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**Axillary lymph node **dissection** in early-stage invasive breast cancer: Is it still **standard** today?**

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**Short running head:** Axillary lymph node extirpation in early breast cancer

**Key words:** breast cancer, axillary lymph nodes, dissection, sentinel, prognosis,  
metastases

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## Abstract

Evaluation of axillary lymph node status by sentinel lymph node biopsy (SLNB) and complete axillary lymph node dissection (ALND) are an inherent part of breast cancer treatment. Increased understanding of tumor biology has changed the prognostic and therapeutic impact of lymph node status. Non-invasive imaging techniques like axillary ultrasound, FDG-PET or MRI revealed moderate sensitivity and high specificity in evaluation of lymph node status. Therefore, they are not sufficient for lymph node staging. Otherwise the impact of remaining micrometastases and even macrometastases for prognosis and treatment decisions is overestimated. Considering tumor biology, the distinction of axillary metastases in isolated tumor cells (ITC, pN0[i+]); micrometastases (pN1mi), and macrometastases (pN1a) is not comprehensible. Increasing data support the thesis that remaining axillary metastases neither increase the axillary recurrence rate nor decrease overall survival. It is doubtful that axillary tumor cells are capable to complete the complex multistep metastatic process. If applied, axillary metastases are sensitive to systemic treatment and are targeted by postoperative tangential breast irradiation. Therefore, the controversy about the clinical relevance of tumor cell clusters or micrometastases in SLN is a sophisticated but not contemporary discussion. Currently, there is no indication for axillary surgery in elderly patients with favorable tumors and clinically tumor-free lymph nodes. Nonetheless, a rational and evidence-based approach to the management of clinically and sonographically N0 patients with planned breast-conserving surgery and limited tumor size is needed now.

## Introduction

The axillary lymph node dissection (ALND) with removal and histopathological examination of at least 10 nodes was an inherent part of surgical treatment of breast cancer for a considerable time. During the last decade ALND was replaced by sentinel lymph node biopsy (SLNB) in patients with clinically and sonographically unsuspected lymph nodes [1-3]. As a consequence the arm morbidity was reduced markedly [4]. The SLNB requires estimated costs of 200-250 € per sentinel labeling and 1,750 € per axillary surgery (Webgrouper DRG Research Group, University of Muenster, Germany). Due to nationwide mammography screening in most industrial countries, a greater number of smaller tumors without axillary lymph node involvement is detected. More than 60% of all primary operable breast cancers do not have axillary lymph node metastases. This in turn means that even SLNB represents an overtreatment and is not indicated in the majority of patients. Non-invasive methods like ultrasound, fluorodeoxyglucose positron emission tomography (FDG-PET), and magnetic resonance imaging (MRI), have gained more importance in staging the axillary lymph nodes. With improved insight into primary tumor biology and metastasis behavior, the relevance of nodal status for adjuvant treatment decisions is decreasing. Currently, in cases with positive sentinel lymph nodes (SLN) the need for completion ALND is arguable. Nevertheless, there is an ongoing discussion about the prognostic impact of isolated tumor cells (ITC, pN0(i+);  $\leq 0.2$  mm), micrometastases (pN1mi;  $>0.2$  mm to  $\leq 2.0$  mm), and macrometastases (pN1a;  $>2.0$  mm) in SLNs. The aim of this review was firstly to assess the imaging techniques in axillary lymph node staging and secondly to evaluate the impact of pathological lymph node status regarding prognosis and treatment decisions. The key question to be answered is: Is there a chance to avoid axillary lymph node

surgery in patients with early breast cancer? This review is not covering the issue of axillary surgery following primary systemic treatment.

## **Materials and methods**

We performed a selective literature search on PubMed database using the search terms “breast cancer & axillary lymph nodes” and “ultrasound or sonography”, “MRI” or “PET” and “sentinel lymph node and micrometastases” for the period from January 2002 to February 2011. Activated limits for search were “Female, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, English”. Contributions to international congresses on breast cancer in 2009 (SABCS, San Antonio Breast Cancer Symposium; ECCO, European Cancer Organization; EBCC, European Breast Cancer Conference) and 2010 (ASCO, American Society of Clinical Oncology) were included. The treatment recommendations of AGO-Mamma (the Breast Group of the German Gynecological Oncology Working Group [5]) and the NCCN (National Comprehensive Cancer Network) Guidelines [6] together with the Cochrane Library [7] were also considered.

## **Imaging techniques**

The exclusion of lymph node metastases by using non-invasive methods could reduce the rate of axillary surgery. However, the experience of examiner and period of availability are crucial for the diagnostic precision and prediction.

