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Controversy

Sentinel node procedure in breast carcinoma: a valid tool to omit unnecessary axillary treatment or even more?

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No one will deny that the existence of lymph node metastasis from invasive breast carcinoma will impact upon the management of the patient as metastasis is associated with a worse prognosis and early treatment leads to a better regional tumour control. More debate exists with regard to the impact of early treatment of lymph node metastasis on overall survival rates [1,2]. Furthermore, it is known that lymphatic dissemination to the axilla follows an orderly pattern [3]. This notion is the basis of lymphatic mapping by the sentinel node concept, as developed for breast cancer by Morton and Guiliano [4]. The concept of sequential dissemination in an orderly fashion has been proven in numerous studies [5]. In addition, it is also known that the breast drains to different nodal basins with a 'main stream' to the axilla. Consequently, lymph node metastases from breast carcinoma are usually found in the axillary basin, but may also be found in the internal mammary chain nodes [6], or even in infra- or supraclavicular or intramammary nodes [7]. With regard to the prognostic value of nodal metastasis, the more tumour-positive nodes that are found, the worse the prognosis of the patient [8]. The involvement of more basins is also prognostically unfavourable [6]. Furthermore, if more tumour-positive nodes are found, combined modality treatment leads to a better locoregional control and survival [9]. Of note, if more tumour-*negative* nodes are found, the patient has a better prognosis [10]. So, if only a few nodes are removed and examined, the prognosis of the patients and locoregional control is worse. It is most likely that it is not the number of removed and examined nodes that is the most important factor, but whether the right node is found and removed, i.e. whether the tumour-positive node is found. Thus, the better the lymphatic staging that is carried out, the better the management and subsequent outcome of the patient.

How, though, are the 'right' tumour-positive node(s) identified to exclude reliably any possible spread? In short, all non-invasive imaging techniques will fail because of their insufficient sensitivity. So the 'right' node has to be removed surgically and carefully examined by the pathologist. One should keep in mind that finding lymph node metastasis primarily serves a diagnostic aim: once lymphatic dissemination is found, locoregional and systemic therapy will follow. Exclusion of lymphatic spread will result in the omission of unnecessary treatments.

Thus the 'right' node has to be removed surgically: but how is this to be achieved? Do we use a complete axillary lymph node dissection (ALND)? Do we use three-, or four- or five-node sampling techniques? Do we use triple node sampling, internal mammary chain node biopsy, infraclavicular node biopsy? Do we use a sentinel node procedure?

Lymphatic mapping by the sentinel node procedure looks very logical and attractive for this purpose. In this issue, Rampaul and MacMillan challenge the validity of the sentinel node procedure in breast cancer because they argue that the science behind the sentinel node procedure is poor due to the lack of uniformity in definitions and techniques, and the lack of any randomised evidence with regard to its efficacy [11]. Nieweg and Bartelink take the sentinel node biopsy procedure a step further: they believe the concept to be proven as valid and advocate lymphatic mapping as a means to find or exclude lymph node metastasis in other places than the axilla in order to improve staging [12].

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The sentinel node procedure in breast cancer is a diagnostic tool, nothing more or less. It has nothing to do with treatment. A new diagnostic tool needs the following steps for its widespread implementation:

1. Biological proof of the concept
2. Validation: the procedure should be equal or better than the standard procedure
3. Standardised (quality assurance)
4. Easy to perform (to master)
5. Low morbidity
6. Cost-effective
7. Application should be possible in routine clinical practice.

As stated, the concept of sequential lymphatic spread of breast cancer is sufficiently proven: lymphatic dissemination of breast cancer is not a random event.

Is the sentinel node procedure sufficiently validated for its purposes? The question raises another of what 'golden standard' the sentinel node procedure should be compared with. In my opinion, there is no 'golden standard' for the identification of lymph node metastasis in invasive breast cancer. The 'full' or 'complete' axillary clearance may result in excellent regional tumour control (but has the drawback of morbidity for what might be unnecessary surgery) and the identification of lymph node metastasis. However, this procedure has a 'false negative' rate of up to 10–20% if the negative nodes are further examined by meticulous histological procedures [13,14]. Thus, even after axillary clearance lymph node metastasis in the axillary region may be missed. It is my educated guess that the randomised studies comparing the sentinel node procedure with axillary lymph node dissection (ALND) (The Milan study performed by Veronesi and co-workers, the National Surgical Adjuvant Breast (NSABP) B-32 from the US and the ALMANAC trial from the UK), will all show identical axillary node-positive rates, and much less morbidity for those patients who have had sentinel node biopsy only.

