

# Sentinel lymph-node biopsy qualification in breast cancer

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## Summary

Lymphatic drainage from the breast is principally to the ipsilateral axilla. In patients with breast cancer the status of the nodes in the axilla is an important prognostic factor and can be used to determine local and systemic treatment. Clinical assessment of the node status is unreliable and imaging techniques, though promising, are at present not practical. The standard policy for management of the axilla is axillary clearance (either level II or III), which is justified by the fact that in both stages the armpit is treated. In those node-negative cases, however, it is an unnecessary operation and is linked to some morbidity. Various methods to obtain nodes for histologic evaluation in an attempt to stage the axilla have been tried. A pectoral node biopsy, where a single node is taken from the axillary tail, has been proven to be unreliable. A triple-node biopsy (pectoral, apical, internal mammary) provides excellent prognostic data but is difficult to perform in patients treated by breast conservation. Four-node sampling has been assessed in Edinburgh in two randomized trials comparing node sampling to level III axillary clearance. The four-node sampling technique was shown to be reliable for staging the axilla, and in node-negative cases no further treatment is required. Detailed morbidity has been evaluated in patients who underwent axillary dissection, and node sampling plus radiation and node sampling without radiation demonstrated that those with node sampling had the least morbidity. Those with radiation have reduced movement around the shoulder joint, and the axillary dissection group have increased swelling of the upper limb and slightly reduced abduction. Sentinel node biopsy is presently being evaluated in several centers by randomized studies. Several large series have shown the method to be accurate (98%) when the sentinel node is identified (about 90% of cases). Sentinel node biopsy should routinely enter the field of axilla surgery and thus patients without clinically recognized disease avoid overtreatment when the sentinel node is free of cancer.

**Key words:** Sentinel-node; Biopsy; Breast cancer; Axillary clearance.

The sentinel lymph node - the first node to receive the lymph flow from the area containing the primary tumor - biopsy is a dramatic development in surgical oncology.

The technique initially used for melanomas [1, 2] and subsequently for breast cancer [3] is based on the hypothesis that sentinel node (SN) status is mandatory for axillary status. If the SN is healthy, the others around the armpit will also be disease-free. If, however, metastatic growth is detected in this node, the others may also be affected, and in such cases it is necessary to carry out a full axillary clearance.

The necessity of avoiding a full axillary dissection is commanding as a consequence of two advances. The first one concerns the detection of breast cancer in a continually lesser size. When the maximum diameter of the tumor is less than 1cm, the probability of lymph node metastases is less than 5%, which means that an operation for axillary clearance is probably unnecessary. It is estimated that in late 2010s the average maximum dimension of cancer in America will be less than 1 cm [4]. On the other hand, there is an increased number of in situ carcinomas, which are not palpable in the majority of cases but can be detected by mammography. In current reports from the USA, in the 1990s in 21 series of 13,125 patients the number of in situ carcinomas revealed by mammography constituted up to 39% of all cancers detected [4].

The second advance concerns the concept that all patients, regardless of age, menstrual status and axillary status, must be treated with adjuvant chemotherapy. This evolution was impressed in the NIH consensus in november 2000, pointing towards a gradual disconnection of the adjuvant treatment from the most important prognostic factor in breast cancer up to now (lymph-node status). However, the complete and unconditionally disqualification of axillary dissection in breast cancer remains controversial mainly because of the fact that there are data (not statistically significant but strongly indicative) implying that the control of limited (not disseminated) disease, probably improves the disease-free interval and the final outcome.

The decision of carrying out complete axillary clearance, when lymph nodes are not clinically involved, or are harboring cancer, does not seem to have an influence on survival. However, simple regular follow-ups cannot be

a determinant of disease-free subjects, till there is clinically certified axillary involvement. Thus sentinel node biopsy seems to be the safest diagnostic procedure to estimate axillary status, and which is mandatory for clearance. Moreover, in cases of T1a and b tumors SN biopsy may be enough considering that if the axilla is positive, the SN is probably the one and only node involved.

In most previous investigations of the sentinel node, blue dye was injected into the peritumoral area, and the coloured node was sought through axillary incision [3]. A few studies on a small series of patients used the lymphoscintigraphic technique [5, 6]. The validity of the sentinel-node strategy has thus been established in breast cancer.