### *Axillary Ultrasound (AUS)*

Clinically palpable axillary nodes are widely considered as contraindication to SLNB in breast cancer. However, various studies have shown that clinical assessment of axillary lymph nodes alone is inaccurate with a false-positive rate up to 40% [8, 9].

Among patients with clinically uninvolved axillary lymph nodes, AUS has additional value in detecting pathological axillary nodes [10, 11]. One third of pathological involved lymph nodes could be predicted preoperatively by ultrasound. AUS combined with fine needle aspiration (FNA) biopsy of suspicious nodes has shown useful results to guide preoperative surgical planning [12, 13]. However, the reported sensitivity for AUS-FNA has varied considerably between different studies [14, 15]. Because of the risk of false-negative results, negative FNA findings are almost followed by SLNB for confirmation.

According to guidelines, a SLNB is only indicated in patients with histologically proven invasive breast cancer and clinically and sonographically insuspect lymph nodes. In a systematic review including 16 studies, in which AUS without palpable lymph nodes was performed, the node size and the morphology were used as criteria for positivity [15]. For lymph node size sensitivity varied between 48.8% (95% confidence interval [CI]: 39.6-58%) and 87.1% (76.1-94.3%) and specificity, between 55.6% (44.7-66.3%) and 97.3% (86.1-99.9%). If lymph node morphology was used as the criterion for positivity, sensitivity ranged from 26.4% (15.3-40.3%) to 75.9% (56.4-89.7%) and specificity, from 88.4% (82.1-93.1%) to 98.1% (90.1-99.9%). After sonographically guided node biopsy, sensitivity varied between 30.6% (22.5-39.6%) and 62.9% (49.7-74.8%) and specificity was nearly 100% (94.8-100%). More recent studies confirmed these percentage rates for AUS-FNA showing sensitivities from 53% to 59% and specificities of 100% [16, 17]. AUS-FNA seems to be most useful in the preoperative assessment of patients with large breast tumors (>2 cm) or with lymph nodes that appear abnormal.

In conclusion, AUS is moderately sensitive and fairly specific in the diagnosis of axillary metastatic involvement. These scattered variabilities are the result of the missing clear criteria for evaluation of axillary lymph nodes by ultrasound. The

classification of axillary lymph nodes on the basis of cortical thickness (cut-off 2.5 mm) and the appearance of the fatty hilum on sonography was effective for predicting the presences of metastases in a recent study [18]. In future, addition of contrast-enhanced color and power doppler ultrasound may improve the sensitivity of AUS [19]. Malignant lymph nodes showed longer contrast enhancement duration compared to benign lymph nodes.

### *FDG-PET*

**FDG-PET** seemed to be an interesting approach as a non-invasive method of staging the axilla in breast cancer patients. In a meta-analysis, 21 studies for clinical use of FDG-PET in investigating axillary nodes were graded on methodological quality of the single studies depending on number and selection of patients, technical details of examination, pro- or retrospective design, and kind of lymph node biopsy [20]. As shown in table 1 best quality studies showed a sensitivity, specificity, positive and negative predictive value of around 80%, whereas in the poorer quality studies the diagnostic accuracy was higher. However, the variability between study designs has made it difficult to compare and aggregate the results of these studies. As well, caution must be exercised when analyzing results from older studies because of the increased accuracy of the newer scanners [20].

In a current meta-analysis of 25 studies including 2,460 patients a trend to lower sensitivity (37–85%) in the most recent published and higher quality studies (year 2005-2009 and sample size  $\geq 25$ ) was detectable, whereas the specificity (84–100%) remained high [21]. This meta-analysis also indicated that the sensitivity of PET is not sufficient to detect small metastatic deposits (micrometastases). Interestingly, the metabolic activity is variable according to the histopathological subtype of breast cancer. The mean tumor maximum standardized uptake value SUV(max) in lymph



node metastases of estrogen receptor (ER)-positive, triple-negative and human epidermal growth factor receptor 2 (HER2)-positive tumors was 6.6, 11.6, and 6.6, respectively [22].

In conclusion, sensitivity and specificity of PET is comparable to AUS, but because AUS is less expensive, AUS remains standard of care these days. The combination of AUS and PET seems to be improved the diagnostic accuracy [23]. The additional benefit of an assessment of distal metastatic spread provided by PET requires further investigation [21].

### *MRI*

Breast MRI assessment of breast cancer patients considered for primary surgical treatment is being used more frequently, especially if breast-conserving surgery (BCS) is planned. During such assessment, regional lymph nodes are usually included. Using different contrast agents, sensitivity ranged from 63–100% and specificity from 56–100% (Tab. 2). Like FDG-PET, contrast-enhanced MRI accuracy showed a close relationship with histopathologic subtypes of invasive breast cancer and its limitation in detection of axillary micrometastases [29, 31, 32]. Adding axillary MRI sequentially after AUS did not significantly improve detection of positive nodes in AUS-negative cases (false-negative rate of 28% and false-positive rate of 18% for MRI) [16].

