The Sentinel node in breast cancer: implications for adjuvant treatment?

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Axillary lymph node involvement: prognostic and therapeutic consequences

Despite continuous efforts to define more advanced and less invasive prognostic factors, surgical staging of the axilla remains the single most important prognostic factor in localized breast cancer. Axillary lymph node dissection (ALND) of the lymph nodes at levels I and II, and level III when metastatic involvement is suspected, should provide an answer as to whether metastatic spread to the axilla has occurred. In addition to the presence of axillary involvement per se, the number of axillary nodes involved has a supplementary prognostic impact. In general the axillary lymph node status is defined as follows: 0, 1–3, 4–9 or >10 involved lymph nodes, with crude 10-year survival rates of 65%–75%, 45%–60%, 25%–30% and <20% respectively. Besides prognostic implications, the number of involved lymph nodes also has therapeutic importance. Systemic adjuvant chemotherapy is offered to all lymph node-positive patients and, as recently reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), produces an absolute improvement of 11% in the 10-year survival of node-positive patients. However, further improvement is clearly warranted and in patients with high-risk primary breast cancer, defined by some authors as having ten or more lymph nodes and by others as having four or more, the value of high-dose chemotherapy with peripheral blood stem cell support is being investigated. Results of the first large randomized trials will be reported in the near future but it is generally not expected that high-dose chemotherapy will have the tremendous impact that was hoped for. In the coming years it is anticipated that the focus of adjuvant treatment will be on further defining the importance of changing the schedule and sequence of relatively standard-dose chemotherapy. In addition, immunotherapy with antibodies against oncogenes, with or without chemotherapy, the development of oncogene/whole cell vaccinations and the importance of interfering with the angiogenesis process will be evaluated.

While axillary lymph node invasion is highly indicative for the prognosis, it clearly is not the only important factor since 25%–35% of patients with node-negative disease die of disease within 10 years of diagnosis. High-risk features of the primary tumour such as size, histological grade, nuclear grade, hormone receptor status and vascular and lymphatic invasion, may override the favourable prognosis as determined by the axillary status. In the EBCTCG overview of 69 trials in 36 000 women the proportional reduction in recurrence and mortality due to adjuvant polychemotherapy was independent of nodal status, with a 7% absolute improvement in 10-year survival in the node-negative patients. Does this imply that adjuvant systemic treatment should be given regardless of the axillary nodal status? The International Consensus Panel on the Treatment of Primary Breast Cancer recently published their recommendations on adjuvant treatment, which are as follows: All lymph node-positive patients should be offered some form of chemotherapy and/or tamoxifen. In lymph node-negative patients it is recommended that patients be categorized into minimal/low risk, intermediate and high-risk groups, where pathological tumour size is considered the most important risk factor. In patients with a tumour size <1 cm, positive oestrogen receptor status, histological and nuclear grade I (the relevance of which is uncertain at this tumour size) and age above 34 years, administration of tamoxifen is optional. If any of these factors are lacking, adjuvant systemic treatment with chemotherapy and/or tamoxifen should be offered.

In view of the foregoing information, what will be the role of sentinel node (SN) biopsy with regard to both prognosis and therapy?

Sentinel node biopsy: implications for adjuvant treatment

In recent years, the intensified mammographic screening programs have resulted in a documented increase in the incidence of patients presenting with T1 tumours. With the well-known relationship between tumour size and risk of axillary lymph node involvement, the number of patients who will undergo ALND for what will appear to be a pathologically negative axilla will increase. Overall, in 70%–80% of patients with localized breast cancer and a clinically negative axilla, pathological examination of the axillary lymph nodes removed by ALND will confirm the clinical findings. Morbidity due to ALND, such as lymphoedema, seromas requiring aspiration and neurological symptoms, has been reported to interfere with daily living in 39% of patients. There is an obvious need for different methods that can obviate unnecessary morbidity while providing similar or even improved diag-

nostic accuracy. In evaluating alternative methods one should, however, consider whether omission of ALND potentially results in loss of therapeutic benefit. Several studies have reported an increased axillary recurrence rate in those patients who did not receive ALND, though the influence on survival seems more controversial. Radiotherapy to the axilla instead of surgical intervention has been reported to be eihter slightly less or equally effective with regard to recurrence, but all of the studies in question were non-randomized.

Of the various approaches that may be used to evaluate the axillary lymph node basin, pathological examination of the SN, defined as the first draining lymph node from the primary tumour, has proven to be the best predictor for metastatic involvement of the axilla. In the largest study published so far, the positive and negative predictive values were 100% and 96% respectively with a specificity of 100% and a sensitivity of 89%. The sensitivity is lower than reported in most other studies but the authors expect that the sensitivity will improve upon application of different methods of injection and adjusted positioning of the patient. Therefore, although the issue of the most accurate and most easy reproducible method of identification of the SN has not yet been resolved, it seems fair to anticipate that SN biobsy will come to replace ALND in patients with T1 and small T2 breast tumours. Indeed, some institutions have already decided to refrain from ALND in T1 breast cancer with a negative SN. Whether this will have an impact on the percentage of axillary recurrences remains to be seen, and may also depend on whether additional adjuvant treatment is given.

