospective trials randomized breast cancer patients to ALND versus no axillary surgery. These studies showed a low axillary recurrences rate, even in the no surgery arms, although nodal involvement in the ALND group ranged from 23 to 40%. No significant differences between the study arms could be found for survival outcomes [12, 42–44]. However, the decreased diagnostic possibilities at the time of inclusion in the trials should be borne in mind. Clinical node positivity (cN+) was solely based on physical examination, since AUS $\pm$ biopsy, positron emission tomography-computed tomography, and magnetic resonance imaging were not or less in use. Their arrival increased the percentage of cN+ patients and allowed the selection of the cN0 group with a lower tumor burden.

Current guidelines define patients who can be saved from axillary surgery. NCCN guidelines define axillary staging as optional for patients with favorable tumors, with serious comorbid conditions, or with a certain indication for adjuvant systemic therapy [45]. The German AGO guidelines recommend avoiding axillary surgery in elderly patients (≥ 60 years, cN0, hormone receptor-positive) with comorbidities and a life expectancy of less than 5 years [46].

Summarizing these data, avoiding axillary surgery in patients with clinically and sonographically unsuspecting lymph nodes seems to be a safe option, although it may slightly increase the risk of locoregional recurrence [31]. Further studies are needed to define subgroups of patients that do not profit from axillary staging and can be spared from its possible side effects.

Ongoing Clinical Trials

Three European trials were designed to compare SLNB versus observation when physical examination and AUS are negative in patients with BCS. The Italian SOUND, German/Austrian INSEMA (Intergroup Sentinel Mamma), and Dutch BOOG 2013-08 trials focus on this question with different inclusion criteria.

The SOUND trial is a prospective randomized multicentric study, designed by the European Institute of Oncology (EIO) of Milan. Eligibility and exclusion criteria were published by Gentilini and Veronesi [47, 48]. Briefly, cT1N0 patients treated with BCS underwent an AUS in order to rule out evident or suspicious nodal involvement. Patients with either negative AUS or negative FNA were randomized to 2 groups: SLNB (+ ALND mandatory in all cases with SLN macrometastases) versus no axillary surgery. The mandatory completion ALND is a critical point with respect to the ACOSOG Z0011 data [49]. The primary endpoint is distant disease-free survival (DDFS) with the assumption to obtain reliable results in a shorter period of time compared to overall survival. Overall, 1,560 women (780 per arm) were required to establish whether the observation group did not have worse outcome than the SLNB group, given a margin Δ of non-inferiority of 2.5% (maximum tolerable 5-year DDFS = 94%) [47]. The first patient was included in January 2012; recruitment closed after 1,464 patients in June 2017.

The goal of the ongoing German/Austrian INSEMA study is to show that a reduced extent of axillary surgery is not inferior with regard to invasive disease-free survival (IDFS) outcome compared to the standard arm in early-stage breast cancer patients. In this trial, patients with breast cancer ≤ 5 cm (T1/T2), node-negative axilla (clinically and/or per imaging), planned BCS, and age ≥ 18 years can be recruited [50]. Patients will be first randomized to either no axillary surgery or SLNB in a 1:4 allocation. Patients with SLNB and pN+(sn) status will be secondly randomized (1:1 ratio) to either SLNB alone or completion ALND in the case of <4 involved nodes (1–3 macrometastases). Due to the unequal-sample-size design, the total number of patients amounts to 6,740. In addition to the SOUND trial, INSEMA aims to clarify certain problems of ACO-SOG Z0011: distribution of axillary isodoses with standard whole-breast irradiation and ignoring of SLNB with micrometastases for second randomization. After first-patient-in on 17 September 2015, the current recruitment (March 2018) for the first randomization is concordant with the planned target ($n = 3,930$ included).