Taken together, all imaging techniques are of high specificity and moderate sensitivity especially in cases with small lymph node metastases. The value of combined imaging techniques for improving the diagnostic accuracy should be considered critically with respect to benefit-cost-ratio.

In the following we have to **discuss** three **fundamental** questions: Firstly, is it really important to know the nodal status for treatment decisions? Secondly, is there a chance to avoid axillary surgery in some cases and how can we select these patients? And thirdly, how is the biological **behavior** of metastatic involved lymph nodes left in situ (**separated by tumor cluster size**)?

### **Lymph node status for prognosis and treatment decision**

Since Halsted first defined the issue of axillary lymph nodes 100 years ago, the lymph node status is the basis for prognosis and treatment decision in breast cancer [33]. It is well known that the prognosis declines with increasing number of metastatic lymph nodes or more precisely, with an increasing lymph node ratio [34, 35]. Larger breast tumors tended to be associated with a greater number of metastatic involved axillary lymph nodes than smaller tumors, indicating that a higher number of involved lymph nodes reflects a longer tumor growth time. In a multivariable logistic regression analysis the molecular subtypes of breast tumors (luminal, luminal/HER2-positive, HER2-positive/ER-negative/progesterone receptor (**PgR**)-negative, and basal-like) had a predictive effect for nodal involvement ( $p=0.000001$ ). Using the **luminal subtype** as reference, the basal subtype has an odds ratio for axillary lymph node involvement of 0.53 (95% CI: 0.41-0.69) **in a model using core biopsy data** [36]. **A Belgian group** reported higher likelihood of being lymph node positive for triple-positive tumors (**HER2 positive/ER positive/PgR positive**) compared to other subtypes (56.2 vs. 35.7%) [37]. Patients older than 70 years were more likely to have positive nodes with increasing age. **The effect of age in older women was most pronounced for small tumors. On the contrary, for very large tumors, the risk of lymph node involvement even decreased with increasing age** [38]. Other studies reported no increase of lymph node involvement in elderly patients when investigating the

relationship in pT-strata and adjusting for other prognostic factors. Taken together, axillary lymph node involvement is the result of different factors and lymph node status at all does not reflect the aggressive behavior of the tumor correctly [39]. Tumor aggressiveness especially in patient without axillary lymph node involvement has primarily to do with biological features of the tumor cells from the primary tumor. Based on this, it seems reasonable that poor outcome depends more on the tumor biology than on lymph node involvement [40-44]. Gene expression analyses of the primary tumor indicated that 51% of lymph node-negative tumors and 49% of lymph node-positive tumors have a poor prognostic signature [45]. The value of gene expression profiling as a prognostic tool in clinical practice is currently being evaluated in two large, prospective, randomised studies (TAILORx, MINDACT). Lymph node status is a good indicator of tumor stage related to the time point of diagnosis, but it does not reflect the real tumor biology, metastatic behavior as well as sensitivity to systemic treatment. Extensive characterization of the primary tumor will be available by gene signatures in future [44-46]. Nevertheless, nodal status is still an established parameter for treatment decisions in current guidelines. According to the NCCN guidelines the indication for post-mastectomy radiotherapy in all patients or for adjuvant chemotherapy in ER-positive/HER2-negative disease is linked to the number of involved lymph nodes [6].

This adherence to treatment recommendations on the basis of axillary nodal status was also observed in own previous work. We have shown that the knowledge of pathologic nodal status influences the indications for postoperative chemotherapy and post-mastectomy radiotherapy [47]. Re-discussion of postoperative tumor board records without information regarding axillary lymph node status resulted in adjuvant treatment recommendations different from the current guidelines in one third of all cases (72 of 207 patients), especially in carcinomas with present lymphangiosis.

However, this **finding** is the result of guidelines which are mostly based on elderly studies with nodal status as an in- or exclusion criterion. More recent studies have confirmed the effectiveness of chemotherapy **and trastuzumab** even in high risk, node-negative patients [48, 49].

