The Risk of Non-sentinel Metastases in Primary Breast Cancer

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Abstract. Background: Sentinel node biopsy (SNB) has been established as standard of surgical care in primary breast cancer. If the sentinel node (SN) is negative, axillary dissection (ALND) is not necessary, but if the SN is positive ALND is warranted. This analysis evaluated associated risk factors for non-sentinel metastases in the case of a positive SN. Patients and Methods: A retrospective analysis of all SNB performed between 10/1999 and 07/2005 was carried out. Results: A total of 406 patients were included: 214 patients (51%) had SNB with ALND while 197 patients (49%) had SNB only. In 41 of 109 nodal-positive patients, the SN was the only nodal metastasis. In the multivariate analysis, the number of positive SN and the presence of lymphatic vessel infiltration were significant risk factors for additional non-sentinel metastases (p=0.05 and 0.047, respectively). The risk for non-sentinel metastases was 25.9% without and 59.2% with these risk factors, respectively. Conclusion: If the SN is positive, ALND remains obligatory.

The axillary lymph node status is still the strongest prognostic factor in primary breast cancer: 60% of all patients have a node-negative axilla at the first time of breast cancer diagnosis (1). In these patients, complete axillary dissection (ALND) causes considerable perioperative morbidity reducing quality of life for at least five years after surgery (2). Thus sentinel node biopsy (SNB) has become an alternative of surgical care in primary breast cancer. SNB allows correct and reliable staging of the axillary nodal status with significantly reduced shoulder arm morbidity (3, 4). It is generally accepted that ALND can be omitted if the sentinel node (SN) is negative (5, 6).

ALND after positive SNB is still mandatory to achieve complete local tumour control and correct nodal staging, although there are several studies showing that the SN is the only tumour-burdened lymph node after complete ALND. Different clinicopathological factors, such as the size of the primary tumour, lymph vessel infiltration (LVI) and the size of the sentinel metastasis, have been found to be predictors of further axillary involvement after positive SNB (7-12).

This analysis will contribute data to the issue as to in which subset of breast cancer patients a complete axillary dissection can be avoided in a routine clinical setting in the case of a tumour-positive sentinel node.

Patients and Methods

Between 10/1999 and 7/2004, 510 SNBs were performed in patients with histologically proven primary breast cancer in our institution. Histological diagnosis was confirmed by core needle biopsy preoperatively (n=450) or by frozen section during the surgical procedure (n=52). For this analysis, all patients who underwent SNB because of ductal carcinoma in situ (DCIS) were excluded, as were those who had received neoadjuvant chemotherapy, or previous excisional biopsy.

All SNBs were performed with combined blue dye and radiocolloid injection. All patients received a lymphoscintigraphy either the day prior to or on the day of surgery. The dose of the injected radioisotope was 20-30 MBq the day before surgery or 10-12 MBq on the day of surgery.

The 99mTc-colloidal albumin (Nanocol®) was injected peritumorally before lymphoscintigraphy, patent blue dye (Patentblau®) was injected subdermally in the operating theatre at least 5 min before surgical incision. For patients with a non-palpable tumour, the radiotracer was injected subdermally in the region of the upper outer quadrant.

An intraoperative gamma-detecting probe (C-Trak, Care Wise Medical, Palo Alto, CA, USA) was used to identify the SN(s). Intraoperative identification of the SN was based on gamma probe detection and blue dye mapping. An SN is

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defined as any blue-stained lymph node or any node with \textit{in vivo} radioactive count more than 3-fold that of the background count (13).

For intraoperative frozen section histological examination, the sentinel nodes were bisected and one half of the nodes stained with haematoxylin-eosin (H&E) and 150-µm sections were taken. The remaining half of the sentinel tissue was embedded in paraffin and sections of 500-µm were taken for final histopathological assessment. No routine immunohistochemical staining was performed.

ALND was completed when the frozen section or the final histopathological result showed one or more positive sentinel nodes. One 25-year-old patient with a T1 hormone receptor-positive and Her2/neu-negative breast cancer exhibited a 3 mm metastasis in only one of 2 sentinel nodes and refused further axillary dissection.

All patient records were reviewed for statistical evaluation. Statistical analysis was performed using logistic regression analysis. Tumor size (T1 \textit{versus} all other sizes), lymphatic vessel infiltration (LVI presence \textit{versus} absence), menopausal status (pre- \textit{versus} postmenopausal), hormone receptor status (positive \textit{versus} unknown \textit{versus} negative), grading (G1 \textit{versus} G2 \textit{versus} G3) and number of positive sentinel nodes (1 \textit{versus} more than 1 positive lymph node) with non-sentinel involvement were tested for correlation. A \textit{p}-value of 0.05 or less was regarded as statistically significant.

\textbf{Results}

A total of 406 patients were included in this study. The median age of all patients was 58.2 years with a range from 29 to 90 years.

The sentinel node was detected in 93% of cases. The average number of SN removed was 2.04. Although the SN was node-negative, we found one or more positive axillary lymph nodes in 3 cases out of a total of 109 node-positive patients, accounting for a false-negative rate of 2.75%.

In 197 patients (49%) the SN was tumour-free and SNB was the only axillary intervention. A total of 209 patients (51%) had SNB with consecutive ALND, whilst 100 patients had both surgical interventions during the implementation and training phase. In 109 patients with ALND (27%), axillary metastases were diagnosed. In 41 of these 109 patients (38%), the SN was the only site of nodal metastasis: 9/41 patients (22%) had only sentinel micrometastases. To date, none of the 406 patients has suffered from axillary recurrence.

