Melanoma surgery and the impact of sentinel node biopsy
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Chapter 4

False-negative sentinel node biopsy in melanoma: an editorial

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The sentinel lymph node biopsy was a valuable addition to our diagnostic armamentarium. The procedure improves staging, results in better prognostic information that we can share with our patients, and increases the chance of survival in node-positive patients. But, there is room for further improvement. How well does the procedure do what it is supposed to do, and how does one examine this? The main question is the following: if there is a metastasis in the nodal basin, how often does the sentinel node biopsy reveal it? This is the sensitivity. And, how often is there a recurrence in the nodal basin in a situation that no node dissection was carried out because the sentinel node was tumor-free? If this happens, the procedure was false-negative. A false-negative result means that a metastasis was present in the nodal basin, but the sentinel node biopsy did not find it. The false-negative rates that have been published in the past few years are not good. For instance, the false-negative rate in Morton’s Multicenter Selective Lymphadenectomy Trial now stands at 20%.[1] This means that one of every five patients with nodal involvement from melanoma is missed by the sentinel node procedure.

There are many potential reasons for false-negative procedures. Perhaps the concept that melanoma disseminates through the lymphatic system in a step-wise fashion from one node to the next is not watertight. Rather than to disseminate in clusters, melanoma tends to disseminate as individual cells that perhaps can pass through a node or narrow collateral lymphatics and settle in the next node downstream. The lack of a commonly accepted definition of a sentinel node implies that one man’s sentinel node is not necessarily somebody else’s.[2] Analysis of 33 patients with a false-negative sentinel node biopsy at the Melanoma Institute Australia showed that there were process deficiencies in nuclear medicine for 31% of these cases, in pathology for 31% and in surgery for 13%.[3] The lymph flow may be diverted to another node – a ‘neo’sentinel node – because the original sentinel node is largely replaced by metastatic disease or because the afferent lymph vessel is blocked by in-transit metastases. Lymph drainage from a melanoma is variable. Reproducibility studies show drainage to another node in 12 - 15% of the patients in whom lymphoscintigraphy is done twice.[4] False-negativity has also been found to be associated with increasing age, lower Breslow thickness, higher Breslow thickness, ulceration, and less lymphovascular invasion. A complete regression of a metastasis in the sentinel node but not in a subsequent node may also be a potential cause for failure.[3]

How does the false-negative rate for melanoma compare to that for other cancers? A recent study of 153 patients who underwent sentinel lymph node biopsy for Merkel cell carcinoma revealed a false-negative rate of 15%.[5] The median duration of follow up was 41 months. The false-negative rate was 19.2% in a series of 92 penile cancer patients with a median follow up
duration of seven years.[6] False-negative sentinel node biopsy rates in vulvar cancer ranged between 5.5% and 27%.[7]

The favorable exception is breast cancer. In patients without completion axillary node dissection, the false-negative rates ranged between 0% and 3% with a weighed combined sensitivity of 100%.[8] The false-negative rate in these patients became evident through nodal recurrence in the axilla. Interestingly, a recent study of sentinel node biopsy in breast cancer patients with back up axillary clearance revealed a false-negative rate of 22.9%.[9] This indicates that metastatic nodes most likely remain in the axilla after a negative sentinel node biopsy, but these nodes do not necessarily develop into clinically apparent disease within the examined time frame. There are reasons that can explain this lack of clinical progression of breast cancer. Radiotherapy to the whole breast after breast conserving surgery and adjuvant systemic therapy are likely to adequately treat involved nodes that remain. But there are also other explanations for the favorable sensitivity in breast cancer compared to melanoma. In contrast to melanoma, lymph drainage from a breast cancer is consistently to the same node(s). And also, about a third of the breast cancers drain to a lymph node in or around the breast but outside the axilla. Such a recurrence in an intramammary node may be interpreted as a local recurrence in lieu of the false-negative sentinel node biopsy that it really was.

But, there is also some good news for melanomologists. At The Netherlands Cancer Institute, the false-negative rate was 29.4% in the first year after the procedure was introduced in 1993, but just 3% in the years thereafter. It takes some time to get the hang of it. So, it is likely that the current performance is better than publications of past series of patients indicate. A meticulous technique and a comprehensive quality control program seem important. The physiology of lymph drainage and the biology of the disease with step-wise spread through the lymphatic system should be kept in mind when deciding which node to remove. Close cooperation of the lymphatic team members also contributes to good results. Single photon emission computed tomography combined with radiologic computed tomography (SPECT/CT) demonstrates more sentinel nodes and provides better information on the location of the nodes. Other innovative imaging technologies are being explored, like the intra-operative gamma camera, fluorescent tracers, and freehand SPECT. These may make the sentinel node procedure easier and more reliable, especially in the difficult cases, and they may reduce false-negative rates. Effective adjuvant systemic therapy that appears to loom on the horizon may also contribute to decreasing the rate of false-negative sentinel node biopsies in melanoma.
REFERENCES