Engel et al. reported 15 reasons to stop axillary surgery entirely [50]. **This paper was hypothesis generating in 2006 without changing current surgical practice. The author's discussion is based on the hypothesis that locoregional and distant metastases develop over time from disseminated tumor cells that originate from the primary and not from the lymph nodes. The current pros and contras for axillary lymph node status and associated treatment decisions are summarized in table 3 using some arguments published by Engel et al..**

### **Definition of patient subgroups without any axillary surgery**

SLNB is a minimal invasive procedure with the same oncologic safety as ALND and low (but not zero) morbidity [51-53]. Therefore, SLNB is suggested to be an optimal approach to reduce the morbidity by the assessment of axillary status in clinically node-negative breast cancer. **But the indication for SLNB in all clinically node-negative patients is questionable because at least 70% of these patients are pathologically tumor-free in the axillary nodes.** Two randomized trials investigated the use of ALND versus no axillary surgery in elderly patients [54, 55]. A third trial randomized patients without any axillary surgery to no axillary treatment versus **axillary radiotherapy (ART)** [56]. The results of all three studies showed a very low rate of axillary recurrences, even in the **arms without axillary surgery**, and comparable disease-free and overall survival (Tab. 4).

In an observational study with 671 consecutive patients, **aged  $\geq 70$  years**, and a clinically **tumor-free** axilla, 172 received and 499 did not receive axillary dissection.

After a median follow-up of 15 years, there was no significant difference in breast cancer mortality between the axillary and no axillary clearance groups. Ipsilateral axillary recurrence rate was zero in the axillary dissection group and relatively low in the no axillary dissection group: 5.8% overall and 3.7% for pT1 patients [57]. These axillary recurrence rates in the non-operated group were much lower than the rate of pathological nodal involvement in the axillary dissection group (33.7% pN+ overall and 29% pN+ for pT1 patients). The authors concluded, that due to a very low cumulative incidence of axillary recurrence in elderly patients with BCS both, SLNB and ALND can be avoided. Axillary dissection should be restricted to the small number of patients who will later develop apparent axillary disease.

Axillary recurrence is rare, although four-times more common in younger women (<40 years) than in older patients (50-60 years) [58]. Current NCCN guidelines consider the performance of ALND as optional in patients who have particularly favorable tumors, in patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with severe comorbid conditions [6]. There is no clear statement in the NCCN guidelines in which patients the SLNB can be avoided.

ART has been used instead of or in addition to axillary sampling or ALND. In 2004, Louis-Sylvestre et al. published results of a prospective randomized trial comparing lumpectomy plus ART versus lumpectomy plus ALND (n=658; median follow-up 180 months; 21% node-positive in the ALND group) [59]. Overall survival rates were identical in both groups, recurrences in the axillary nodes were less frequent in the ALND group (1% versus 3%, p=0.04). As an alternative to completion ALND for SLNB positive patients, ART has been suggested [60]. This concept is undergoing prospective evaluation by the EORTC trial, "After Mapping of the Axilla: Radiotherapy versus Surgery?" (AMAROS) [61]. The trial is full recruited, but definitive data will not

be available for years. ART in the setting of no prior axillary surgery has generally been associated with less morbidity than that seen with ALND. The incidence of morbidity after SLNB combined with ART has not been well characterized [62].

## **In situ left metastatic involved axillary lymph nodes and prognosis**

### *Macrometastases*

SLNB trial arms with immediate conventional ALND showed false-negative rates up to 9.8% regarding accuracy of SLNB [2, 63]. Even after ALND of level I and II, up to 30% of positive lymph nodes remain in the axilla, 15% of these present as 'skip metastases' [64, 65]. Rudenstam et al. reported nodal involvement in 28% of the patients who had axillary dissection [54]. Isolated lymph node recurrences are rare (<2%) in patients with BCS and lymph node-positive disease [58, 66, 67].

The presentation of the prospective, multicentric ACOSOG Z0011 trial at the ASCO Congress 2010 was a landmark for the discussion about surgical options in pN+ patients after SLNB. According to the protocol, nearly 900 patients with clinically T1-2 cN0 cM0 breast cancer and BCS with metastatic involved sentinel nodes (routine hematoxylin and eosin [H&E] detected) were randomized to no further axillary dissection or completion ALND [68]. Targeted enrollment was 1,900 women, but the trial closed earlier due to lower than expected accrual and event rates. Both arms were comparable with respect to pathological tumor size, grading, histological tumor type, hormone receptor status and systemic treatment. After a median follow up of 6.3 years there were no significant differences between SLNB alone and SLNB plus ALND arms concerning 5-year local recurrence rate (1.6% versus 3.1%), 5-year disease-free survival (83.9% versus 82.2%), or 5-year overall survival (92.5% versus 91.8%). The local axillary recurrence rate was 0.9% for SLNB alone and 0.5% for SLNB+ALND [68, 69]. Because all patients were treated with opposing and

tangential field irradiation, a local effect on the axilla could not be excluded completely, however it seems very unlikely in this dimension [58, 66].