The Dutch BOOG 2013-08 trial is a non-inferiority randomized controlled multicenter trial. Women with cN0 T1–2 invasive breast cancer undergoing BCS will be randomized to SLNB versus no SLNB. In the case of SLNB and involved nodes, additional treatment is provided according to local guidelines. In contrast to SOUND and INSEMA, patients with neoadjuvant chemotherapy are included as well. The primary endpoint is the regional recurrence rate after 5 years; the estimated sample size is 1,644 patients [51]. The current status of recruitment is $n = 506$ (March 2018).

From the View of the Medical Oncologist

Marcus Schmidt

From a medical oncologist's point of view, SLNB is required in patients who undergo primary surgery. For proper planning of adjuvant systemic therapies, knowing the nodal status of a patient is still of utmost importance, even in the era of a rapidly increasing understanding of tumor biology.

It is well accepted that anthracycline- and taxane-containing adjuvant chemotherapy reduces the risk of breast cancer mortality by approximately one-third [52]. It is evident that the proportional reduction in mortality depends on the level of risk of the individual patient. In order to avoid over- as well as under-treatment, it is advisable to select the appropriate treatment strategy on the basis of a careful risk assessment for each individual patient.

An important pathologic factor for risk stratification in primary breast cancer is the nodal status [53]. Moreover, Jatoi et al. [54] showed that nodal metastasis is not only a marker of diagnosis at a later point in the natural history of breast cancer but also a marker of an aggressive phenotype. Even in the era of a more thorough understanding of tumor biology in early breast cancer, nodal status remains an important prognostic factor. When developing a gene expression signature for estrogen receptor(ER)-positive/HER2-negative early breast cancer, we realized that the prognostic accuracy could be substantially improved after including the number of

involved lymph nodes in the model [55]. The molecular information of EndoPredict® (EP) (Myriad Genetics, Salt Lake City, UT, USA) was consequently combined with the clinical parameters nodal status and tumor size, resulting in the molecular and clinical risk score, EndoPredict-clin (EPclin) which outperformed all conventional clinicopathologic risk factors in prospective-retrospective validation studies [56]. It is evident that nodal status is a strong prognostic factor regardless of gene expression signature [6]. This again emphasizes the relevance of established clinicopathologic factors like nodal status for a comprehensive and reliable assessment of the risk of recurrence for an individual patient. Indeed, node-positive status is a well-established prognostic factor arguing for adjuvant chemotherapy [6].

Especially in node-negative breast cancer, risk assessment with conventional clinicopathologic factors is not always sufficient to guide chemotherapy. Gene expression signatures might be used in selected ER-positive/HER2-negative patients [6]. In any case, this implies that knowledge of the nodal status is of paramount importance when selecting the most appropriate systemic therapy for a given patients.

Concerning patients with HER2-positive early breast cancer, nodal status is important to select the chemotherapy backbone. Node-negative patients with HER2-positive breast cancer measuring up to 3 cm in greatest dimension fare very well when trastuzumab is combined with weekly paclitaxel [57]. Furthermore, nodal status is important when deciding which HER2-positive patient benefits from dual antibody blockade with trastuzumab and pertuzumab. In the recently published APHINITY study, only node-positive but not node-negative patients had improved IDFS with the addition of pertuzumab to trastuzumab and chemotherapy [58].

Even when considering the duration of adjuvant endocrine therapy in hormone receptor-positive breast cancer patients, nodal status plays an important role. Current consensus recommendations approve an extended endocrine therapy for patients with intermediate/high 'clinical risk' (node-positive) [6].

In conclusion, knowing the lymph node status is important when selecting the most appropriate systemic therapy. Omitting assessment of axillary lymph nodes would lead to less individualized treatment decisions. Because of this, SLNB is required in patients who undergo primary surgery.

The Radiation Therapy Perspective

Birgitte Vrou Offersen

The status of the axilla in early breast cancer patients is of utmost importance because it is a strong prognostic factor and guides optimal locoregional and systemic therapy. From an RT perspective, there are essentially 2 types of radiation treatment planning: local RT and locoregional RT. Local RT involves irradiation of only the residual breast after BCS, and it can be whole breast or partial breast treatment planning. Locoregional RT includes irradiation of the breast/chest wall and regional nodes, including all or selected levels I–IV, the Rötter nodes, and the internal mammary nodes [59, 60].

