Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
Estourgie, S.H.

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CHAPTER 8

WHAT IS A FALSE NEGATIVE RESULT FOR SENTINEL NODE PROCEDURES IN BREAST CANCER?

Susanne H Estourgie, Omg o E Nieweg,
Emiel JTh Rutgers, Bin BR Kroon

Department of Surgery, The Netherlands Cancer Institute/
Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

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The sentinel node procedure is widely performed in breast cancer patients. The rate of identification of nodes generally exceeds 95%, and the reported false negative rates have not been alarming so far. In determining the rate of false negative results, a mistake that is sometimes made is to calculate the rate over the entire group of patients, both those who are axilla-positive and those who are axilla-negative. The outcome is too flattering with this approach. It is not possible to miss metastasis in a patient who has no metastasis. The false negative rate should be calculated over the entire group of axilla-positive patients, as follows:

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\text{false negative rate} = \frac{\text{no. of false negative procedures}}{\text{no. of false negative} + \text{true positive procedures}} \times 100%.
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At the recent meetings of the American and European Societies of Surgical Oncology, we sensed confusion over the definitions of the sentinel node and a false negative result. Morton and colleagues initially defined the sentinel node as that node to which the tumor drains directly. Later, this definition became a subject of discussion. Various investigators came up with their own definitions, which was understandable because specialists from different fields were involved. Recently, Morton's definition has been endorsed at a consensus meeting of a group of experts. This commentary focuses on defining a false negative sentinel node procedure. The definition is more complicated than it seems and has substantial implications for the false negative rate. As more experience is gained, the surgeon may see more cases in which it is difficult to determine whether they are false negative. Questions that come to mind when a patient has a tumor-free sentinel node include: what if an additional palpable, non-radioactive, unstained lymph node is found during operation and turns out to be tumor-positive? What if a tumor-positive non-sentinel node is found in the axillary tail of a simple mastectomy specimen? What if additional sections of the sentinel node show metastatic disease at a later stage after all?

In our opinion, there are three credible definitions of a false negative finding on sentinel node procedures. The first one follows the original definition of the sentinel node, which is based on direct drainage from the primary lesion site. This node is identified by lymphoscintigraphy, a probe, or blue dye. This procedure is a sentinel node biopsy per se with the identification of this particular lymph node as its sole purpose. The result of this procedure would be false negative if this sentinel node is disease-free at initial pathologic evaluation, but a tumor is established in any axillary lymph node at any time.

The second definition is based on the assumption that the results of the procedures are truly positive if a tumor-positive node is found during the standard sentinel node procedure within the limits of its protocol. A palpable, tumor-positive, non-sentinel node in combination with a tumor-free sentinel node would not be defined as a false negative finding if palpation of the biopsy wound is a standard technique in a given institution. Coincidental removal of other nodes is obviously not part of such a protocol. Therefore, the finding of these other nodes can cause false negative results. Also, a pathologic sampling error would result in a false negative procedure, because the pathologist must perform additional serial sectioning to find tumor cells in the sentinel node.

Finally, one can call the results of a sentinel node procedure false negative only if axillary recurrence occurs during follow-up evaluation. This means that the "sentinel node biopsy" is considered in fact a comprehensive axillary staging operation. Its purpose is to detect metastatic
DEFINITION FALSE NEGATIVE RESULT

disease in the axilla. The procedure involves excision of the sentinel node per se and removal of other nodes that look suspicious. Unintended excision of tumor-positive nodes in the axillary tail of a total mastectomy specimen or together with the sentinel node will not lead to false negative results. The results of the procedure are false negative only when dissemination comes to light later through recurrent disease.

At our institute, results of a sentinel node procedure are considered falsely negative if the initial pathologic evaluation reveals no tumor cells in the sentinel node but one or more non-sentinel nodes are tumor-positive. These cases can either be detected right away by means of deliberate or incidental removal of other nodes, or during follow-up evaluation as a clinical recurrence. Palpation of the biopsy wound is standard procedure at our institute, but nonradioactive and unstained nodes are considered non-sentinel nodes and therefore cause false negative results. Coincidentally excised tumor-positive nodes cause the results to be falsely negative if the sentinel node is tumor-free. Our policy is to perform a complete axillary lymph node dissection if no sentinel node can be identified during surgery. These cases are not defined as having false negative results, because no sentinel node was removed. In summary, we follow the first definition, which yields seven false negative results out of 600 sentinel node biopsy procedures. If we were to use the second definition, only three cases would be considered to have false negative results. Only one patient had an axillary recurrence after 22 months, so the third definition of a false negative finding would improve our results dramatically. The difference in false negative rate between the first and the last definition is a factor of seven!

During a recent Dutch symposium on breast cancer, a survey was conducted among approximately 100 surgeons and nuclear medicine physicians. This showed that 8% were in favor of the first definition of a false negative result, 33% were in favor of the second definition and 59% were in favor of the last definition.

The first definition of a false negative result, as discussed above, has been used universally in learning phase studies. Lately, however, we sense a shift toward the use of the last definition. In our opinion, this definition is too broad. The second definition encourages removal of apparently tumor-positive, non-sentinel nodes while discouraging the indiscriminate removal of non-sentinel nodes that is tempting when following the last definition. Therefore, the second definition best serves the clinical purpose, which is to establish metastatic disease but in the least disruptive manner. One may even consider redefining the term ‘sentinel node’ as a lymph node that is or has been on a direct drainage pathway. The influence of different definitions on the rate of false negative results of sentinel node procedures is evident. To enable comparison of false negative rates between different institutes, either consensus should be obtained or a detailed description of the definition used should be given when results of sentinel node procedures are published.

REFERENCES