According to these findings the German AGO Breast Group has adapted the current guidelines in March 2011. The completion ALND is not longer recommended (only “+/-“ grade of recommendation) in patients with positive sentinel nodes and: cT1/2, cN0, less than three sentinel nodes involved, BCS plus tangential breast irradiation, and no alternative ART [5]. The ACOSOG Z0011 data are supported by a retrospective SEER database analysis (1998-2004) including 26,986 patients with positive sentinel nodes [70]. Among those, 4,425 (16.4%) underwent SLNB alone, and 22,561 (83.6%) underwent SLNB with completion ALND. Contrary to the Z0011 study, the SEER analysis was not restricted to BCS (21.2% with total mastectomy in the SLNB alone arm). At a median follow-up of 50 months, there were no statistically significant differences in overall survival between patients with SLNB alone versus complete ALND.

Of 97,314 patients from the US National Cancer Database who underwent SLNB and who had nodal metastases, 20.8% underwent SLNB alone, and 79.2% underwent SLNB with complete ALND [71]. In patients with macroscopic nodal metastases and a median follow-up of 63 months, there was a non-significant trend towards better outcomes for complete ALND compared to SLNB alone: axillary recurrence HR=0.58 (95% CI: 0.32-1.06) and overall survival HR=0.89 (95% CI: 0.76-1.04). A randomized controlled trial with 30 years follow-up indicated that clearing the internal mammary or axillary lymph nodes has no impact on long-term survival [72]. Moreover, tumor location affects the frequency of lymph node metastases but not the survival. Janni et al. showed that 25.8% of patients with a tumor in the medial **quadrant of the** breast have axillary lymph node metastases compared with 35.5% of patients with a lateral **localized** breast tumor [73]. Despite the 10% difference, survival time was similar for

both tumor locations. There is no additional survival advantage in clearing level III of the axilla compared with clearing **restricted to** levels I and II [74].

The Memorial Sloan-Kettering Cancer Center (MSKCC) developed nomograms to predict the likelihood of a positive sentinel node or finding additional positive non-sentinel nodes in patients with involved SLNs [75, 76]. The nomograms are a statistical approach for calculation metastatic axillary risk by combining different histopathologic factors (plus age, which is incorporated in the sentinel nomogram) and are available online ([www.mskcc.org/mskcc/html/15938.cfm](http://www.mskcc.org/mskcc/html/15938.cfm)). Although the first published MSKCC nomogram for patients with positive SLN has been validated by numerous centers, clinicians were unlikely to change their surgical plan based on nomogram results [77]. Additionally, this model seems not reliable predictive for positive non-SLN in cases with micrometastatic positive SLN [78].

### *Micrometastases*

The SLN is the most likely site of regional metastasis, and gives pathologists the opportunity to concentrate detection techniques on one or a few lymph nodes. The use of step sectioning and immunohistochemistry for SLN analysis results in a higher detection rate of micrometastases (International Union Against Cancer classification: pN1mi, >0.2 mm to  $\leq 2.0$  mm) and isolated tumor cells (pN0(i+),  $\leq 0.2$ mm) [79-81].

**Pathologists should follow published recommendations for the management of SLN [2, 82, 83].**

Breast cancer micrometastases have lower tumor proliferation rates and angiogenesis than breast cancer macrometastases [84]. These characteristics may explain a **discrimination** of micro- and macrometastases. The distinction between pN1mi and pN0(i+) depends on 0.1 mm. Why should 0.1 mm in **tumor cluster** size determine different prognosis? Any tumor spread to axillary lymph nodes indicates



that the tumor cells are able to metastasize. Therefore the meaningfulness of distinction between pN1mi and pN0(i+) and also pN1a must be challenged [85].

Tan et al. reported a significant decreased disease-free and overall survival for pN0(i+) patients (HR=1.7 [95% CI: 1.0-2.9]) compared to pN0(i-) in a retrospective analysis with 17.6 years follow-up [86]. Many studies confirmed that the occurrence of pN1mi and pN0(i+) depends on the tumor biology and the location of micrometastases (sinusal versus parenchymal) [66, 87-94]. However, the clinical relevance and therapeutic implications of pN1mi and pN0(i+) in the SLN remain a matter of debate.