Evidently, after ALND, lymph node metastasis at other sites will be missed as well. All other sampling procedures will result in somewhat more or less false-negative procedures. The five-node sampling procedure, as performed by Ahlgren and colleagues [15], may also provide for adequate information on lymph node involvement in the axilla, as the false-negative rate measured by a back-up axillary clearance is compared with that of the sentinel node procedure.

In experienced hands, the sentinel node procedure will identify over 95% of the axillary lymph node micrometastasis in all node-positive patients; in other words, missing the positive nodes in 0–5%. Of course individual small series will have large Confidence Intervals (CIs) in the false-negative rates, but the current evidence compiled suggests a 0–5% false-negative rate after back-up axillary clearance [16]. The published series on a 'wait-and-see' policy after a negative sentinel node procedure shows a clinical false-negative/axillary relapse rate of 0–1% [17–20], although this is after a relatively short follow-up.

Lymphatic mapping by the sentinel node procedure is able to identify axillary lymph node metastasis in most patients, irrespective of the tracer technique that is used, and may thus be compared with other surgical techniques dedicated to find axillary lymph node metastases. Lymphatic mapping is better than ALND or four-node sampling as it may identify lymph node metastasis beyond the axilla: in the internal mammary chain nodes, intramammary and infra- or supraclavicular nodes. This 'extra-axillary mapping' is only accomplished if tracers are injected in the breast parenchyma in or near the tumour: only in that situation is the retromammary lymphatic drainage reached this and will lead to nodes at the aforementioned sites [21]. However, the clinical relevance of finding lymph node metastasis at these sites is an area of debate [22–24]. Will better staging result in better outcomes? Data from the previous experiences suggests that, improved staging of axillary lymph node metastasis will lead to better outcomes. Therefore, it is likely that better staging of lymph node metastases at other sites will also lead to better outcomes.

What may be the advantages of finding lymph node metastasis at other sites?

Firstly, the finding of lymph node metastasis while the axillary lymph nodes are negative may result in the upstaging of the patient. Since most node-negative patients will receive adjuvant systemic treatment on the basis of their primary tumour characteristics, this information will lead to a change in the prognostic information given to the patient, resulting in adjuvant chemotherapy being proposed to the patient, although in a few patients only. We have found extra-axillary lymph nodes in approximately 30% of patients, in 20% of these patients their nodes are tumour-positive (irrespective of the site of metastasis). In half of the patients in whom we have removed the extra-axillary nodes, these nodes are the only positive nodes, while the axillary nodes are negative. So, if extra-axillary sentinel nodes are not examined, 2–3% of patients with tumour-positive lymph node metastasis will be missed.

Secondly, to guide the treatment of extra-axillary lymph node basins as the internal mammary chain nodes and supraclavicular nodes. It is not clear whether elective internal mammary chain node irradiation will result in a better survival. Its role in the locoregional treatment of breast cancer is challenged and subject of a randomised study carried out by the European Organisation for Research and Treatment of Cancer (EORTC) Radiotherapy Group. Internal mammary chain node irradiation may be associated with late sequelae such as

an increased incidence of cardiovascular complications. As stated by Nieweg and Bartelink and others [12,25], its sounds intuitively logical to irradiate the internal mammary chain nodes if metastasis are encountered by the sentinel node procedure, and to omit if sentinel nodes at those sides are tumour-negative. Whether radiation to the internal mammary chain nodes could be omitted if the lymphoscintigraphy shows no drainage is more speculative.

Better staging may have led to better outcomes in the past. However, the differences in clinical outcome with respect to finding tumour positive internal mammary chain and supraclavicular nodes is likely so small that one may ask whether it is worth pursuing investigations of these nodes. Nonetheless, the concept of lymphatic mapping to achieve better staging remains logical and has potential clinical implications and therefore it is very important that study groups investigate these more elaborate techniques and report their experiences. As stated by Nieweg, whether a randomised study, to provide final proof of the utility of this concept, will ever be possible is questionable. Bevilacqua and colleagues have therefore suggested using a selection algorithm for IMC biopsy [26].

