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Controversy

Implications of lymphatic mapping for staging and adjuvant treatment of patients with breast cancer

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Abstract

Lymphatic mapping has become a frequently used technique for staging the axilla in patients with breast cancer. In addition to sentinel nodes in the axilla, lymphoscintigraphy depicts sentinel nodes outside the axilla in up to 34% of patients. An increasing number of surgeons are now pursuing these extra-axillary nodes and are able to harvest them with limited morbidity in up to 87% of the patients concerned. Improved accuracy of staging is the result. Surgeons, radiotherapists and medical oncologists should consider the implications of the presence or absence of metastatic disease in such nodes. Incorporating the tumour status of these extra-axillary sentinel nodes in the management of patients will lead to a better selection of those who may benefit from post-operative radiotherapy to the internal mammary lymph node chain and from adjuvant systemic treatment.

Keywords: Keywords; Breast neoplasms; Sentinel lymph node; Neoplasm staging; Radiotherapy, adjuvant; Chemotherapy, adjuvant; Hormone treatment; Diagnostic techniques and procedures

Lymphatic mapping with sentinel lymph node biopsy results in a more accurate staging of breast cancer. This confronts the clinician with new questions and decisions that have to be made today although answers from clinical trials will not be available for the next 10–15 years. The burning questions are: what is the clinical relevance of micrometastases, what should be done with sentinel nodes outside the axilla and under which circumstances should adjuvant regional and systemic treatment be administered.

It has been shown that the node that receives drainage directly from the primary tumour—the sentinel node—is the first to be involved when lymphatic dissemination occurs [1]. Experienced surgeons identify the sentinel node in some 95% of breast cancer patients and patients without lymph node metastases can now be spared axillary node dissection [2,3]. In addition to this major step forward, lymphatic mapping results in more accurate staging than elective axillary node dissection. In clinical practice, the latter surgical procedure is a fairly crude way of examining the axilla. The surgeon usually does not remove all the lymph nodes from the axilla and the pathologist also does not recover all the nodes from the chunk of tissue that is submitted. Pathologists sample lymph nodes sparsely and may not examine every node they recover from the specimen. With lymphatic mapping, the surgeon provides the pathologist with the *one* node that is most likely to contain metastatic disease. Most pathologists make an extra effort to examine this particular node with serial sections and immunohistochemistry to determine its tumour-status. More accurate staging is the logical result although false-negative sentinel node biopsies may limit the effect. Fortunately, false-negative results are infrequent [4], only four cases of axillary recurrence have been reported after the abandonment of routine axillary node dissection [5–8].

The more exhaustive histological examination will lead to more patients who are identified as having micrometastasis. Unanswered questions are whether a

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patient with just a few tumour cells in the sentinel node needs treatment of the remainder of the lymph node field and whether such a patient should receive adjuvant systemic treatment. Most of these patients will probably not have disease elsewhere and will not benefit from additional therapy. How much overtreatment is acceptable? Randomised studies are clearly needed, but answers will not be available within the next 10–15 years as long-term follow-up is required in breast cancer.

Lymphatic mapping has now been taken one step further to include nodes outside the axilla. This will improve the accuracy of staging even more. Sentinel nodes along the internal mammary vessels behind the ribs are visualised on the lymphoscintigraphy images [9–12]. Sentinel nodes have also been identified in the subclavicular and supraclavicular fossae, between the pectoralis muscles and within the breast parenchyma [11,13]. Depending on the tracer injection technique, sentinel nodes may be found outside the axilla in up to 34% of patients [14]. Some surgeons have now begun to pursue these nodes and are able to harvest them in up to 87% of the patients concerned with limited morbidity [12,15,16].

The pursuit of sentinel nodes outside the axilla requires surgeons, radiotherapists and medical oncologists to consider the implications of the presence or absence of metastatic disease in such nodes. Currently, many patients with either a primary tumour over a certain size, or in a medial quadrant of the breast, or with axillary node metastasis are routinely given prophylactic radiotherapy to the internal mammary node chain [17]. The value of this approach has never been established and is in fact the subject of ongoing randomised trials in Europe and Canada. What *has* been shown is that formerly used radiotherapy techniques damage the heart, leading to an increase in cardiac deaths [18]. Despite the fact that radiotherapy techniques have improved [19], one wonders whether it is reasonable to give radiotherapy to the internal mammary node chain if lymphoscintigraphy does not show drainage to these nodes. Or, pressing this issue even further, is it reasonable to give radiotherapy if scintigraphy does show drainage there and the sentinel node is harvested, but is found to be free of disease? Common sense suggests otherwise. It seems logical to refrain from radiotherapy to the internal mammary lymph nodes when the sentinel node in this area is tumour-free even in the presence of axillary node metastasis. The parasternal region should be irradiated in patients with proven tumour-positive nodes along the internal mammary artery. Radiotherapists should modify protocols for internal mammary lymph node irradiation accordingly.

Is a patient with favourable primary tumour characteristics, a tumour-free axilla and metastasis in a sentinel node outside the axilla a candidate for adjuvant systemic therapy? Oncologists will be confronted with this situation in a small percentage of patients [11,16]. Involvement of the internal mammary node chain indicates a high risk of blood-borne metastases at distant sites [20,21]. Again, common sense suggests that protocols be adapted to include these patients.

Incorporating the tumour-status of sentinel nodes outside the axilla in adjuvant radiotherapy and systemic treatment protocols may lead to better patient selection and improved regional control and survival. One would like to examine these issues in randomised trials, but such trials will be difficult to conduct. For instance, patients may be reluctant to undergo radiotherapy to the internal mammary node chain when the sentinel node there is disease-free. Likewise, the informed patient with metastasis in such a node may be hesitant to accept the risk of being excluded from adjuvant radiotherapy or systemic treatment.

In the future, trials of adjuvant therapy should require lymphatic mapping for accurate staging. Sentinel node-positive patients are obvious targets for adjuvant systemic treatment. But what about sentinel node-negative patients? Patients with a melanoma of at least 1 mm Breslow thickness and a tumour-free sentinel node have an excellent 89% 5-year survival [22]. If there exists an analogy between the two diseases, sentinel node-negative breast cancer patients may have such a good prognosis that adjuvant systemic treatment is not advantageous. If there is no such analogy, other novel techniques such as mRNA micro-array analysis of the primary tumour appear to be helpful in the selection of patients for adjuvant systemic therapy [23]. Will this new technique to determine the biology of the primary tumour obviate the need for lymph node staging in the next few years? Perhaps, but the biology of the tumour clones that make up a lymph node metastasis may prove to be even more relevant for a patient's future [24].

The more accurate staging that results from lymphatic mapping has led to modifications of the TNM staging system [25]. More changes based on sentinel node technology can be foreseen. Until now, a metastasis detected in a supraclavicular lymph node is palpable and the disease has usually passed through involved axillary nodes in a step-wise fashion to get there. Such a metastasis is currently classified as N_{3c} because it is associated with a poor prognosis. A metastasis in a supraclavicular *sentinel* node is not palpable and, by definition, has reached that node directly, without passing through other nodes first. A tumour-positive supraclavicular sentinel node carries a prognosis that is probably not much worse than is true for an involved axillary sentinel node (usually N_1). A future evaluation of the TNM system needs to address such issues.

In conclusion, the consequences of lymphatic mapping in breast cancer extend beyond axilla-conserving surgery. More accurate staging is another result and this feat

demands modification of the indications for both adjuvant radiotherapy and systemic treatment. Implications for future trials of adjuvant treatment and for the reliability of the staging system have to be considered as well.

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