A recent meta-analysis including 297,533 patients from 58 studies published between 1977 and August 2008 divided patients into three categories according to the method of pathological assessment of the lymph nodes: cohort studies with single-section examination (n=285,638 patients), occult metastases studies with retrospective examination of negative lymph nodes by step sectioning and/or immunohistochemistry (n=7,740 patients), and SLNB studies with intensified work-up of the sentinel but not of the non-SLN (n=4,155 patients) [95]. In the cohort studies, axillary lymph node metastases of 2 mm or less in diameter were associated with poorer overall survival (HR=1.44, 95% CI: 1.29-1.62), occult metastases were associated with poorer 5-year disease-free survival (RR=1.55, 95% CI: 1.32-1.82) and overall survival (RR=1.45, 95% CI: 1.11-1.88), although these endpoints were not consistently assessed in multivariable analyses. SLNB studies are limited by small patient numbers, SLNB alone or complete ALND in pN1mi and/or pN0(i+), different systemic treatments, and short follow-up.

As shown in table 5, nine of 12 studies reporting survival outcome, demonstrate no associations between occult metastases and overall survival. The MIRROR study (Micrometastases and Isolated tumor cells: Relevant and Robust or Rubbish) has

found pN0(i+) and also pN1mi to be indicators of poor prognosis compared to pN0 [89]. The MIRROR-trial is also a retrospective cohort study including only patients with favorable tumor characteristics for whom adjuvant systemic treatment was not indicated according to the Dutch treatment guidelines. ITCs or micrometastases in regional lymph nodes were associated with a reduced 5-year rate of disease-free survival among patients who did not receive adjuvant therapy (HR 1.5 [95% CI: 1.15-1.94] for ITC and HR 1.56 [95% CI: 1.15-2.12] for pN1mi). In patients with ITC or micrometastases who received adjuvant therapy, disease-free survival was significantly improved as compared with the node-positive, no-adjuvant-therapy cohort [89].

A recent study showed that the actual rate of positive non-SLNs for patients with SLN micrometastases or ITCs who underwent completion ALND was significantly less than that predicted by the MSKCC nomogram [104]. The rate of axillary recurrence for included 116 patients with stage I to III breast cancer was negligible, regardless of the extent of axillary staging. The NSABP trial B-32 investigated the clinical significance of occult metastatic disease in selected sentinel nodes – primary pathologically negative [96]. Occult metastases were detected in 15.9% of 3,887 patients: 11.1% with ITC clusters, 4.4% with micrometastases, and 0.4% with macrometastases. Occult metastases were an independent prognostic variable; however, the magnitude of the difference in overall survival at 5 years was small (94.6% with and 95.8% without detectable metastases). The authors conclude, that identification of occult metastases does not appear to be clinically useful for patients with newly diagnosed disease in whom systemic therapy can be recommended on the basis of the characteristics of the primary tumor.

**Do lymph node metastases metastasize?**

The key question, whether regional lymphatic metastases can further metastasize to distant organs like the liver, lung or bone or not, is currently unanswered [105]. The process of metastatic spread is highly complex involving more than 250 genes, multiple mutations and cell evolutions, and is organotropic [105-109]. Metastatic spread of tumor cells to regional lymph nodes via lymphatic vessels is not a passive, but a highly complex active process with specific interaction of tumor cells and lymphatic tissue [110]. If radio-labeled tumor cells are injected into the afferent nodal lymphatic vessel, they rapidly appear in the efferent lymphatic vessel and the thoracic duct, showing, that the lymph node is not only a simple cell-filter [111]. Metastasis to lymph nodes is positively correlated to enhanced peritumoral lymphangiogenesis, which results from expression of vascular endothelial growth factor (VEGF)-C. VEGF-C binds to the VEGF receptor (VEGFR)-3 on lymphatic endothelial cells and induces lymphangiogenesis [112, 113]. High levels of VEGF-C and VEGFR-3 are not only associated with an increase of lymph node metastasis but also with poor overall survival without affecting the growth of the primary tumor. VEGF-C-induced lymphangiogenesis in SLN promotes tumor metastasis spread to distant sites [114, 115]. These results implicate the possibility of further metastasis to distant organs from the lymph nodes via the thoracic duct. According to the soil and seed hypothesis of Paget the fate of a circulating tumor cell is also strongly controlled by the organ of metastasis resting upon complex cell-cell and cell-matrix interactions. Key players in lymph node metastasis are the chemokines CXCL12 and CCL21, produced by the lymphatic tissue. They are attractants for tumor cells which express the chemokine receptors CXCR4 or CCR7 [110]. High expression of these receptors is associated with higher incidence of lymph node metastasis in breast cancer patients [116, 117]. A significant number of patients show discordant quantitative expression of molecular markers between primary and nodal disease indicating a

organotropy [118]. This concept of organ site specificity corroborates the hypothesis, that lymph node metastases do not further spread or if they do only into lymph nodes down stream the metastatic one. The **lack** of lung metastases in patients with a palliative peritoneo-venous shunt in cases of malignant ascites impressively emphasizes this hypothesis [119]. But as a result of genetic instability, metastases that are initially of clonal origin, continuously acquire a genetic heterogeneity which could result in metastatic transformation of some cells, that permit a further spread to distant sites [119]. However, animal studies with inhibition of lymph node metastases are inconsistent and do not clearly confirm the hypothesis of a “metachronous seeding” [120].

