E7. Clinical consequence of a positive sentinel node

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Sentinel node procedure: the standard of care

From the ever-growing published experience on the sentinel node procedure in breast cancer, it becomes clear that this procedure is here to stay. In experienced hands, it offers the same staging opportunities as a full axillary clearance. From the last St Gallen consensus discussion in March 2005 [1], it was clear that sentinel node biopsy is considered standard for lymphatic staging in patients with invasive breast cancer <3 cm, and no clinical involvement of ipsilateral axillary lymph nodes.

Uncertainty still exists on the role of sentinel node biopsy as a lymphatic staging procedure, in relation to upfront or neoadjuvant chemotherapy, in multifocal or larger (particularly >5 cm or locally advanced) breast cancers, and in ductal carcinoma *in situ* (DCIS).

When can the sentinel node procedure be considered as standard of care [2,3]?

- If a surgeon and his/her team can show a low false negative rate (<5%);
- If a surgeon and his/her team can show a high identification rate of the sentinel node (over 95%).

The lowest false negative and highest identification rates are achieved when the surgeons/gynaecologists:

- Use the combined technique by pre-operative lymphoscintigraphy, pre-operative injection of blue dye and intra-operative use of blue dye and Gamma-probe;
- are experienced (learning phase of at least 20 procedures performed personally, and a caseload of more than 6 procedures per month);
- Work within a multidisciplinary team with the nuclear medicine specialist and pathologist.

From two large European studies [4,5] it is clear that when these criteria are met, the identification rate is high (Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial: 96%, After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial: 98%). Both trials have an intensive audit and quality control programme, which has led to these satisfactory figures.

If the quality criteria are met, the clinical false positive rate, i.e. the number of patients with axillary lymph node metastases after a negative sentinel node procedure, is low: approximately 0.5% after an average of 3–4 years of follow-up [6].

Once cancer cells are found by the pathologist, the following questions arise:

- What is a +ve sentinel node?
- Prognostic value: always adjuvant treatment?
- Where is the +ve sentinel node (the issue on non-axillary nodes)?
- Optimal regional treatment of +ve sentinel node?

Micrometastases, isolated tumour cells and prognosis

One of the pressing questions in the treatment of breast cancer patients is the clinical relevance of micrometastases (0.2–2.0 mm) and submicrometastases (<0.2 mm) in the sentinel node. Since the introduction of the sentinel node procedure, the pathological work-up has changed markedly. Sentinel nodes are evaluated at multiple levels, stained with both haematoxylin-eosin and immunohistochemistry (CAM 5.2), and now a single tumour cell is occasionally distinguished. The clinical implications of these small metastases are unknown. Are isolated tumour cells capable of producing regional and distant recurrences? What is the chance that more nodes are involved? Should patients with a micrometastasis in the sentinel node be advised to undergo axillary lymph node dissection? A meta-analysis by Cserni and colleagues has shown that the rate of non-sentinel node involvement in the presence of micrometastatic and submicrometastatic disease in the sentinel node is 20% [7]. This rate is 9% if only immunohistochemically detected metastases are identified. Several studies have focused on possible factors associated with non-sentinel node metastasis: a tumour load in the sentinel node greater than 2 mm, extranodal extension of a metastasis, more than one tumour-positive sentinel node, a >2 cm diameter of the primary tumour, and lymphovascular invasion of the primary tumour [8–15]. Few studies about the long-term follow-up of patients with micrometastasis have been published [16]. Some authors find that the presence of micrometastatic disease in axillary nodes has an effect on both disease-free survival and overall survival [17–19]. Others find no relationship between these two, but show an association between the primary tumour characteristics and the prognosis [20,21].

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Currently, this issue remains unsolved. Patients with isolated tumour cells in the sentinel node have a moderate chance of additional metastasis and may have a somewhat worse overall prognosis compared with patients with tumour-negative sentinel nodes. For now, it seems one should consider both the tumour load of the sentinel node as well as the primary tumour characteristics when advising a patient with regard to complete axillary lymph node dissection. With regard to adjuvant systemic therapy, some patients will receive chemo- or hormonal therapy based on the primary tumour characteristics, hormonal receptor status, or the patient's age. As patients with micro- and isolated tumour cells are not considered N1 patients, adjuvant treatment is not routinely offered.

Non-axillary sentinel nodes

Lymphatic drainage from the breast is primarily towards the lower axilla, but other sites where metastatic tumours may travel include the internal mammary chain, level III of the axilla (subclavicular group), the supraclavicular fossa, the pre-pectoral nodes (intramammary nodes) and the interpectoral group [22–25]. Many surgeons remove only the axillary nodes, for the pursuit of the other modes may be time-consuming and technically demanding. The presence of metastasis in locations outside the axilla seems to indicate a worse prognosis compared with patients with no metastasis at all. Patients with tumour-negative sentinel nodes in the axilla and tumour-positive ones in the internal mammary chain have an equal prognosis and vice versa. The prognosis is even worse when both basins contain metastasis [27–29]. Tumour-positive intramammary nodes are also predictors of poor outcome [30].

Even though involved non-axillary nodes influence prognosis, it is debatable whether treatment of these nodes improves survival. Some studies demonstrated a survival benefit by treating nodes in the internal mammary chain [26,31] while others show no difference [32]. In the Netherlands Cancer Institute, nodes outside the axilla are pursued and non-axillary sentinel nodes are visualised in approximately 27% of patients. Two-thirds of these nodes are in the internal mammary chain. In total, of the patients in whom the unusually situated node was pursued, 16% contained metastasis. The treatment was altered in 18% of these patients to more appropriately serve their individual needs [33–35]. Since nodes in the axilla, internal mammary chain and intramammary nodes seem to be of clinical relevance, we assume that this is true for all sentinel nodes regardless of their location.

Summary

In patients with macro- or micro-metastases >0.2 mm in their sentinel lymph nodes from the axilla, further treatment of the axilla is advised. Complete axillary clearance is standard of care.

If metastases are found in sentinel nodes removed from sites other than the axilla, radiation therapy of the regional lymph node area (internal mammary chain, periclavicular) seems warranted.

The event of macrometastases in any sentinel lymph node will put the patient in a higher prognostic risk category, for which adjuvant systemic treatment is indicated. The independent prognostic relevance of micrometastases (<0.2 mm) only is unclear, and the patient may have at maximum a slightly impaired prognosis; here the primary tumour characteristics should prevail in the indication for adjuvant systemic treatments.

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