What might be the consequence of the SN procedure with regard to indications for systemic adjuvant treatment?

As long as features of the primary tumour such as histological and nuclear grade, oncogene expression and microvessel density have not been proven to have the same prognostic value as the number of involved axillary lymph nodes, a positive SN biopsy should be followed by ALND of levels I and II. As stated above, systemic adjuvant treatment is still modified according to the number of LNs involved. Should other factors in combination with a positive SN prove able to provide the same information with regard to prognosis and therapeutic intervention, radiation therapy could be considered as an alternative to reduce the risk of local recurrence.

One caveat in the SN procedure is that, in evaluating its significance as a prognostic and therapeutic tool, careful pathological examination of the SN using additional methods has revealed micrometastases (<2 mm) in LNs that otherwise would have been considered negative. In general, 9%–33% conversion from node-negative to node-positive disease by immunohistochemical staining (IHC) has been reported. More recently, reverse transcriptase-polymerase chain reaction (RT-PCR) has been applied to detect marker genes and has been reported to detect micrometastases in 3%–55% of axillary lymph nodes without metastases by conventional haematoxylin and eosin staining (HE) and IHC. However, differences in the sensitivity and specificity of the various RT-PCR assays need to be determined before routine application is allowed. The prognostic significance of these micrometastases differs in the various (retrospective) reports from no influence on overall survival to a significant decrease in disease-free as well as overall survival. It has been argued that the fact that the proportional reductions in recurrence and mortality following adjuvant chemotherapy are independent of the nodal status, with a 7% absolute benefit in 10-year survival (see earlier) in node-negative patients, might be explained by treatment of patients with micrometastatic lymph node disease.

What will be the therapeutic relevance of micrometastatic disease in the SN? Firstly, the predictive value of an SN with only micrometastases needs to be established. If, upon IHC or RT-PCR, an SN converts from tumour-negative to micrometastatic-positive should a routine ALND then be performed? Furthermore, what should be the systemic approach in patients in whom only the SN is involved with micrometastatic disease? Based on the recommendations of the International Consensus Panel, as mentioned above, all patients with a T1c tumour size or larger should be offered adjuvant systemic treatment regardless of their nodal status. This policy has already been implemented in many institutions. So, the finding of micrometastatic disease by IHC or RT-PCR could have an impact with regard to systemic adjuvant treatment in patients with T1a and T1b disease. If one decides that the presence of micrometastases in the SN has the same impact on outcome as a positive LN found by routine histological examination, then more patients with small tumours will receive adjuvant chemo- and/or radiotherapy. It comes down to the consideration that the >95% 5-year survival in T1a–b disease is decreased by the presence of micrometastases in the SN in such a way that it outweighs the morbidity (including the chance of permanent infertility and early menopause in young patients) and costs associated with the administration of adjuvant chemotherapy.

So, SN biopsy might induce a danger of over-staging and therefore over-treatment of the patient with a T1a–b tumour, but could it also result in under-treatment? Failure to identify the SN or the presence of skip metastases could result in a false-negative SN procedure. As stated earlier, it is expected that the sensitivity rate will be improved by adapting the methods of identification. Skip metastases to level II, which will be found by ALND but not by SN biopsy, have been reported to occur in <5%. On the other hand, non-axillary drainage such as to the internal mammary chain can be identified by the radioisotope SN procedure but not by a routine ALND. In general it is thought that in 9%–17% of lymph nodes removed by ALND, the metastases are missed by the pathologist. It therefore seems that for an individual patient the chances of being under-diagnosed are not likely to be higher following an SN procedure then after an ALND.

And again, if the recommendations of the Consensus Panel, with regard to systemic adjuvant treatment are followed a false-negative procedure would only have an impact for patients with T1a–b breast tumours, for whom treatment with tamoxifen is optional.

In conclusion, with its high positive predictive value and the expected improvement of its sensitivity, SN biopsy will probaly prove of benefit as a prognostic indicator of axillary lymph node involvement. However, the prognostic significance of micrometastatic disease in the SN needs to be addressed. With regard to the therapeutic implications, omission of ALND might result in an increase in the percentage of axillary recurrences, especially in false-negative cases.

Finally, with more advanced histopathological methods of identification of metastatic disease, the percentage of patients with SN-positive disease will increase. This could have an impact on the treatment of patients with small T1a–b tumours for whom systemic adjuvant therapy otherwise would have been optional. In this regard it is again essential to define the prognostic impact of "micrometastatic-only" SN disease. Characteristics of the primary tumour might have to be taken into account in order to make a decision as to who should and who should not receive adjuvant systemic treatment. Obviously, a randomized approach will provide the best answer and this should be thoroughly considered in the design of future studies.

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