It is widely accepted that also small tumors could early spread to distant sites. Micrometastases have occurred in 20-40% of carcinomas in the absence of other detectable signs of spread [88, 121]. Micrometastases as well as the number of circulating tumor cells are associated with the incidence of distant metastases as well as with the overall survival of breast cancer patients [122-124]. For patient's prognosis, these parameters of tumor spread could be more relevant than the likelihood of a metastasis from lymph nodes [125, 126]. Therefore we need effective treatment strategies for these probably stem cell like tumor cells [127-130]. In conclusion, there is increasing doubt, that lymph node metastasis are able to metastasize. The life threatening effect of lymph node metastases is overestimated.

### **Conclusion:**

**Increasing** data suggest that surgical management of the axilla by SLNB or ALND has no influence on recurrence-free and overall survival in all breast cancer patients. **However, sample size and length of follow-up are substantially different between cited studies, so that definitive conclusions can not be made.** Case reports suggest

that patients with axillary metastases alone after SLNB, who had undergone delayed ALND, have no prognostic disadvantage. With the exception of the ACOSOG Z0011 trial, there are no data from large randomized clinical trials that support or refute this hypothesis. There is high evidence to avoid any axillary surgery in elderly patients with favorable tumor biology (older than 60 years, pT1, G1-2, hormone sensitivity, no clinically and sonographically involved axillary lymph nodes).

It might be academically interesting to discuss about micrometastases and immunohistochemically detected tumor cells or tumor cell clusters in the SLN. On the other hand, we urgently need to initiate randomized clinical trials to avoid any axillary surgery in most patients with breast cancer and no clinically considerable enlarged axillary lymph nodes. As the ACOSOG Z0011 trial has shown, patients can be motivated to participate in randomized trials with restricted axillary surgery. Nonetheless, a rational and evidence-based approach to the management of clinically and sonographically N0 patients with planned BCS and limited tumor size is needed now. Risk estimates using the MSKCC nomogram to predict likelihood of SLN metastases may be helpful for the decision regarding pro or contra axillary surgery outside from clinical trials. In patients with BCS without any axillary surgery an additional regional treatment effect can be expected by postoperative external beam radiotherapy because traditionally defined tangential breast fields include the majority (60%-90%) of level I lymph nodes [62].

Surgeons, radiologists, and pathologists should work together to avoid unnecessary axillary surgery. There is an urgent need for simple but reproducible and validated sonographic criteria to categorize patients as cN0/iN0 (imaging N0) correctly in the preoperative setting. Future studies should also include patients with total mastectomy and favorable tumor biology to prove the value of axillary clearance for local recurrence and survival rates. It took some decades to replace the radical

Halsted theory by new paradigms including BCS. Similarly, the performance of axillary surgery has to be questioned.

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**Tab. 1: Diagnostic accuracy of FDG-PET in staging axillary nodes. Summarized results of a meta-analysis [20].**

Quality of Study*	Number of Studies / Pts.	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
A (best)	3 / 675	78	85	80	84
B	4 / 222	67	89	82	78
C	8 / 207	96	84	78	97
D (poor)	6 / 167	78	99	99	76

\* depending on number and selection of patients, technical details of examination, pro- or retrospective design, method of lymph node biopsy.

**Tab. 2: Diagnostic accuracy of MRI in staging axillary nodes.**

Author	Number of pts.	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Harada (2007) [24]	33	86	97	91	96
Stadnik (2006) [25]	10	100	80	80	100
Murray (2002) [26]	47	100	56	38	100
Michel (2002) [27]	20	82	100	100	-
Memarsadeqhi (2006) [28]	22	100	98	98% accuracy	
Suzuma (2002) [29]	62	91	100	91% accuracy	
Stets (2002) [30]	9	63	86	75% accuracy	