The standardisation of the sentinel node procedures appears to be its weakest point: different injection techniques, different tracers, different volumes, different time intervals between injection and surgery, single tracer technique (radioactive tracers or blue dye), double tracer technique (radioactive and blue dye), triple technique (radioactive, blue, lymphoscintigraphy and probe). However, from the vast experience published in the literature, some general guidelines can be distilled [27–30].

- If only the sentinel node in the axilla is wanted (axillary treatment should be omitted in those patients who have tumour-negative sentinel nodes), it does not seem to matter where the tracer or what type of tracer is injected into the breast: with all kinds of techniques the sentinel node in the axilla can be found with high published-identification rates and low false-negative rates after a decent learning curve and in a well trained team.
- If the aim is lymphatic mapping to find all possible tumour-positive sentinel nodes outside the axilla, parenchymatous (intra- or peritumoral) injection with a ^{99m}Tc isotope is mandatory. Without a lymphoscintigram, extra-axillary sentinel nodes are very difficult to identify.
- The lowest false-negative rates are seen with well trained surgeons and teams, who have an identification rate of over 95% in patients with not too large tumours (up to 4–5 cm), uni-centric and with clinical (or ultrasound-tested) negative axillary nodes. The use of the combined technique (blue dye, isotope, lymphoscintigraphy and probe, particularly for those who are starting) also provides high identification rates. Furthermore, palpation of the axilla after removal of the sentinel nodes to search for possible microscopic suspicious nodes has to be carried out. A careful work-up by the pathologist is mandatory. If the sentinel node contains micrometastasis, either identified by Haematoxylin/Eosin or by immunohistochemistry with cytokeratins, the chance of finding tumour-positive non-sentinel nodes in the axilla is 10–20%. Thus, applying careful histology in multiple slices (including immunohistochemistry) of the sentinel node is a tool to reduce the false-negative rate [31].
- In almost 100% of patients, sentinel nodes can be identified by experienced surgeons working in experienced teams, after a learning curve of at least 20–30 cases and by maintaining experience by performing at least six procedures a month [32,33].

The sentinel node procedure is therefore as easy to master as any normal surgical procedure in breast cancer. Quality can be controlled by simple and undisputable outcome measures: such as the number of cases performed by the individual surgeon on a monthly basis or by an identification rate of $>95\%$ [34].

There is no doubt that the sentinel node procedure is associated with a limited morbidity, particularly compared with axillary clearance [35–37]. However, late sequelae of the sentinel node procedure are not negligible. Mild pain and numbness are reported in 10–30% of patients after one year, limitation in arm functions in 5–10% and arm swelling in 0–3%. This limited morbidity indicates that the procedure should only be performed in the right patient, by the right surgeon and for the right indications.

It is likely that the sentinel node procedure is cost-effective [38]. Expenses include the procedure, the scans, the tracers, the double operation if the sentinel node is positive (axillary clearance), and the more elaborate work-up of the sentinel nodes by the pathologist. This is balanced by gains such as less axillary clearances in T1-2 N0 patients (approximately 60%), consequently less morbidity, an earlier regain of the ability to work, less late morbidity, less histological work-up of many nodes from axillary clearances. Sentinel node procedures can be performed in a general hospital setting where pathology and nuclear medicine are available. This can be performed either in a 1- day or 2-day procedure.

In summary, the sentinel node biopsy has been proven to be a useful tool to identify or to exclude lymph node metastases in the axilla in most patients with invasive breast cancer. If general recommendations regarding the learning curve and the technique are followed, the pro-

cedure can be mastered easily by a sentinel node team (breast surgeon, nuclear medicine physician and pathologist). Chasing sentinel nodes outside the axilla will improve staging and may have an impact upon treatment decisions in a relatively small percentage of patients. It is as yet unclear whether this will have an impact upon overall outcome. As in the past, better staging has led to better outcomes, improved staging by lymphatic mapping can not be neglected and deserves careful study, may be in a randomised trial. The clinical relevance of finding lymph node metastases outside the axilla (internal mammary chain nodes) by lymphatic mapping is recognised by its incorporation in the new International Union Against Cancer (UICC)-TNM classification of breast cancer [39].

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