The reliability of sentinel-node diagnosis on frozen sections may also be questioned. Immediate and reliable intraoperative information on the condition of the sentinel node is vital for the technique's success, since the surgeon must decide whether or not to do a total axillary dissection. The results of a trial [7] conducted at the European Institute of Oncology on 107 out of 163 women with breast cancer showed that in 18 cases (17%) the intraoperative diagnosis was falsely negative because micrometastatic foci were subsequently identified on permanent sections. This percentage is high enough to cause concern, and may represent a limiting factor for the sentinel-node biopsy procedure. A patient whose sentinel node is negative in frozen section but is positive on histology will require a further operation to clear the axillary, which is likely to increase her distress. To help limit this distress, the patient should be fully informed about the problem of intraoperative false-negative results. It is important also to develop techniques to improve the frozen-section examination. Future research should concentrate on more reliable ways to identify microfoci of metastatic cells; in this respect, a rapid cytokeratin immunocytochemically assay seems promising [8]. We have just started here in the Democritus University of Thrace Department of Obstetrics and Gynecology to qualify another procedure to detect SN status – touch imprint cytology. We believe some conclusions will be reached shortly.

The same study [7] confirmed the hypothesis of SN biopsy qualification over a total axillary dissection and that the margin of error falls from around 3% to zero if the cancer is smaller than 1.5 cm in diameter, as is often the case. This study also highlighted the pathological variables that predict metastatic spread to the axillary lymph nodes. The highest predictive value was associated with pericancer vascular invasion.

An expected development of sentinel-node biopsy will be used for patients undergoing primary (neoadjuvant) chemotherapy. One of the drawbacks of neoadjuvant chemotherapy is that it can destroy small metastatic foci and down-stage the axilla before it is examined histologically after chemotherapy. Sentinel-node biopsy before chemotherapy, which reliably predicts the state of the axilla, may address this issue. On a cautionary note, however, a small number of lymph nodes identified as negative by standard histological techniques may have occult micrometastases. We believe, therefore, that patients should be followed up carefully with frequent examination of the axilla so that a possible recurrence of disease in the axilla is swiftly detected and the axillary nodes removed. However, data from other studies [9, 10] indicate a low rate of axillary metastases during follow-up of patients with clinically negative nodes which were not dissected at the time of primary surgery.

Conclusively, we believe that SN biopsy is an important step forward in the search for more conservative treatments for patients with breast cancer.

## References

- [1] Morton D., Wen D., Cochran A.: "Management of early-stage melanoma by intraoperative lymphatic mapping and selective lymphadenectomy: an alternative to routine elective lymphadenectomy or watch and wait". *Surg. Oncol. Clin. N. Am.*, 1992, 1, 247.
- [2] Morton D., Wen D., Wong J. *et al.*: "Technical details of intraoperative lymphatic mapping for early stage melanoma". *Arch. Surg.*, 1992, 127, 392.
- [3] Giuliano A. E., Kirgan D. M., Guenther J. M., Morton D. L.: "Lymphatic mapping and sentinel lymphadenectomy for breast cancer". *Am. Surg.*, 1994, 220, 391.
- [4] University of Athens, Faculty of Medicine, and "Laikon" General Regional Hospital of Athens, Second Preparatory Department of Surgery, Breast Surgery Ward; 5<sup>th</sup> Annual International Meeting and Workshop on Breast Cancer: From diagnosis to treatment. Lecture: "The validity of sentinel node in breast cancer and techniques to locate it". Athens, September 2001.
- [5] Krag D. N., Weaver D. L., Alex J. C., Fairbank J. T.: "Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe". *Surg. Oncol.*, 1993, 2, 335.

- [6] Albertini J. J., Lyman G. H., Cox C. *et al.*: "Lymphatic mapping and sentinel node biopsy in the patient with breast cancer". *J.A.M.A.*, 1996, 276, 1818.
- [7] Veronesi U., Paganelli G., Galimberti V. *et al.*: "Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes". *Lancet*, 1997, 349, 1864.
- [8] Chilosì M., Lestani M., Pedron S. *et al.*: "A rapid immunostaining method for frozen sections". *Biotechnic. Histochem.*, 1994, 69, 235.
- [9] Fisher B., Redmond C., Fisher E. R. *et al.*: "Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation". *N. Engl. J. Med.*, 1985, 312, 674.
- [10] Greco M., Agresti R., Raselli R., Giovanazzi R., Veronesi U.: "Axillary dissection can be avoided in selected breast cancer patients. Analysis of 401 cases". *Anticancer Res.*, 1996, 16, 3913.

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