In the multivariate analysis, the number of positive sentinel nodes \textit{p}=0.005; relative risk (RR) 4.2, 95% confidence interval (CI) 1.5-11.3 and lymph vascular invasion \textit{p}=0.047; RR 3.3, 95% CI 1.0-10.7) were independent and significant predictors of non-sentinel metastasis. No influence on non-sentinel metastasis could been seen with menopausal status, grading or hormone receptor status. The tumour size nearly reached a significant level at \textit{p}=0.057. A total of 9 micrometastases were found in the SN and only in one patient with a micrometastatic SN were a further 3 non-sentinels found.

The patient characteristics as well as sentinel and nodal status are shown in Table I.

\textbf{Discussion}

ALND as a diagnostic procedure has a marked acute and chronic morbidity. ALND as a therapeutic option is still a focus of debate. The meta-analysis of Orr showed a 5.4% survival benefit after ALND (14), but systemic therapy in all of the 6 studies of this meta-analysis was insufficient (15). Other authors claim axillary lymph node involvement as a marker for tumour cell dissemination and not as a potential source of tumour dissemination itself (16). This hypothesis
may be supported for a subset of patients with the results of the IBCSG 10-93 trial: between 1993 and 2002 the International Breast Cancer Study Group conducted a trial with women older than 60 years with clinically node-negative operable breast cancer in whom adjuvant tamoxifen was considered indicated, regardless of pathological nodal status. Patients were randomly assigned to primary surgery plus axillary clearance followed by pathological nodal status. The IBCSG found no statistical difference in the axillary recurrence rate or in the disease-free or overall survival rates (17).

SNB has become a clinical routine alternative to ALND to reduce shoulder arm morbidity as long as the SN is tumour-negative. As noted above, surgical therapy and/or irradiation (18-20) influence survival of breast cancer patients cannot be excluded. For this reason, complete ALND is still mandatory if the SN is tumour-positive.

There are different studies and a small meta-analysis (21) that showed the SN to be very often the only site of nodal metastasis. The following factors were validated that may predict no further nodal involvement in case of a positive sentinel node: small size of the primary tumour (T1a and T1b), no lymph vascular invasion and small size of the sentinel metastasis [micrometastases or metastases detected only by immunohistochemistry (IHC)].

In our study we confirmed the influence of lymph vascular invasion on additional axillary node involvement. The number of positive non-sentinel lymph nodes was evaluated as an independent predictive risk factor for further lymph node metastases. A subset analysis of the NSABP B 32 trial, presented at the San Antonio Breast Cancer Symposium 2005, confirmed these findings (22). In our study, the number of histologically proven micrometastases was low, with n=9 patients, and only one patient was diagnosed as having additional positive lymph nodes. No statistical analysis was performed with this finding due to the small sample size.

According to the national recommendations on SNB (6), immunohistochemical investigation of SN is not part of our routine procedure. In contrast to the literature, an increasing size of the primary breast tumour showed no predictive risk for non-sentinel metastases. The great majority of patients who underwent SNB in our clinic had pT1c tumours, where the risk of positive sentinel lymph nodes does not exceed 35%. Therefore the number of larger tumours (>pT2) might be too small in this study to detect a statistical influence of larger breast cancers on non-sentinel metastases.

The meta-analysis of non-sentinel involvement described a 15-20% risk of positive axillary lymph nodes in the case of sentinel micrometastases that were diagnosed using H&E staining, and a risk up to 10% of further positive axillary nodes after detection of IHC-positive SN (21). In our study, the risk of further nodal involvement was minimally higher (25.9%) for those patients who had only one positive sentinel node without any additional risk factors. However, in the case of at least one coexisting risk factor, the risk of non-sentinel metastases increased dramatically up to 59%.

Following the recommendations of the German Society of Senology and the ASCO guidelines (5, 6), SNB with a micrometastatic finding in one or more sentinels should be followed by classic ALND, even though in 75-80% of patients it is only to demonstrate that no other lymph nodes are involved. No further ALND is recommended for IHC-positive sentinels because of the uncertain prognostic value of these findings. Following the recommendations of the St. Gallen consensus conference for adjuvant systemic treatment, almost 95% of all patients with primary breast cancer receiving any kind of systemic treatment should expect a reduction of local recurrence by 2-13.4% (23). The risk of axillary relapse after avoiding further axillary clearance after a micrometastatic and risk-free positive sentinel therefore seems to be very low. However, ALND after a positive SN as determined using H&E staining is still strictly recommended. The question whether this can be avoided will perhaps be answered by the ACOSOG Z-010 and Z-011 trials.

**Conclusion**

In this retrospective analysis of 406 consecutive patients with SN biopsy between 1999 to 2004, we investigated predictive factors for non-sentinel lymph node involvement. Routine H&E staining was performed in all cases, the immunohistochemistry examination in the clinical routine setting was not established. Of 109 nodal-positive patients, 41 showed the sentinel node to be the only site of axillary metastasis. In concordance with the literature, the risk of non-sentinel metastases increased with lymph vessel infiltration and the number of positive SNs. The number of patients with only microscopic sentinel metastasis was too small in this study to reach statistical significance. Although it is still unclear whether omission of axillary clearance after findings of a microscopic positive sentinel has substantial influence on survival, ALND in such a situation should be performed unless further data are available.

**References**