In many countries, the shift from local RT to locoregional RT occurs when one macrometastasis is present in the axilla, and since locoregional RT per se causes more dose to heart and lungs and thereby increases the risk of serious late effects, it is very important to know for sure if a macrometastasis is present [61–64]. Highly specialized centers report positive SLNB in less than 20% of their patients; however, a nationwide evaluation of SLNB between 2010 and 2015 by the Danish Breast Cancer Group (DBCG) revealed macrometastases (not just positive nodes) in 21% of all SLNB, and in the group with sentinel macrometastases, 14% had pN2 disease and 6% had pN3 disease at ALND [37, 64]. Preoperative ultrasound was performed as part of the DBCG guideline. These findings strongly indicate that evaluating the status of the axilla with palpation and ultrasound is difficult, and that SLNB adds valuable information for the optimal selection of adjuvant treatment.

Virtually all developed countries recommend locoregional RT if pN2–3 disease is present, so if SLNBs are abandoned, patients with cN0pN2–3 disease are recommended neither potentially life-saving chemotherapy nor locoregional RT. Based on the results from the above-mentioned DBCG retrospective study, the likelihood of having cN0pN2–3 disease is low (approximately 4%); however, the consequences of not being offered evidence-based treatment may be serious for these patients. It is also very likely that the statistic power of trials testing omission of SLNB is too low to detect this problem. The trials testing omission of SLNB (SOUND, INSEMA, and BOOG 2013-08) all have 5-year endpoints (DDFS, IDFS, and regional recurrence, respectively). Hopefully, these trials will recruit their planned number of patients, and results from nearly 10,000 patients will then be able to guide future directions. It will be paramount to follow the results from these trials also at 10 years and more.

When reporting outcome after SLNB only or after no SLNB, it is absolutely necessary to report RT-related technical information also. After results were reported from the ACOSOG Z0011 trial, it became clear that there had been virtually no control during the trial on details of the RT, so it was stated that ‘high tangents’ after BCS were recommended [65]. Using modern RT techniques based on meticulous target volume delineation followed by conformal radiation treatment planning to ensure optimal dose homogeneity and as low a dose as possible to organs at risk, ‘high tangents’ are not an option [59, 60]. In women who have been influenced by gravity for many years, there may be several centimeters from the

caudal edge of the humeral head to the cranial edge of the clinical target volume of the residual breast, thus radiation dose to level I is often very modest if the patient is not having locoregional RT. If the target for RT is not defined and delineated, it will not be adequately treated.

In the next 5–10 years, the surgical and radiation treatments of the axilla will be further refined based on new evidence currently collected in several trials. Until results from those trials are available, SLNB remains of pivotal importance in cN0 early breast cancer patients to inform optimal adjuvant locoregional and systemic therapy.

Conclusion

Currently, axillary surgery for breast cancer is a staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastasis depends mainly on the biologic behavior of the primary tumor (seed-and-soil model) [30]. Post-surgical therapy should therefore be based on biologic tumor characteristics rather than nodal involvement. However, some recommendations are still influenced by nodal status: the indication for regional node irradiation in $\geq$ pN2a disease, the decision of adding chemotherapy to endocrine treatment, the choice of chemotherapy regimen, the type and duration of endocrine treatment, or the adjuvant indication for dual anti-HER2 therapy. At the moment, it is still unclear what level of information is needed to properly treat our patients. The ongoing trials will hopefully help us to understand whether we might take the best decisions without the pathologic evaluation of nodal status. Improved staging power of imaging modalities is further desired in light of the low sensitivity of AUS.

SOUND, INSEMA, and BOOG cannot provide all the answers; for example, it remains unclear whether patients without SLNB can be offered partial breast irradiation alone in low-risk situations (allowed option in SOUND) and whether SLNB can also be avoided in patients with stage T1–2 tumors who have a mastectomy indication.

Disclosure Statement

We declare that there are no conflicts of interest related to this review.

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