**Tab. 3:** Reasons for and against knowledge of lymph node status for treatment decisions.

Contra	Pro
<ul style="list-style-type: none"> <li>• Tumor biology is more important than nodal status regarding prognosis and treatment</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Treatment mismatch if node status is unknown (especially in ER-positive, HER2-negative disease)</b></li> </ul>
<ul style="list-style-type: none"> <li>• Any axillary surgery increases costs and morbidity</li> </ul>	<ul style="list-style-type: none"> <li>• <b>dose-dense and/or dose-intense chemotherapy in patients with 4 or more involved lymph nodes</b></li> </ul>
<ul style="list-style-type: none"> <li>• Axillary recurrences are very seldom, even in node positive patients</li> </ul>	<ul style="list-style-type: none"> <li>• Resection of metastases as a potential source of distant metastases</li> </ul>
<ul style="list-style-type: none"> <li>• Delayed surgery of involved lymph nodes is without overall survival disadvantages</li> </ul>	<ul style="list-style-type: none"> <li>• Tumor volume reduction</li> </ul>
<ul style="list-style-type: none"> <li>• Distant metastasis even in pN0 patients</li> </ul>	<ul style="list-style-type: none"> <li>• Nodal status as an indicator for or against radiotherapy after mastectomy</li> </ul>
<ul style="list-style-type: none"> <li>• Seldom axillary metastases in patients with medial tumor location,</li> </ul>	<ul style="list-style-type: none"> <li>• pN for staging, study inclusion and comparison of outcome necessary</li> </ul>
<ul style="list-style-type: none"> <li>• Systemic treatment acts also in axillary lymph node metastases</li> </ul>	
<ul style="list-style-type: none"> <li>• There is no evidence that lymph node metastases are able to metastasize</li> </ul>	
<ul style="list-style-type: none"> <li>• Leaving involved lymph nodes in situ does not increase axillary recurrences or metastasis</li> </ul>	

**Tab. 4:** Prospective randomized clinical trials comparing axillary lymph node dissection versus no axillary surgery. Veronesi et al. randomized patients with no axillary surgery to none further treatment versus radiotherapy of the axilla.

	Pts.	N	Follow-up (mo)	Axillary recurrences	DFS	OAS
Rudenstam (2006) [54]	>60 y, pT1-2* cN0,	473	78	0.9 vs 2.5%	67% vs 66% p=.7	75% vs 73%; p=.8
Martelli (2005) [55]	>65 y, pT1 cN0, Tam	219	60	0 vs 1.8%	95% both p=.9	96% both p=.9
Veronesi (2005) [56]	>45 y, Tumor <1.2 cm, cN0,	435	63	0.5 vs 1.5%	97 vs 95% p=.19	99 vs 97% p=.23

\* 42% pts. with tumors >2 cm, y = years, **mo = months**

DFS = disease-free survival

OAS = overall survival

**Tab. 5: Summary of studies reporting outcome (follow-up >24 months) of patients (case numbers  $\geq 150$ ) with isolated tumor cells pN0(i+) and micrometastasis pN1mi (International Union Against Cancer classification, >.2 mm to  $\leq 2.0$  mm) in sentinel lymph node (SLN)**

Author	Study design	Accrual period	N	Follow-up	
Weaver (2011) [96]	prospective, multicenter	1999-2004	3,887	95.6 mo	Occult metastases pN1a) in initial nega significant impact o
Maaskant-Braat (2011) [97]	population-based	1996-2006	6,803	50 mo, 36 mo for pN0(i+)	pN1mi or pN0(i+) in significant OAS diff (discrimination betw
Langer (2009) [80]	prospective cohort	1998-2002	150	77 mo	No significant differe between pN0 and pN
de Boer (2009) [89]	population-based	before 2006	2,707	5.1 y	pN(i+) and pN1mi s 5y-DFS in cases wi
Montagna (2009) [98]	prospective cohort	1997-2002	3,158	6.3 y	Among SLNB group pts. with pN0 or mini micrometastasis 0.2
Reed (2009) [92]	prospective, multicenter	1996-2005	1,259	4.9 y	pN1mi, but not pN0 positive nodes (27% recurrence rate
Gobardhan (2009) [99]	prospective cohort	1999-2007	703	40 mo	Risk of distant meta than in pN0 group, or OAS between pN
Tan (2008) [86]	retrospective	1976-1978	368	17.6 y	Clear trend toward w increasing tumor clu
Cox (2008) [100]	retrospective review	1997-2004	2,381	1.5-2.1 y	Poorer OAS/DFS for pts.; additional axilla pN0(i+)
Nagashima (2006) [101]	prospective cohort	1999-2004	375	30 mo	No difference in DMF
Imoto (2006) [102]	retrospective cohort	1998-2000	165	73 mo	No difference in 6y-D and pN0 pts.
Fan (2005) [103]	retrospective	1997-2002	390	31.1 mo	No difference in LRF

OAS = Overall survival, DMFS = Distant metastases-free survival, DFS = Disease-free survival; BCSS = Breast cancer-specific survival, pts. = patients; LRR = Local recurrence rate; mo = months; y = years; ITC = isolated tumor cells